When should HAART be started? How can a failing drug regimen be improved? What new drugs can we expect over the next few years? What are the options for patients with lipodystrophy syndrome? How to treat children or coinfected patients?

To answer these and many more questions, HIV physicians need to be constantly updating themselves. "HIV 2012/2013" will help them – with clear-cut recommendations for everyday practice.

This textbook will be updated every year and is available at www.hivbook.com.

Previous issues are available in several languages – Spanish, Romanian, Russian, Portuguese, Vietnamese and Persian.

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HIV Medicine is an ever-changing field. The editors and authors of HIV 2012/13 have made every effort to provide information that is accurate and complete as of the date of publication. However, in view of the rapid changes occurring in HIV medical science, HIV prevention and policy, as well as the possibility of human error, this site may contain technical inaccuracies, typographical or other errors. Readers are advised to check the product information currently provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician who relies on experience and knowledge about the patient to determine dosages and the best treatment for the patient. The information contained herein is provided "as is" and without warranty of any kind. The contributors to this site, including the editors and the Medizin Fokus Verlag, disclaim responsibility for any errors or omissions or for results obtained from the use of information contained herein.
Preface 2012/2013

The goal remains the same – to make a textbook that is easily readable and can be used in the daily practice of HIV treatment. As in previous years, all the chapters of HIV 2012/2013 have been thoroughly revised.

Again, special emphasis was put on actuality. This is underlined by the fact that in the antiretroviral therapy chapter alone, more than 200 are dated in the years 2011 and 2012.

Previous issues of the progenitor “HIV Medicine” were available in several languages, such as Spanish, Romanian, Portuguese, Vietnamese and Persian. There have been a Russian issue in 2011.

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HIV 2012/2013 is also freely available on the Internet (www.hivbook.com), because we firmly believe that this is the way medical textbooks should be handled in the 21st century. Research, knowledge, and expertise in the field of HIV can be shared and accessible to those who are dedicated to the treatment and care of individuals affected by HIV.

Christian Hoffmann, Jürgen K. Rockstroh
Hamburg, Bonn – September 2012

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<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>AIN</td>
<td>Anal Intraepithelial Neoplasia</td>
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<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BAL</td>
<td>Bronchoalveolar Lavage</td>
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<tr>
<td>BGA</td>
<td>Blood Gas Analysis</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CROI</td>
<td>Conference on Retroviruses and Opportunistic Infections</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Topography</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic T Cells</td>
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<tr>
<td>CVC</td>
<td>Central Venous Catheter</td>
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<tr>
<td>DD</td>
<td>Differential diagnosis</td>
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<tr>
<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
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<tr>
<td>EAP</td>
<td>Expanded Access Program</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr-Virus</td>
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<td>ED</td>
<td>Erectile Dysfunction</td>
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<td>ELISA</td>
<td>Enzyme Linked Immunosorbent Assay</td>
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<td>ELISPOT</td>
<td>Enzyme Linked Immunosorbent Spot Assay</td>
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<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>FDC</td>
<td>Follicular Dendritic Cells</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte Colony-Stimulating Factor</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
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<tr>
<td>HAART</td>
<td>Highly Active Anti-Retroviral Therapy</td>
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<tr>
<td>HbsAG</td>
<td>Hepatitis B Surface Antigen</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
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<td>Hepatocellular Carcinoma</td>
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<td>HCV</td>
<td>Hepatitis C Virus</td>
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<td>HDL</td>
<td>High-density Lipoprotein</td>
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<tr>
<td>HHV-8</td>
<td>Human Herpesvirus 8</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HIVAN</td>
<td>HIV-Associated Nephropathy</td>
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<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<td>Human Papillomavirus</td>
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<td>HSR</td>
<td>Hypersensitivity Reaction</td>
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<td>HSV</td>
<td>Herpes Simplex Virus</td>
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<tr>
<td>IC50</td>
<td>50% Inhibitory Concentration</td>
</tr>
<tr>
<td>IRIS</td>
<td>Immune Reconstitution Inflammatory Syndrome</td>
</tr>
</tbody>
</table>
XVIII Abbreviations

ITP  Idiopathic Thrombocytopenic Purpura
ITT Analysis  Intention-to-Treat Analysis
IU  International Unit
CHD  Coronary Heart Disease
KS  Kaposi’s sarcoma
LDH  Lactate Dehydrogenase
LDL  Low-Density Lipoprotein
LGV  Lymphogranuloma venereum
LIP  Lymphocytic Interstitial Pneumonia
LTNP  Long-Term Non-Progressor
MAC  Mycobacterium Avium Complex
MCD  Multicentric Castleman’s Disease
MDR  Multi-Drug Resistant
MHC  Major Histocompatibility Complex
MRT  Magnet Resonance Tomography
MSM  Men who have sex with men
NASBA  Nucleic Acid Sequence Based Amplification
NHL  Non-Hodgkin’s Lymphoma
NK-Cells  Natural Killer Cells
NNRTI  Non-nucleoside Reverse Transcriptase Inhibitor
NRTI  Nucleoside Reverse Transcriptase Inhibitor
OHL  Oral Hairy Leukoplakia
OI  Opportunistic Infection
PBMC  Peripheral Mononuclear Cell
PCNSL  Primary Central Nervous System Lymphoma
PCP  Pneumocystis Pneumonia
PCR  Polymerase Chain Reaction
PEL  Primary Effusion Lymphoma
PEP  Post Exposure Prophylaxis
PI  Protease Inhibitor
PML  Progressive Multifocal Leukoencephalopathy
PNP  Polyneuropathy
PrEP  Pre-Exposure Prophylaxis
RNA  Ribonucleic Acid
SD  Sexual Dysfunction
SIV  Simian Immunodeficiency Virus
STD  Sexually Transmitted Diseases
STI  Structured Treatment Interruption
TAM  Thymidine Analogue Mutation
TCR  T Cell Receptor
TDM  Therapeutic Drug Monitoring
TSH  Thyroid-stimulating Hormone
VL  Viral Load
VZV  Varicella Zoster Virus

For abbreviations of antiretroviral agents, see ART chapter.
PART 1

The Basics
1. Introduction

Acquired Immune Deficiency Syndrome (AIDS) was first described as a new clinical entity in 1981. Initial reports were based on an unusual increase in the incidence of Kaposi sarcoma (KS) and *Pneumocystis* pneumonia (PCP), diseases that were considered at that time to occur rarely. While both diseases are occasionally observed in different populations (e.g., KS in older men from the Mediterranean region or PCP in patients with leukemia after intensive chemotherapy), the occurrence of these diseases as indicators for severe immunodeficiency had not been observed before in otherwise healthy young individuals. Because the initially affected population were men who had sex with men (MSM) the disease as well as those with the disease were highly stigmatized. Though initially lifestyle and behavioral factors were hypothesized to be causally related, finally in 1983 the human immunodeficiency virus (HIV) was identified as the true cause of AIDS.

In 1987 the first antiretroviral agent, AZT (zidovudine, Retrovir®) was licensed for the treatment of HIV. Despite the failure of this therapeutic concept in terms of monotherapy in achieving long-term suppression of HIV replication, symptoms and clinical manifestations of HIV infection were temporarily relieved with AZT (at 1500 mg/day) and the occurrence of AIDS was slightly delayed. What happened next is unprecedented in medicine to date – within a few years of its discovery an inevitably deadly disease turned into a disease with durable and effective treatment options. The rapid introduction of additional antiretroviral drug classes and the concept of highly active antiretroviral therapy (HAART, an acronym that will be replaced in this book by ART) enabled a durable suppression of viral replication thereby preventing disease progression – as long as the antiretroviral drugs were tolerated and regularly taken. Long-term toxicities and the emergence of resistance led to a search for and identification of further promising drugs with other therapeutic mechanisms of action or better resistance profiles. In parallel, administration modalities and tolerability of antiretroviral drug regimens improved significantly. In 2012 several HIV therapies are available that only require an intake of 1–3 tablets a day mostly resulting from the introduction of fix-dose combinations.

All these advances should not be confused with the fact that lifelong medical therapy will probably lead to substantial problems, especially in terms of adherence to therapy and possible long-term toxicities. With only 15 years of experience so far, the latter aspect has thus far only been captured in part. Infection with HIV should still be avoided at all costs. Apart from further improvement of ART and development of new therapeutic concepts such as eradication, a main focus of our endeavors must be the prevention of HIV in order to contain the further spread of disease.

The HIV epidemic

In 1981 the first three clinical descriptions of AIDS were published in the Morbidity and Mortality Weekly Report and later the New England Journal of Medicine. These reports described an epidemic of community-acquired *Pneumocystis* pneumonia, in most cases combined with oral thrush in previously healthy homosexual men, as well as chronic ulcerating perianal herpes infections (Gottlieb 1981a, Gottlieb 1981b, Masur 1981, Siegal 1981). A little later, in June 1982, a notice from the Centers for Disease Control and Prevention (CDC) on three PCP cases among hemophiliacs was issued (CDC 1982a). In the same year a case of cryptosporidiosis in a hemophiliac patient from
Pennsylvania (Eyster 1982) and an AIDS manifestation in an infant after a blood transfusion were reported (CDC 1982b). The occurrence of AIDS among hemophiliacs triggered a discussion of whether a viral infection could cause AIDS (Marx 1982). In particular, the similarity of populations at risk for AIDS and hepatitis B led to the hypothesis of a viral agent causing AIDS.

Studies on AIDS patients comprising different populations at risk quickly revealed common characteristics: compared to healthy controls, all AIDS cases had diminished counts of CD4-positive T lymphocytes. Conversely, a relative and absolute increase in CD8-positive T lymphocytes and a reduced mitogen-induced proliferative capacity of lymphocytes was observed (Gottlieb 1981, Masur 1981, Siegal 1981, Mildvan 1982, Stahl 1982). It became quickly clear, however, that the manifestation of AIDS was not a prerequisite for developing an immune deficiency. A defect of cellular immunity, associated with a generalized lymphadenopathy, had already been described very early in otherwise asymptomatic men who had sex with men (Kornfeld 1982, Stahl 1982). In January 1983 two cases of hemophiliacs with a lymphadenopathy syndrome were reported, both with significant dysfunction of cellular immunity (Ragni 1983). This led to the assumption that the lymphadenopathy syndrome and the observed cellular immune defects may have been precursors to AIDS and that a transmission of the AIDS causative agent via blood products was probable. Subsequently numerous studies on altered states of cellular immunity among hemophiliac patients were published. The main finding was a reduced CD4/CD8 ratio, the result of a relative and/or absolute decrease of CD4 lymphocyte counts together with elevated CD8 T cell counts. Only those patients who had been treated with small amounts of blood-clotting factors or where blood-clotting factors had been derived from small donor pools showed normal lymphocyte subpopulations (Luban 1983, Rasi 1984).

The altered immunological findings among hemophiliacs were discussed controversially. In part they were attributed to a chronic antigen exposure due to the blood-clotting factor substitution. Other groups considered this hypothesis unlikely, given the fact that, prior to the advent of AIDS, no enhanced risk for infections was observed among hemophiliacs compared to other populations (except for viral infections, in particular hepatitis B and non-A-non-B-hepatitis via receipt of blood products). Overall, at that time no indication was seen to call into question the concept of blood-clotting substitution therapy among hemophiliacs (Anonymous 1983, Goldsmith 1983). As an alternative explanation of AIDS, particularly among the transmission group of men who have sex with men, coinfection with human cytomegalovirus, use of injection drugs, inhalation of amyl nitrate (poppers) and exposure to foreign proteins (spermatozoa) were discussed (Essex 1997).

In 1983 different working groups raised the hypothesis that a variant of the T-lymphotropic retrovirus (HTLV-I), which had been discovered in 1980 by Gallo and colleagues, could be the causative agent of AIDS (Essex 1983, Gallo 1983). Several arguments were in favor of this hypothesis. At that time HTLV-I was the only known virus with the potential to infect human CD4-positive T lymphocytes (Poiesz 1980). In addition HTLV-I shared the same transmission routes with the potential AIDS agent, i.e., sexual contacts, blood-to-blood and perinatal transmission (Essex 1982). First experiments to isolate virus related to HTLV-I or -II were only partially successful. Though cross-reactive antibodies with HTLV-related genome sequences were found in a small subset of AIDS patients, the overall assay reactivity was weak and suggested a coinfection with HTLV. The observations led to the assumption of a genetically more distant virus, one with weaker assay reactivity, as a putative etiologic agent. Indeed, only a short time later HTLV-III, later renamed Human Immunodeficiency Virus type I (HIV-1), was discovered as the causative agent of
AIDS (Barré-Sinoussi 1983, Popovic 1984). In 2008 the French research group of Luc Montagnier and Francoise Barré-Sinoussi received the Nobel Prize in Medicine for their discovery of HIV-1.

Transmission routes

The main transmission routes of HIV are
1. unsafe sex with an HIV-infected partner
2. sharing injection paraphernalia with an HIV-infected partner
3. vertical transmission of HIV from the HIV-infected mother to the newborn (before or at birth; or later, due to breastfeeding)

All other transmission routes, for the most part case reports, are notably rare. Among these are transmissions due to transfusion of blood or blood products in countries where blood donations are not routinely screened for HIV. Extremely rare are transmissions due to contact with HIV-positive blood through open wounds or mucosa, or transmission of HIV after a bite (Bartholomew 2008). Recently three cases were reported where mothers infected their newborns probably via pre-chewed food (Gaur 2008). These transmission routes however are of a casuistic nature. Large case registries, in particular from the CDC, which have investigated into other transmission routes of HIV, clearly show that daily contacts of everyday life, such as the shared use of toilets or drinking from the same glass, cannot transmit HIV. Case registries in the health care setting, which analyze contact via saliva, urine, or infectious blood with intact skin, did not find a single transmission of HIV (Henderson 1990).

Potentially favorable factors and risks

Sex

The most important transmission route for HIV is sexual contact. The prerequisite for sexual transmission is direct exchange of infectious body secretions / fluids. The highest viral concentrations are found in blood and seminal fluid. A study investigating heterosexual transmission of HIV in female partners of HIV-positive hemophiliacs in Bonn found a seroconversion rate of HIV of 10% (Rockstroh 1995). The risk for sexual transmission was significantly higher if the HIV-positive partner suffered from advanced immunodeficiency or an advanced clinical stage of HIV infection. It is important to note that a precise calculation of transmission risk after one individual exposure is not possible. Various environmental factors have an influence on the actual transmission risk, such as specific sexual practices, concurrent sexually transmitted diseases, skin lesions, circumcision and mucosal trauma, that are difficult to take into account. The average transmission risks according to different sexual practices are shown in Table 1.

The correlation of transmission risk with the level of HIV viremia has important epidemiological implications. In environments where body fluids like blood and seminal fluid are exchanged with many persons over days or weeks, the risk of meeting people who have been recently infected, and thus who are highly infectious, is high. Likewise, the probability of infecting someone else between the transmission event and the detection of HIV antibodies is high. The later stage of disease is also a highly infectious period, as HIV infection progresses and higher viral loads are again observed as one gets closer to falling below 200 CD4 T cells or AIDS. Sexually transmitted diseases and infections disrupt physiological skin and mucosal barriers and enhance the risk for HIV transmission. This is particularly true for endemic areas with a high prevalence of other sexually transmitted diseases. Primarily genital herpes lesions have been identified as a potential co-factor facilitating HIV transmission in endemic areas (Mahiane 2009).
Table 1: Likelihood for HIV transmission. (Modified from the guidelines of the German and Austrian AIDS Society; please see also www.daigenet.de)

<table>
<thead>
<tr>
<th>Type of contact / partner</th>
<th>Probability of infection per contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsafe receptive anal intercourse with HIV-positive partner</td>
<td>0.82% (95% CI 0.24–2.76) Range 0.1–7.5%</td>
</tr>
<tr>
<td>Unsafe receptive anal intercourse with partner of unknown HIV serostatus</td>
<td>0.27% (95% CI 0.06–0.49)</td>
</tr>
<tr>
<td>Unsafe insertive anal intercourse with partner of unknown HIV serostatus</td>
<td>0.06% (95% CI 0.02–0.19)</td>
</tr>
<tr>
<td>Unsafe receptive vaginal intercourse</td>
<td>0.05–0.15%</td>
</tr>
<tr>
<td>Unsafe insertive vaginal intercourse</td>
<td>0.03–5.6%</td>
</tr>
<tr>
<td>Oral sex</td>
<td>No known probability, although case reports have been described, in particular after reception of seminal fluid into the mouth (Lifson 1990)</td>
</tr>
</tbody>
</table>

Note: 95% CI = Confidence Interval according to a large US HIV seroconverter Study (Vittinghoff 1999).

The observation that the level of HIV RNA is obviously critical in the infectiousness of an HIV-positive person, has recently initiated a controversial discussion regarding the possibility of a seropositive person having “safe” unprotected sex. The Swiss Commission for AIDS (“Eidgenössische Kommission für AIDS-Fragen”, EKAF) proposed to classify HIV-infected persons who are on ART with a plasma HIV RNA below the level of detection for at least 6 months, if they are adherent to therapy, regularly come to medical examinations, and if they do not have any signs of any other sexually transmitted diseases, as persons who most likely do not transmit HIV via sexual contact and therefore may have unprotected sex if they want (Vernazza 2008). The intention of the EKAF recommendation is to manage fears of HIV transmission and to enable a normal sex life, as far as possible, in persons with and without HIV. The EKAF recommendation is not agreed to by all HIV experts. Recently a case report from Frankfurt raised questions (Stürmer 2008), where HIV transmission occurred, though HIV viral load was not detectable and the HIV-positive partner was on successful ART (see chapter on Prevention).

**Sharing injection paraphernalia**

Sharing injection paraphernalia is the most important HIV transmission route for persons who use drugs intravenously. Due to the usually quite large amount of blood that is exchanged when sharing needles, the transmission risk is high. The aspiration of blood to control the correct intravenous position of the needle constitutes the reservoir for transmission. With the introduction of needle exchange programs, the installation of needle vendors, methadone substitution and multiple other preventive measures and social programs, HIV transmission rates have significantly decreased within intravenous drug users in Western Europe. In Eastern Europe, where intravenous drug use constitutes a criminal offence and no clean needles are provided, one sees an unyielding continual increase of HIV transmissions in this population. One can only hope that the success of prevention efforts in Western Europe will lead to a more liberal management and implementation of prevention programs in Eastern Europe.
Vertical transmission
Without intervention up to 40% of newborns born to HIV-1-positive mothers are infected with HIV-1. The most important risk factor is viral load at the time of delivery. Since 1995 the mother-to-child transmission rate of HIV-1-infected mothers has been reduced to 1 – 2%. These low transmission rates were reached through the combination of antiretroviral therapy / prophylaxis for the pregnant woman, elective caesarian section prior to the start of labor (no longer necessary if the maternal HIV viral load is successfully controlled under ART and HIV-RNA is persistently undetectable), the antiretroviral post-exposition prophylaxis for the newborn and substitution for breast feeding. For details refer to the chapter “HIV and Pregnancy” as well as to the European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults (HIV Med. 2008 Feb;9(2):65-71; please also visit the website http://www.europeanaidsclinicalsociety.org/).

Blood
The transmission of HIV via blood and blood products has been largely reduced on a global scale, though the risk is not completely eliminated. In Germany blood and blood products are considered safe. Since 1985 all blood donations are tested for HIV-1 via antibody tests, and since 1989 also against HIV-2. For a few years now blood donations are additionally tested via PCR to identify donors who may be in the window of seroconversion and where the HIV ELISA is still negative. Persons with so-called risk behavior, i.e., active injection drug users, sexually active men and women as well as immigrants from high-prevalence countries are excluded from blood donations.

Occupationally-acquired HIV infection
The overall risk for HIV infection after a needlestick injury is estimated to be around 0.3%. The risk for HIV transmission is significantly higher if the injury occurred using a hollow needle – e.g., during blood withdrawal – than with a surgeon’s needle. For details on post-exposure prophylaxis (PEP) please refer to the respective chapter in this book. On the other hand, the risk of infecting a patient with HIV when the medical personnel is HIV-positive is extremely low. In 1993 19,036 patients of 57 HIV-infected physicians, dentists or medical students were screened for HIV infection (CDC 1993a). While 92 patients tested HIV-positive, none of the transmissions was related to the health practitioner.

Non-suitable transmission routes
In general, HIV-transmission due to day-to-day contact between family members is unlikely. It is important to avoid blood-to-blood contacts. Thus, razor blades or tooth brushes should not be commonly shared. In cases of cannula or needle usage, these should be safely deposited in appropriate sharps-containers and not be placed back into the plastic cover.

Insects
All studies that have investigated the possible transmission of HIV via insects have come to the same conclusion, that it is not possible. This holds true as well for studies performed in Africa with a high AIDS prevalence and large insect populations (Castro 1988).
Introduction

The natural course of HIV infection

The natural course of HIV – in the absence of antiretroviral therapy – is shown in Figure 1. Shortly after infection a so-called acute retroviral syndrome is observed in some patients. This syndrome is characterized mainly by lymphadenopathy, fever, maculopapular rash, myalgia and usually does not last longer than four weeks (see chapter on Acute HIV Infection).

The symptoms are unspecific and variable so that the diagnosis of HIV infection is rarely made without additional testing. A period of several years follows where most patients are clinically asymptomatic.

Thereafter symptoms or diseases may occur, classified according to the CDC classification as category B (Table 2). Among these, oral thrush, oral hairy leukoplakia and herpes zoster are particularly noteworthy, and HIV infection as an underlying diagnosis should always be taken into account. Diseases of category B are not AIDS-defining, however their occurrence is defined as symptomatic of HIV infection and hints to a disturbed cellular immune system.

Still later in the course of HIV infection AIDS-defining illnesses occur at a median of 8–10 years after infection. Without highly active antiretroviral therapy these illnesses eventually lead to death after a variable period of time.

The level of HIV RNA, which reaches extremely high values shortly after primary infection, usually decreases to less than 1% of the maximum value at the time of first HIV antibodies and remains on a relatively stable level for a number of years. This level is called the viral set point. The level of the viral set point determines the speed of disease progression. While most patients with less than 1000 HIV RNA copies/ml are usually not affected by AIDS even 12 years after primary infection, more than 80% of patients have developed AIDS only 2 years after infection if the viral load remains at levels above 100,000 copies/ml (O’Brien 1996).

The higher the viral set point the faster the decrease of CD4 T cells. CD4 T cells usually drop considerably during acute primary infection. Subsequent CD4 counts recover after a few months to values within the normal range, though pre-infection values are rarely reached. Normal values for CD4 T cell counts vary from laboratory to laboratory, however these are usually in the range of absolute CD4-positive T lymphocytes in adults of 435–1600/µl or relative percentage between 31–60% of total lymphocytes. For children other values apply (see chapter on Pediatrics).

Figure 1: The natural course of HIV infection
### Table 2: Clinical categories of HIV infection according to CDC Classification

<table>
<thead>
<tr>
<th>Category A</th>
<th>Asymptomatic HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute, symptomatic (primary) HIV infection</td>
</tr>
<tr>
<td></td>
<td>Persistent generalized lymphadenopathy (LAS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B</th>
<th>Symptoms or signs of diseases that do not fall into Category C but are associated with a disturbed cellular immunity. Among these are:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacillary angiomatosis</td>
</tr>
<tr>
<td></td>
<td>Infections of the pelvis, in particular complications of fallopian tube or ovarian abscesses</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster in the case of more than one dermatome or recurrence in the same dermatome.</td>
</tr>
<tr>
<td></td>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms like fever or diarrhea lasting &gt;1 month</td>
</tr>
<tr>
<td></td>
<td>Listeriosis</td>
</tr>
<tr>
<td></td>
<td>Oral hairy leukoplakia (OHL)</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal candidiasis (oral thrush)</td>
</tr>
<tr>
<td></td>
<td>Vulvovaginal candidiasis, either chronic (&gt;1 month) or difficult to treat</td>
</tr>
<tr>
<td></td>
<td>Cervical dysplasia or carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category C</th>
<th>AIDS defining diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candidiasis of the bronchia, trachea, or lungs.</td>
</tr>
<tr>
<td></td>
<td>Oesophageal candidiasis</td>
</tr>
<tr>
<td></td>
<td>CMV infections (except liver, spleen and lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>CMV retinitis (with loss of vision)</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy, HIV-related</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex infections: chronic ulcer (&gt;1 month); or bronchitis, pneumonia, oesophagitis</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>Isosporiasis, chronic, intestinal, duration &gt;1 month</td>
</tr>
<tr>
<td></td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td></td>
<td>Coccidioidomycosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidiosis, chronic, intestinal, duration &gt;1 month</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, Burkitt</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, immunoblastic</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, primary CNS</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium, other or not identified species</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, bacterial, recurrent (&gt;2 within a year)</td>
</tr>
<tr>
<td></td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Salmonella Sepsis, recurring</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis, cerebral</td>
</tr>
<tr>
<td></td>
<td>Wasting Syndrome</td>
</tr>
<tr>
<td></td>
<td>Cervix carcinoma, invasive</td>
</tr>
</tbody>
</table>
During the progressive course of HIV infection a gradual decrease of CD4 T cells is observed. The risk for AIDS-defining illnesses increases with time when CD4 T cells decrease below 200. To ascertain the level of immunodeficiency the relative percentage of CD4 T cells should also be taken into account.

Under certain conditions (e.g., under myelosuppressive interferon therapy) low absolute CD4 T cell counts are observed in the context of leuko- and lymphopenia, while the immune status assessed by the relative CD4 T cell count remains normal. 200 CD4 T cells/µl correspond to approximately 15% of CD4 positive lymphocytes. Conversely, the absolute CD4 T cell count may suggest false high values, e.g., after a splenectomy.

Patients can be categorized depending on the speed of the CD4 T cell decrease (Stein 1997) to those with a high risk of disease progression (loss of more than 100 CD4 T cells/µl within 6 months), those with a moderate risk of disease progression (loss of 20–50 cells/µl per year) and those with a low risk of disease progression (loss of less than 20 cells/µl per year).

While the overall risk for AIDS increases if the CD4 T cell count drops below 200 cells/µl, considerable differences exist for the risk of individual AIDS manifestations (see chapter on AIDS). As an example, opportunistic infections usually occur at far lower CD4 T cell counts than AIDS-associated malignancies (Schwartländer 1992). Apart from the level of HIV RNA and CD4 T cell count, the age of the patient is another important risk factor for progression to AIDS (Figure 2). A 55-year-old patient with a CD4 T cell count of 50 cells/µl and an HIV RNA of 300,000 copies/ml has an almost twice as high risk of developing AIDS within six months as a 25-year-old patient. This explains why the latest antiretroviral treatment guidelines for HIV have included individual factors such as age and level of HIV viral load into their algorithms regarding when to start treatment.

In the pre-ART era the average time between the first manifestations of AIDS and death was 2–4 years. Without therapy probably more than 90% of all HIV patients die from AIDS. Today, the progression of HIV infection to AIDS can be halted with treatment. After reaching a maximal suppression of HIV RNA, CD4 T cell counts usually recover and patients regain an almost normal life expectancy.

**Figure 2**

Risk for AIDS according to CD4-cellcount, HIV-RNA and age
The level of HIV RNA or the viral set point is dependent on a variety of host-specific factors such as HLA-type, chemokine receptor mutations and other, as yet unidentified, factors. In addition, virus-related factors associated with HIV disease progression have to be taken into account.

It is important to visualize that the level of plasma viral load represents an equilibrium between new and dying HIV.

Disease progression stage

In order to classify the progression of HIV infection in most clinical settings the 1993 CDC classification is still being used that takes the clinical presentation and CD4 T cell count into account (Table 3).

Table 3: Classification of HIV disease according to the 1993 CDC classification

<table>
<thead>
<tr>
<th>CD4 T cells</th>
<th>Asymptomatic or acute HIV disease</th>
<th>Symptomatic but not stage A or C</th>
<th>AIDS-defining illness*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500/μl</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>200–499/μl</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>&lt; 200/μl</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>

*for AIDS-defining conditions please refer to Table 2.

In 2008 a revised version of the CDC classification of HIV disease was presented. This revised version has been combined into a single case definition for adolescents ≥ 13 years and adults and is summarized in Table 4. Aim of the revised version was to introduce a simplified classification for continued epidemiological monitoring of HIV and AIDS, which reflected the improved diagnostics and treatment possibilities in the HIV field. In addition to the three stages listed below a fourth new stage (HIV infection, stage unknown) was introduced for patients in whom no CD4-counts or patient history were available.

Table 4: Classification of HIV-disease according to the 2008 classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>AIDS-defining illness*</th>
<th>CD4 T cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>&gt; 500/μl or ≥ 29%</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>200–499/μl or 14–28%</td>
</tr>
<tr>
<td>3 (AIDS)</td>
<td>Documented AIDS – defining illness</td>
<td>or &lt; 200/μl or &lt;14%</td>
</tr>
<tr>
<td>unknown</td>
<td>No information available</td>
<td>No information available</td>
</tr>
</tbody>
</table>

*the AIDS-defining illnesses have remained unchanged and are listed in Table 2.

As a general rule for the classification of a patient, the stage is always adapted according to progression of disease (e.g., someone who is previously asymptomatic, CD4 T cell count 530/μl, they are a Category A; but if they develop oral thrush, their CD4 T cell count drops to 320/μl, they are Category B2). Reclassification upward upon improvement is not considered. If we take the same example as before and the patient has received fluconazole therapy and ART, and at present is asymptomatic and their CD4 T cells have returned to 550/μl the CDC stage remains at B2. The case definitions of the revised 2008 CDC classification are intended for public health surveillance and not as a guide for clinical diagnosis. Whereas in Europe the term AIDS is only used in cases of clinically manifest AIDS, in the US a CD4 T cell count below 200 cells/μl is also considered AIDS.
Epidemiology

The Human Immunodeficiency Virus probably emerged in the 1920s or ‘30s when the Simian Immunodeficiency Virus (SIV) jumped host from the chimpanzee to the human in Western Africa (Worobey 2008). The oldest HIV-positive human blood sample was found in Kinshasa (Zaire, now the Democratic Republic of Congo) and dates back to 1959 (Zhu 1998). After the first description of AIDS in 1981 by now almost all countries in the world have been affected by HIV.

The first to be infected are usually persons from so-called high-risk groups (intra-venous drug users, professional sex workers, men who have sex with men) and subsequently other population groups are infected via unsafe sex. In industrialized countries homosexual sex is frequently the most common mode of transmission, whereas in countries of the former Soviet Union intravenous drug use (sharing injection paraphernalia) is the most common mode of transmission. In Africa most infections occur due to heterosexual intercourse.

Table 5: AIDS epidemic according to UNAIDS, 2011 (www.unaids.org)

<table>
<thead>
<tr>
<th>Region</th>
<th>HIV-infected adults and children</th>
<th>HIV prevalence among adults in 2010</th>
<th>New infections 2010</th>
<th>Yearly deaths due to AIDS 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan-Africa</td>
<td>22,900,000</td>
<td>5.0%</td>
<td>1,900,000</td>
<td>1,200,000</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>470,000</td>
<td>0.2%</td>
<td>59,000</td>
<td>35,000</td>
</tr>
<tr>
<td>South and Southeast Asia</td>
<td>4,000,000</td>
<td>0.3%</td>
<td>270,000</td>
<td>250,000</td>
</tr>
<tr>
<td>East Asia</td>
<td>790,000</td>
<td>0.1%</td>
<td>88,000</td>
<td>56,000</td>
</tr>
<tr>
<td>Oceania</td>
<td>54,000</td>
<td>0.3%</td>
<td>3300</td>
<td>1,600</td>
</tr>
<tr>
<td>Latin America</td>
<td>1,500,000</td>
<td>0.4%</td>
<td>100,000</td>
<td>67,000</td>
</tr>
<tr>
<td>Caribbean</td>
<td>200,000</td>
<td>0.9%</td>
<td>12,000</td>
<td>9,000</td>
</tr>
<tr>
<td>Eastern Europe and Central Asia</td>
<td>1,500,000</td>
<td>0.9%</td>
<td>160,000</td>
<td>90,000</td>
</tr>
<tr>
<td>Western and Central Europe</td>
<td>840,000</td>
<td>0.2%</td>
<td>30,000</td>
<td>9,900</td>
</tr>
<tr>
<td>North America</td>
<td>1,300,000</td>
<td>0.6%</td>
<td>58,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Total</td>
<td>34,000,000</td>
<td>0.8%</td>
<td>2,700,000</td>
<td>1,800,000</td>
</tr>
</tbody>
</table>

The prevalence and subsequent implications on the epidemic are markedly different from country to country. Whereas HIV/AIDS constitutes a rather marginal health care problem in industrialized countries, in Sub-Saharan Africa AIDS has become the most common cause of death: every 5th death in Africa is due to AIDS. The overall life expectancy has decreased in some African states by more than 20 years. More than 10 million children have been orphaned. The economies of hard-hit states have and are continuing to suffer from dramatic slumps. According to UNAIDS, in 2010 around 34 million people were infected with HIV/AIDS worldwide (of whom 50% were women 1.82 million persons died from AIDS in 2010 (see also table 5). Overall this is a significant reduction from the previous AIDS-associated deaths of 2.2 million and reflects the success of a wider access to antiretroviral therapy particularly in sub-Saharan Africa. It also is encouraging that between 1997 and 2010 the number of new yearly HIV-infections has gone back by 21%. Most profoundly affected countries remain the regions of Sub-Saharan Africa, where more than 23 million people are infected with HIV. The highest dynamic of spread and incidence rates are currently
observed in countries of the former Soviet Union, in particular Estonia, Latvia, Russia and the Ukraine, as well as in South and South-East Asia. In Germany in 2011, around 73,000 people were HIV-positive, among them 14,000 women (Table 6).

Table 6: Epidemiology of HIV/AIDS in Germany (modified according to www.rki.de)

<table>
<thead>
<tr>
<th>Population</th>
<th>Total numbers (lower and upper estimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with HIV/AIDS in 2011</td>
<td>73,000 (66,000–88,000)</td>
</tr>
<tr>
<td>Men</td>
<td>59,000 (53,000–64,000)</td>
</tr>
<tr>
<td>Women</td>
<td>14,000 (12,700–15,200)</td>
</tr>
<tr>
<td>Children</td>
<td>200</td>
</tr>
<tr>
<td><strong>According to transmission group</strong></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>46,500 (41,900–51,300)</td>
</tr>
<tr>
<td>Persons infected via heterosexual contacts</td>
<td>10,500 (9,700–10,750)</td>
</tr>
<tr>
<td>Persons from high prevalence regions / countries</td>
<td>9,000 (8,600–9,600)</td>
</tr>
<tr>
<td>Intravenous drug users</td>
<td>6,800 (5,600–7,900)</td>
</tr>
<tr>
<td>Hemophiliacs and received blood transfusions</td>
<td>450</td>
</tr>
<tr>
<td>Mother to child transmission</td>
<td>420</td>
</tr>
</tbody>
</table>

**Summary**

The first serological evidence for HIV infection was found in human sera from Zaire dating to 1959, Uganda dating back to 1972 and Malawi to 1974 – evidence that HIV was circulating in Africa at those times. The first cases of AIDS were then described in the US in 1981. The discovery of HIV as the cause of AIDS was made in 1983. Since then HIV/AIDS has emerged as a worldwide epidemic which continues to spread today – 30 years later – with some 2.7 million new infections each year. In particular the high infection rates in Eastern Europe and Asia demonstrate the immense challenges that need to be met in current and future implementations of prevention measures. Even though the success of antiretroviral therapy in the treatment of HIV infection appears to enable a normal life expectancy for HIV-infected patients, knowledge on the natural course of HIV infection remains important. Not only in order to make the correct decision on when to start ART in an individual patient, but also to correctly diagnose HIV in patients with first symptoms of HIV infection who have not previously shown AIDS manifestations, this knowledge is important. In light of the fact that in Europe about 50% of all HIV-infected persons do not know their HIV status, tremendous challenges remain in the area of early diagnosis of HIV infection. Joint efforts are being made (www.HIVeurope2007.eu) in order to diagnose HIV infection earlier and thus enable physicians and patients to start ART on time, as well as to lower new infection rates by counseling patients on transmission modes and prevention.

**References**

2. HIV Testing

CHRISTIAN NOAH

Early diagnosis of HIV infection is important: On the one hand, it allows the patient access to antiretroviral therapy. On the other hand, it is crucial in order to avoid further transmission. Despite extensive testing possibilities and recommendations HIV infection continues to be recognized and diagnosed more often than not at a later stage. At the time of initial diagnosis approximately one third of HIV patients already have an immunodeficiency with a CD4 T cell count below 200/µl or suffer from an AIDS-related illness (RKI 2011). Every pregnant woman should be offered an HIV test. HIV testing also plays an important security role in blood and organ donation.

The basics of HIV diagnostics

The diagnosis of HIV infection is primarily based on a laboratory screening test. A reactive result of a screening test has to be confirmed by an alternative assay (confirmatory test). Due to its relatively high sensitivity, the 4th generation test (“Combo test”) which simultaneously detects both HIV-specific antibodies and p24 antigen should be used (Breast 2000, Weber 2002, Sickinger, 2004, Skidmore 2009, Bentsen 2011). A “seronegative” chronic HIV infection is an absolute rarity and irrelevant in practice (Spivak 2010). Any approved screening test detects all known HIV types (HIV-1 and -2), HIV groups and HIV subtypes.

There are numerous commercial systems available for screening. However, the basic technological principle is the same for all and is based on antigen-antibody binding. The prototype assay is the ELISA (enzyme linked immunosorbent assay). Its central element is a plastic plate with 96 wells (microtiter plate). The surface of each cavity is coupled with HIV antigens and HIV antibodies. When a patient’s serum or plasma containing HIV antibodies is placed into one cavity, antibodies bind to the coupled antigen. An enzyme-labelled second antibody is then added, which recognizes and binds to human antibodies. Finally a substrate is added that is converted by the enzyme at the second antibody. The result is a colour change, measured photometrically. The optical density correlates with the HIV antibody concentration in the sample of the patient – the higher the intensity, the more antibodies present in the sample.

Based on this prototype several advances have improved the efficiency and effectiveness of the screening test (Perry 2008). Modern test systems are highly automated to achieve a very high degree of standardization and generate a result in significantly less than one hour. In these systems, the solid phase consists of microparticles coupled with the virus antigens and antibodies. Accordingly, the method is referred to as a “microparticle enzyme immunoassay” (MEIA).

The measured value is usually an index without dimensions, calculated from the ratio of the measured value of the patient sample and the negative control (Sample/Control, S/Co). Values below 1 are considered negative, values above 1 as reactive. It should always be called “reactive” and not a “positive” result to document that this result needs to be confirmed by a second test.

With the screening test, sensitivity has the highest priority (this way, no infection should be missed), while a high specificity is preferred for the confirmatory test. Screening tests approved in Germany require a specificity of 99.5%. That means that one in 200 HIV-negative samples could have a false-reactive test result. False-reactive results are caused for example by stimulation of the immune system (e.g., viral
infections, pregnancy, vaccinations, autoimmune diseases). Thus, in certain patient
groups (e.g., pregnant women, dialysis patients) an increased proportion of false reac-
tive test results can occur.

To confirm a reactive screening test result a Western Blot (immunoblot) analysis is
typically carried out. Viral proteins (antigens) are separated by their molecular weight
via electrophoresis and transferred to a membrane, which is then used as a test strip.
An advancement in terms of standardization is the so-called line blot which is pro-
duced by spraying recombinant HIV antigens directly onto a test membrane. The
test strip is incubated with the serum or plasma of the patient. If HIV-specific anti-
bodies are present, they bind to the antigen. Analogous to the ELISA (see above) the
resulting antibody-antigen complex will become visible on the test strip using an
enzyme-labeled second antibody and a corresponding substrate. According to the
antibody specificities present in the sample a corresponding band spectrum occurs
on the test strip.

The various HIV proteins are assigned to three functional groups (“p” – protein,
“gp” – glycoprotein. The numbers refer to the molecular weight):

- envelope proteins (env): gp41, gp160, gp120
- polymerase proteins (pol): p31/p34, p39/p40, p51/p52, p66/p68
- core proteins (gag): p17/p18, p24/p25, p55

The formation of antibodies after infection follows a specific kinetic: while p24 and
gp120 antibodies are detectable early, the p31 band usually occurs later in the course
of infection (Fiebig 2003). A Western Blot is considered positive when at least two
or three bands are visible. With regard to the antibody specificities, the criteria for a
positive result are internationally not uniformly defined. According to the German
guidelines, based on the DIN 58 969 Part 41 (“serodiagnosis of infectious diseases –
immunoblot”), a test result is considered positive when antibodies against an env
protein and also against a gag protein and/or a pol protein are detected. According
to WHO criteria a Western Blot is positive when antibodies against at least 2 env
proteins are detectable. For example, a Western Blot with a gp120 and p24 band
would be interpreted borderline according to the WHO and positive to the German
criteria. However, a weak band spectrum may indicate an early phase of an HIV infec-
tion and further tests such as PCR should be carried out (see below).

Compared to a 4th generation screening test the p24 antigen is not included in the
confirmatory test. In the case of “reactive screening test – negative confirmatory
test”, acute HIV infection where HIV-specific antibodies are not yet formed although
the p24 antigen is present cannot be excluded. Such a result should be checked after
2–3 weeks. If a patient is concerned regarding an acute infection (acute retroviral
syndrome, recent exchange of bodily fluids with an HIV-infected person) the imple-
mentation of an HIV PCR is useful. The PCR is also recommended in case of a highly
positive screening and negative confirmatory test result. It is recommended to consult
the laboratory to discuss the adequate procedure.

Ideally, the laboratory will use a Western Blot, which also covers antibodies for HIV-
2. In general, a synthetic HIV-2 peptide is used for this purpose. In case of a reactive
HIV-2 band, this result must be confirmed by an HIV-2-specific Western Blot.
As an alternative to the Western Blot for confirmation of a reactive screening test an
immunofluorescence assay (IFA) is available, although less common.

To exclude sample confusion each first positive test result should be confirmed by
examination of a second sample. If a patient is suspected to have an HIV infection,
the result of viral load measurement can be used for confirmation (see chapter on
HIV monitoring). In this case, a second serological test is not necessary.

In addition to the serological test systems, molecular methods for detection of HIV
RNA (PCR, bDNA) are available. The quantitative detection of HIV RNA (a viral load
determination) is one of the essential components of the monitoring of HIV infection (Wittek 2007, Thompson 2010).

In the context of primary HIV diagnosis however, HIV PCR, is reserved only for specific issues such as the suspicion of acute infection or vertical transmission (see below). For the general exclusion of HIV transmission, HIV PCR is only conditionally suitable and cannot replace the serological HIV test. Furthermore, the commercially available test systems have not been validated yet by the manufacturers for primary diagnosis.

**Rapid tests**

Rapid HIV tests functionally correspond to a screening test, i.e., a reactive result must be confirmed by a Western Blot analysis. Rapid tests can be carried out quickly, easily and without any equipment expense and can therefore be used as so-called “point of care” tests. In addition to plasma and serum, full or capillary blood (from the fingertip or the ear lobe) is suitable as test material, so that no centrifuge is required. In some test systems urine or oral transudate (not saliva) may be used. However, rapid tests exhibit less sensitivity if specimens others than serum or plasma are used (Pavie 2010). Results are available within 15 to 30 minutes. Most frequently, rapid tests are based on immuno-chromatographic methods. Other techniques such as particle agglutination and immunofiltration are also used (Branson 2003, Greenwald 2006).

Rapid tests produced according to the European directive  98/79/EC on in vitro diagnostic medical devices (CE marking) are considered safe. These tests exhibit a high sensitivity and specificity in studies (Huppert 2010). However, apparently there are limitations regarding diagnosis of primary HIV infection: Almost all currently available rapid tests only detect HIV antibodies but not p24 antigen, corresponding to an (outdated) HIV test of the 3rd generation. Since 2009 a certified 4th generation rapid test (Determine HIV-1/2 Ag/Ab Combo, Inverness Medical) is available for the first time which not only detects HIV antibodies but also p24 antigen. However, in a comparative study the test exhibited deficiencies regarding the recognition of primary HIV infections. About one third of the samples of patients with acute HIV infection tested falsely negative. Reactivity was delayed by one week compared to a reference test (Mohrmann 2009). Rapid tests should be used only for initial orientation. The results of the testing should be confirmed at the earliest opportunity in a routine laboratory with a standard HIV test.

Rapid tests are particularly suitable for use in emergency situations where the test result has immediate consequences. These include emergency operations and needle-stick injuries. Also in pregnant women with unknown HIV status at delivery a rapid test can be useful. However, the cooperating laboratory should be contacted to indicate the need for a rapid HIV result. When necessary, the result of a conventional HIV test can be available within one hour upon receipt of the sample. Rapid tests are also useful in countries with poor medical infrastructure (UNAIDS/WHO 2009) and in the context of low-threshold testing for individuals who would otherwise not be tested.

**The diagnostic window**

The “diagnostic gap” or “window” indicates the time period between transmission of a pathogen and the onset of biochemical measurable infection markers such as antibodies, antigen or nucleic acids (Busch 1997).

At the earliest, HIV antibody production begins two weeks after transmission. HIV-
specific antibodies can be detected after four weeks in 60–65% of cases, after six weeks in 80%, after eight weeks in 90% and after twelve weeks in 95% of cases. The p24 antigen is detectable about five days before seroconversion (the first occurrence of specific antibodies). Therefore, 4th generation diagnostic tests can shorten the diagnostic gap by simultaneous detection of p24 antigen. The earliest lab marker is HIV RNA that is detectable approximately seven days before the p24 antigen (Fiebig 2003). In many cases HIV RNA can be detected by the second week after transmission. However, a negative result at this time point cannot exclude an infection.

A negative result in the HIV screening test precludes the existence of HIV antibodies and p24 antigen at the time of testing. The security of this result, however, depends particularly on the time interval from the possible transmission event. This has important consequences:

1. HIV testing immediately after a possible transmission is not meaningful, as no HIV antibodies are yet formed. An HIV test should therefore be carried out at the earliest in the 3rd week after exposure. Exception: If it needs to be documented for legal reasons (e.g., needle stick injury) that at the time of transmission no existing HIV infection was present.
2. An HIV infection can not be ruled out until three months after possible transmission with sufficient certainty. Check-ups should be performed two and six weeks and three months after exposure. A further test (after six months) is appropriate only in exceptional cases, for example, if there is suspicion of acute retroviral syndrome.
3. A negative test result is dependable only in the case of no re-exposure within the past three months (from the time of the original exposure).

**HIV diagnostics in newborns**

In newborns of HIV-infected mothers maternal antibodies may remain detectable until the age of 18 months. The antibodies are transplacentally transferred from the 32nd week of gestation although they do not have any protective effect. A positive HIV testing result in the newborn indicates previous HIV exposure. However, a serological HIV test for the detection or exclusion of vertical transmission of HIV is not sufficient as a positive result will be expected in any case (Read 2007).

According to the German-Austrian recommendations for HIV therapy in pregnancy and in HIV-exposed infants (2011) at least two negative PCR results are required to exclude HIV transmission. The first HIV PCR should be performed after the first month of life (sensitivity 96%, specificity 99%), then again because of the nearly 100% sensitivity and specificity after the third month. Vertical transmission can be ruled out, however, only if there was no renewed risk of transmission in the meantime through breastfeeding.

Even with negative PCR results, the disappearance of maternal antibodies should be documented at least once. In the case of positive results, these must be confirmed by examination of a second sample.

**HIV diagnostics after occupational exposure**

After a needlestick injury or other occupational exposure a hepatitis B and C and HIV infection of the index patient should be excluded (of course, consent of the index patient is required). With regard to the potential necessary rapid start of post-exposure prophylaxis (PEP) a needle stick injury should always be considered an emergency. The earlier PEP is initiated, the better the chances of success. According to the German-Austrian recommendations for post-exposure prophylaxis of HIV
infection (2008) PEP should preferably be started within 24 hours of HIV exposure. If a rapid result of an HIV screening test is not available for logistical reasons, an HIV rapid test should be considered. To save time, PEP can be initiated immediately and terminated at any time in the case of a negative result. If the index patient has no symptoms consistent with acute retroviral syndrome the negative result of the screening test excludes HIV infection with a high level of security. An HIV PCR test should be considered only if there is evidence of acute HIV infection of the index patient. Conversely, if the index patient is infected with HIV or if the HIV status is unknown, HIV screening should be performed in the exposed person. For legal reasons, the first HIV test should take place immediately after the needlestick injury to document that no HIV infection was present at the moment of the accident. Check-ups should be carried out at 6 weeks, at 3 and at 6 months. If the index patient is infected with HIV, testing at 12 months is recommended (Ridzon 1997, Ciesielski 1997).

What is relevant in practice?

• **The legal situation:** Although HIV infection has become manageable, the HIV test still retains a special status in laboratory diagnostics. Because of possible medical, social and legal consequences, an informed consent of the patient is required before performing an HIV test. Testing against the wishes of the patient is an invasion of privacy, potentially corresponding with legal consequences for the doctor. A written consent is not required, but the consent should be documented. In children or infants, the patient’s parents or legal guardians must agree. With the aim to increase the readiness for testing and to enable early access to adequate antiretroviral therapy the Centers for Disease Control’s recommendations for HIV testing have been revised. These include a so-called “opt-out” screening concept: The patient is informed about the HIV test, but it will be performed provided the patient does not explicitly reject testing (Branson 2006).

• **Advice:** There should not be any HIV testing without counseling and education. The patient should be informed about the testing algorithm and the possibilities and limitations of HIV testing. Particularly, the limitations of the (frequently demanded) HIV PCR in primary diagnostics should be addressed: while a sensitive method for detection, it is only conditionally suitable for the rapid exclusion of HIV infection or transmission. Due to the distress caused to the patient, the high cost of the PCR as a counter argument against the method is a rare deterrent for the patient. During the consult, all the possibilities of the test result and in particular the “diagnostic window” should be noted. A desired HIV test could also be an occasion to discuss the risk of transmission in general (also for other sexually transmitted diseases) and appropriate prevention methods with the patient.

• **Reporting:** A negative test result can possibly be reported by telephone if the patient has been previously advised of its value. The diagnosis of HIV, however, has to be given in a personal counseling interview by a physician (or expert virologist) only (in many places, the result can be given by a registered nurse or counselor). The response of a patient cannot be assessed adequately when reporting is done by telephone. Sometimes patients can develop suicidal thoughts. Similarly, the negative result of a confirmatory test following a reactive screening test should be personally discussed with regard to the possibility of an acute infection. Patients should be directed to an HIV-focused practice. In addition, the patient should be advised of regional counseling and care centers. The result of a reactive HIV screening test should never be reported before the result of the confirmatory test is available.
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3. Pathogenesis of HIV-1 Infection

ANDREA RUBBERT, GEORG BEHRENS AND MARIO OSTROWSKI

Since the initial description of the Human Immunodeficiency Virus type I (HIV-1) in 1983 (Barré-Sinoussi 1983, Gallo 1983) and HIV-2 in 1986 (Clavel 1986), these two viruses have been identified as the primary cause of Acquired Immunodeficiency Syndrome (AIDS). As HIV-1 is the major cause of AIDS in the world today, our discussion will be primarily limited to HIV-1 infection. Worldwide, the number of HIV-1 infected persons exceeds 33 million (according to UNAIDS), the majority of whom live in the developing countries of Sub-Saharan Africa, Asia and South America.

Despite all the therapeutic advantages achieved over the last decade, including the evolution of “HAART”, once an individual has become infected, eradication of the virus is not possible. In addition, new problems relating to the short- and long-term toxicity of drug treatments and the occurrence of resistance mutations in both circulating and transmitted viruses are emerging. In most countries in South East Asia and Africa, the incidence and prevalence of HIV-1 infection continues to increase and surpass that of Europe and North America.

However, due to the high costs of drug regimens and the lack of healthcare infrastructure in these developing countries, the widespread use of ART is currently still partial at best. The further course of the HIV-1 pandemic, therefore, mainly depends on how and to what degree developing countries with a high HIV-1 prevalence are able to take advantage of the medical progress achieved in Europe and North America, and whether an effective prophylactic vaccine will become available in the near future (see also chapter on Preventive HIV-1-Vaccine).

An understanding of the immunopathogenesis of HIV-1 infection is a major prerequisite for rationally improving therapeutic strategies, developing immunotherapeutics and prophylactic vaccines. As in other virus infections, the individual course of HIV-1 infection depends on both host and viral factors.

The course of infection with HIV-1 in HIV-infected humans may vary dramatically, even if the primary infection comes from the same source (Liu 1997). In individuals with a long-term non-progressive HIV-1 infection (i.e., lack of decline in CD4 T cell counts, or chronic infection for at least 7 years without the development of AIDS), a defective virion has been identified (Kirchhoff 1995). Thus, infection with a defective virus, or one that has a poor capacity to replicate, may prolong the clinical course of HIV-1 infection. However, in most individuals, HIV-1 infection is characterized by a replication-competent virus with a high daily turnover of virions.

Host factors may also determine whether or not an HIV-1-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors that represent about 5% of all infected patients. The identification and characterization of host factors contributing to the course of HIV infection, including immunological defense mechanisms and genetic factors, will be crucial for our understanding of the immunopathogenesis of HIV infection and for the development of immunotherapeutic and prophylactic strategies.

The structure of HIV-1

HIV-1 is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. Visna in sheep, simian immunodeficiency virus (SIV) in monkeys, or feline immunodeficiency virus (FIV) in cats are typical examples of lentivirus infections.
Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. HIV-2 is genetically more closely related to SIV found in sooty mangabeys (SIV<sub>sm</sub>) rather than HIV-1 and it is likely that it was introduced into the human population via monkeys. Both HIV-1 and HIV-2 replicate in CD4 T cells and are regarded as pathogenic in infected persons, although the immune deficiency may be less severe in HIV-2-infected individuals.

The morphologic structure of HIV-1

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes, which are integrated into this lipid membrane, and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment. Glycoprotein gp120 can be detected in the serum as well as within the lymphatic tissue of HIV-infected patients. During the process of budding, the virus may also incorporate different host proteins from the membrane of the host cell into its lipoprotein layer, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may facilitate adhesion to other target cells. The matrix protein p17 is anchored to the inside of the viral lipoprotein membrane. The p24 core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT). The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11 (Gelderbloom 1993) (Fig. 1).

Figure 1: Structure of an HIV virion particle. For detailed explanations see text.
The organization of the viral genome

Most replication competent retroviruses depend on three genes: gag, pol and env: gag means “group-antigen”, pol represents “polymerase” and env is for “envelope” (Wong-Staal 1991) (Fig. 2). The classical structural scheme of a retroviral genome is: 5’LTR-gag-pol-env-LTR 3’. The LTR (long terminal repeat) regions represent the two end parts of the viral genome, that are connected to the cellular DNA of the host cell after integration and do not encode for viral proteins. The gag and env genes code for the nucleocapsid and the glycoproteins of the viral membrane; the pol gene codes for the reverse transcriptase and other enzymes. In addition, HIV-1 contains six genes (vif, vpu, vpr, tat, rev and nef) in its 9kB RNA that contribute to its genetic complexity. Nef, vif, vpr and vpu were classified as accessory genes in the past, as they are not absolutely required for replication in vitro. However, the regulation and function of these accessory genes and their proteins have been studied and characterized in more detail over the past few years. The accessory genes nef, tat and rev are all produced early in the viral replication cycle.

Tat and rev are regulatory proteins that accumulate within the nucleus and bind to defined regions of the viral RNA: TAR (transactivation-response elements) found in the LTR; and RRE (rev response elements) found in the env gene, respectively. The tat protein is a potent transcriptional activator of the LTR promoter region and is essential for viral replication in almost all in vitro culture systems. Cyclin T1 is a necessary cellular cofactor for tat (Wei 1998). Tat and rev stimulate the transcription of proviral HIV-1 DNA into RNA, promote RNA elongation, enhance the transportation of HIV RNA from the nucleus to the cytoplasm and are essential for translation. Rev is also a nuclear export factor that is important for switching from the early expression of regulatory proteins to the structural proteins synthesized later on. Nef has been shown to have a number of functions. It may induce downregulation of CD4 and HLA class I molecules (Collins 1998) from the surface of HIV-1-infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8 T cells and to avoid recognition by CD4 T cells. Nef may also interfere with T cell activation by binding to various proteins that are involved in intracellular signal transduction pathways (Overview in: Peter 1998). In
SIV-infected rhesus macaques, an intact *nef* gene was essential for a high rate of virus production and the progression of disease. HIV-1, with deletions in *nef*, was identified in a cohort of Australian long-term non-progressors (Kirchhoff 1995). However, more recent reports indicate that some of these patients are now developing signs of disease progression including a decline of CD4 T cells. Thus, although deletions of the *nef* gene may slow viral replication, they cannot always prevent the eventual development of AIDS.

*Vpr* seems to be essential for viral replication in non-dividing cells such as macrophages. *Vpr* may stimulate the HIV LTR in addition to a variety of cellular and viral promoters. More recently, *vpr* has been shown to be important for the transport of the viral pre-integration complex to the nucleus (Overview in: Miller 1997) and may arrest cells in the G2 phase of the cell cycle.

*Vpu* is important for the virus “budding” process, because mutations in *vpu* are associated with persistence of viral particles at the host cell surface. Membrane molecules such as tetherin (CD317) can bind *vpu*-deficient HIV-1 and prevent viral release. Thus, *vpu* can be considered as a viral escape mechanism in order to antagonise this effect (Neil 2009) and appears to be of great importance for the evolution of the pandemic virus (Sauter 2009). *Vpu* is also involved when CD4-gp160 complexes are degraded within the endoplasmic reticulum and therefore allows recycling of gp160 for the formation of new virions (Cullen 1998).

Some recent publications have highlighted a new and important role for *vif* in supporting viral replication (Mariani 2003). *Vif*-deficient HIV-1 isolates do not replicate in CD4 T cells, some T cell lines (non-permissive cells) or in macrophages. *Vif*-deficient isolates are able to enter a target cell and initiate reverse transcription, but synthesis of proviral DNA remains incomplete. *In vitro* fusion of permissive and non-permissive cells leads to a non-permissive phenotype, suggesting that the replication of HIV depends on the presence or absence of a cellular inhibitor. This endogenous inhibitory factor was identified as APOBEC3G (Sheehey 2002). APOBEC3G (apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G) belongs to a family of intracellular enzymes that specifically deaminate cytosine to uracil in mRNA or DNA resulting in an accumulation of G-to-A mutations that lead to degradation of viral DNA. By forming a complex with APOBEC3G, *vif* blocks the inhibitory activity of APOBEC3G (Fig. 3a).

Of interest, the antiviral activity of APOBEC3G is highly conserved among various species, whereas the blockade of APOBEC3G by *vif* is highly specific for HIV. HIV-1 *vif* does not complex to murine or rhesus APOBEC3G. In the absence of *vif*, APOBEC3G is incorporated into newly formed viral particles and in subsequently infected target cells synthesis of proviral DNA is blocked (Fig 3b). In contrast, in the presence of *vif*, APOBEC3G is complexed, degraded and not incorporated in newly formed virions. APOBEC3G is expressed in lymphocytes and macrophages representing the primary target cells of HIV infection. In DC, the activation status of the cells influences the amount of APOBEC3G. Upon DC maturation there is an increase of APOBEC3G expression (Pion 2006).

There are still a lot of open questions regarding the regulation of intracellular APOBEC3G. For example, whether there is a critical amount of intracellular APOBEC3G that restricts HIV infection in the presence of *vif*, or whether genetic polymorphisms of APOBEC3G exist that may potentially affect the course of disease, is not clear. In addition, the enzymatic function of intracellular APOBEC3G in lymphocytes may depend on the cellular activation status (Chiu 2005). Meanwhile, the epitopes by which *vif* and APOBEC3G interact with each other have been characterized and the pathway of intracellular degradation of the APOBEC3G-*vif* complex explored. Of note, specific inhibitors that block the interaction of *vif* and APOBEC3G
or that interfere with the intracellular degradation of APOBEC3G could represent promising future treatments. In principle, blockade of cellular structures will likely be associated with a minimal risk that the development of resistance might compromise the efficacy of an antiviral agent. Therefore, targeting vif and APOBEC3G probably represents an interesting therapeutic track.

In summary, these data explain not only why vif is essential for HIV replication but also show why HIV replication is species-specific. Another cellular factor (see below) has also been discovered which explains species specificity of HIV replication. The crucial role for APOBEC3G or other cytidine deaminases might not be restricted to HIV-1. An accumulation of G-to-A mutations was also demonstrated in various HBV isolates. In vitro, the accumulation of HBV DNA is dramatically reduced in the presence of APOBEC3G but co-transfection with vif can revert this inhibition.

Vpx is a structural protein, which is only found in HIV-2 and SIV variants in primates (green mangaby (SIVagm), macaques (SIVmac)). Vpx was used to identify an novel viral restriction factor called SAMHD1 (sterile alpha motif and HD domain 1), for whom HIV-1 apparently does not have a counter strategy. SAMHD1 plays a part in the pathogenesis of the genetically-determined encephalopathy Aicardi-Goutiéres syndrome. In addition, it is supposed to have a negatively regulating role in inter-
feron responses. There is evidence that SAMHD1 inhibits HIV-1 replication through depletion of the intracellular pool of deoxynukleosid-triphosphates. Vpx can counteract this effect by facilitating the proteosomal degradation of SAMHD1. Thus, SAMHD1 is a novel antiviral restriction factor, which inhibits the early steps in HIV-1 replication (Goldstone 2011, Lahouassa 2012).

**The HIV replication cycle**

**HIV entry**

CD4 as a primary receptor for HIV

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60% of T lymphocytes, on T cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglial cells of the central nervous system. The extracellular domain of the CD4 on T cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T cells consist of 25 and 38 amino acids, respectively. Within the extracellular part of CD4, four regions D1–D4 have been characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40–55) are important for the bonding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

The identification of the gp120 binding site on the CD4 receptor of CD4 T cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, the aim being the inhibition of viral spread. However, it became evident that even though laboratory viral isolates were easily neutralized by sCD4, neutralization of primary patient-derived isolates was not achieved.

In contrast, sCD4 was able to induce conformational changes within the viral envelope that promoted the infection of target cells.

CD4 attaches to the T cell receptor complex (TCR) on CD4 T cells and binds to HLA class II molecules on antigen-presenting cells. The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4 T cells (Banda 1992). In the past couple of years, the idea of blocking CD4 as the primary cellular receptor of HIV has regained an interest. PRO542 represents a genetically engineered tetravalent CD4-IgG2 fusion protein that not only inhibits viral replication *in vitro*, but also shows an impressive antiviral efficacy in patients with high viral load that were in the initial clinical trials (see the chapter on ART).

CD4, as a primary and necessary receptor for HIV-1, HIV-2 and SIV, was already characterized in 1984 (Dalglish 1984). However, experiments using non-human cell lines transfected with human CD4, showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Therefore the existence of additional human co-receptors necessary for viral entry was postulated. On the other hand, some laboratory HIV-1 isolates, as well as some HIV-2 and SIV isolates are able to infect human cells independently from CD4. Interestingly, monoclonal antibodies against CD4-induced conformational (CD4i) epitopes to bind to the gp120 of CD4-independent viruses. This observation suggests that the gp120 of CD4-independent viruses already exposes the regions that are necessary for co-receptor recognition and binding and therefore binding to CD4 is not a prerequisite of entry for these viruses. CD4-independent viruses are easy to neutralize using the serum of HIV-infected patients, suggesting that the immune response selects against CD4-independent viruses (Edwards 2001).
Chemokine receptors as co-receptors for HIV entry

A milestone for the characterization of the early events leading to HIV-1 entry was an observation by Cocchi and co-workers in 1995. CD8 T cells from HIV-infected patients are able to suppress viral replication in co-cultures with HIV-infected autologous or allogenic CD4 T cells, and this is independent from their cytotoxic activity (Levy 1996). Cocchi identified the chemokines MIP-1α, MIP-1β and Rantes in supernatants from CD8 T cells derived from HIV-infected patients, and was able to show that these chemokines were able to suppress replication in a dose-dependent manner of some, but not all, viral isolates tested (Cocchi 1995). MIP-1α, MIP-1β and Rantes are ligands for the chemokine receptor CCR5, and a few months later several groups were able to show that CCR5 is a necessary co-receptor for monocytotropic (M-tropic) HIV-1 isolates (Deng 1996, Doranz 1996, Dragic 1998). A few weeks earlier, the chemokine receptor CXCR4 (fusin) was described as being the co-receptor used by T cell-tropic (T-tropic) HIV isolates (Feng 1996). Monocytotropic (M-tropic) HIV-1 isolates are classically those viruses that are most easily propagated in macrophage cultures, are unable to infect T cell lines (i.e., immortalized T cells), but are able to easily infect primary T cells from peripheral blood samples. Conversely, T cell-tropic HIV-1 isolates have classically been identified as being those that are easily propagated in T cell lines, and grow poorly in macrophages, but are also able to easily infect primary T cells from peripheral blood samples. It should be noted that both M-tropic and T-tropic HIV-1 variants can easily infect primary human non-immortalized T cells in vitro.

Chemokines (Chemotactic cytokines) and their receptors have been previously characterized with regard to their role in promoting the migration (chemotaxis) of leukocytes and their pro-inflammatory activity. They are proteins of 68–120 amino acids which depend on the structure of their common cysteine motif, and may be subdivided into C-X-C (α-chemokines), C-C (β-chemokines) and C-chemokines. Chemokines typically show a high degree of structural homology to each other and may share the receptors they bind to. Chemokine receptors belong to the group of receptors with seven transmembranic regions (7-transmembrane receptors) and are intracellularly linked to G-proteins.

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Figure 4: Inhibition of viral entry of CCR5-utilizing (monocytotropic) and CXCR4-utilizing (T cell tropic) HIV isolates by the natural ligands of the chemokine co-receptors CCR5 and CXCR4.
SDF-1 (stromal cell-derived factor 1) was identified as the natural ligand of CXCR4 and is able to inhibit the entry of T-tropic HIV-1 isolates into activated CD4 T cells. Rantes (regulated upon activation T cell expressed and secreted), MIP-1α (macrophage inhibitory protein) and MIP-1β represent the natural ligands of CCR5 and are able to inhibit the entry of M-tropic HIV-1 isolates into T cells. A schematic model is depicted in Fig. 4. T-tropic HIV-1 isolates mainly infect activated peripheral blood CD4 T cells and cell lines and use CXCR4 for entry into the CD4-positive target cell. M-tropic isolates are able to infect CD4 T cells, monocytes and macrophages, and depend on the use of CCR5 and CD4 for viral entry.

The interaction of gp120 and the cellular receptors is now understood in more detail. Gp120 primarily binds to certain epitopes of CD4. Binding to CD4 induces conformational changes in the gp120 that promote a more efficient interaction of the V3 loop of gp120 with its respective co-receptor. Membrane fusion is dependent on gp120 co-receptor binding. Gp41, as the transmembrane part of the envelope glycoprotein gp160, is crucial for the fusion of the viral and host cell membrane. Similar to influenza hemagglutinin, it was postulated that subsequent to the binding of gp120 to CD4, a conformational change is induced in gp41 that allows gp41 to insert its hydrophobic NH₂ terminal into the target cell membrane. Gp41 has been compared to a mouse trap and a crystallographic analysis of the ectodomain of gp41 seems to confirm that (Chan 1997). The identification of crucial amino acid sequences for this process was used to synthesize peptides that bind to gp41 within the domains, are critical for the induction of conformational changes, and that may inhibit membrane fusion.

T-20 is the first of several peptides that bind to gp41 and has been tested in clinical trials for suppressing viral replication (see chapter on ART). T-20 is available as a therapeutic option for patients with advanced HIV. One disadvantage of T-20 is that it must be taken subcutaneously twice a day. Using transfected cell lines, besides CCR5 and CXCR4, other chemokine receptors, such as CCR3, CCR2, CCR8, CCR9, STRL33 (“Bonzo”), Gpr 15 (“Bob”), Gpr 1, APJ and ChemR23, were identified and shown to be used for entry by certain HIV isolates (Deng 1997, Liao 1997). HIV-1 may also bind to certain integrins such as α4β7 and perturb cell function and migration (Arthos 2008). APJ may represent a relevant co-receptor within the central nervous system. Despite this broad spectrum of potentially available co-receptors, CCR5 and CXCR4 seem to represent the most relevant co-receptors for HIV-1 in vivo.

The importance of CCR5 as the predominant co-receptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (Liu 1996). In vitro experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically have a 32-basepair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5. As expected, all of them were infected with CXCR4-using HIV-1 isolates. In epidemiological studies, the allelic frequency of the CCR5 gene deletion is 10–20% among Caucasians, particularly amongst those of Northern European descent. The frequency of a homozygous individual is about 1% in Caucasians (Dean 1996). Studies conducted on African or Asian populations, however, do not find this 32-basepair deletion, suggesting that this mutation arose after the separation of these populations in evolutionary history.

Individuals that are heterozygous for the 32-bp deletion of the CCR5 show a decreased expression of CCR5 on the cell surface and are more frequently encoun-
tered within cohorts of long-term non-progressors compared to patients who have a rapid progression of disease (Dean 1996). In addition, HIV-infected individuals who are heterozygous for the 32-bp deletion, have a slower progression to AIDS, a better treatment response to ART and lymphoma incidence is decreased. These data demonstrate that the density of CCR5 on the cell surface is not only a limiting factor for replication of HIV in vitro but in vivo as well.

In addition to the 32-bp deletion, other genetic polymorphisms with regard to chemokine receptors (CCR2) or their promoters (CCR5) have been described. Based on the occurrence of these polymorphisms within defined patient cohorts, they are associated with a more rapid or a more favorable course of disease, depending on the particular polymorphism (Anzala 1998, Winkler 1998). More recent studies shed light on the impact CCL3L1-CCR5 genotypes have not only on disease progression but also on response to antiretroviral therapy (Ahuja 2008). The mechanism appears to be independent of viral entry mechanisms but rather related to the quality of the cell-mediated immune response (Dolan 2007).

In patients who have a rapid progression of disease (rapid drop in CD4 T cell count), virus isolates that use CXCR4 as a predominant co-receptor tend to be frequently isolated from their cells in comparison to patients with a stable CD4 T cell count. The expression of co-receptors on CD4 lymphocytes depends on their activation level. CXCR4 is mainly expressed on naive T cells, whereas CCR5 is present on activated and effector/memory T cells. During the early course of HIV-1 infection, predominantly M-tropic HIV-1 isolates are detected. Interestingly, M-tropic HIV-1 isolates are preferentially transmitted regardless of whether or not the source predominantly harbors T-tropic isolates. At present, it remains unclear whether this in vivo preference of M-tropic HIV-1 isolates is determined by selected transportation of M-tropic isolates by sub-mucosally located dendritic cells or whether the local cytokine/chemokine milieu favors the replication of M-tropic viruses. Intriguing studies

Figure 5: Strategies to block infection by CCR5-tropic HIV. Blockage of CCR5 on the cell surface by non-agonistic ligands (A) or monoclonal antibodies (B). Alternatively, CCR5 cell surface expression can be reduced by siRNA or Intrakine. For further details see text.
suggest that M-tropic HIV-1 viruses are able to ‘hide’ more easily from the immune system by replicating in macrophages, in comparison to T-tropic viruses, thus giving them a survival advantage in the infected individual.

The blockade of CCR5, therefore, seems to represent a promising target for therapeutic intervention (Fig. 5). In vitro, monoclonal antibodies to CCR5 (2D7 and others) are able to block the entry of CCR5-using HIV isolates into CD4 T cells and macrophages. Small molecule inhibitors of CCR5 have been designed and preliminary clinical trials (see chapter on ART) demonstrate a significant reduction of plasma viremia in HIV-infected patients (Fätkenheuer 2005). In vitro studies as well as experiments using SCID mice do suggest that blockade of CCR5-using isolates may alter their tropism towards increased usage of CXCR4 (De Clercq 2001).

Small molecule inhibitors such as T-22, ALX40-4C or AMD3100 are able to inhibit CXCR4 and are also subject to preclinical and clinical trials (see chapter on ART). Other CCR5 inhibitors have been used as mucosal microbicides in monkey models and could represent a future preventive approach (Veazey 2005).

Strategies are currently being developed to modulate expression of chemokine receptors. Intrakines are chemokines that stay within the cytoplasm and are able to capture and bind to their corresponding receptor on its way to the cell surface (Chen 1997). Short interfering RNA (siRNA) represents a new molecular tool that is able to selectively inactivate target genes. Double-stranded RNA is split by the enzyme dicer-1 into short pieces (21-23-mers). These oligomers may complementarily bind to longer RNA sequences that are subsequently degraded. This strategy is currently employed in plants and used for its antiviral activity. The use of siRNA against CCR5 can prevent the expression of CCR5 in vitro and targeting of gag can effectively block viral replication (Song 2005).

Although the therapeutic use of chemokine receptor blockers seems promising, a lot of questions still remain unanswered. In knockout mice it was demonstrated that the absence of CXCR4 or SDF-1 is associated with severe defects in hematopoiesis and in cerebellar development (Zou 1997). Currently, it remains unclear whether the blockade of CXCR4 in postnatal or adult individuals may affect other organ systems.

**Post-fusion events**

Following membrane fusion the viral core uncoats into the cytoplasm of the target cell. Alternatively, receptor-mediated endocytosis and dynamin-dependent fusion with intracellular compartments (Miyauchi 2009) can lead to viral inoculation. HIV can enter into rhesus lymphocytes but replication is stopped before or during early reverse transcription. This intracellular blockade is mediated by a cellular factor, TRIM5α, a component of cytoplasmic bodies whose primary function is not yet understood. TRIM5α from various species exhibits differential inhibition on various retroviruses. For example, TRIM5α from rhesus macaques, TRIM5αrh, more profoundly inhibits HIV replication than human TRIM5α, whereas SIV (simian immunodeficiency virus) which naturally infects Old World monkeys, is less susceptible to either form of TRIM5α thus explaining in part the species specificity of HIV for human cells (Stremlau 2004). TRIM5α from human cells or non-human primates is able to inhibit replication of other lentiviruses and represents a novel cellular resistance factor whose definitive biological significance has yet to be fully characterized. TRIM5α serves as a mechanism for intracellular recognition and activation of the unspecific immune response (Pertel 2011), but it is unclear how exactly TRIM5α blocks reverse transcription and it has been hypothesized that TRIM5α interferes with the incoming virus capsid protein, targeting it for ubiquitination and proteolytic degradation.
HIV-1 entry into quiescent T cells is comparable to HIV-1 entry into activated T cells, but synthesis of HIV-1 DNA remains incomplete in quiescent cells (Zack 1990). The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle (Fig. 6). Blockade of the RT by the nucleoside RT inhibitor AZT was the first attempt to inhibit viral replication in HIV-1 infected patients. Today, numerous nucleoside, nucleotide and non-nucleoside RT inhibitors are available for clinical use and have broadened the therapeutic arsenal substantially since the mid-eighties.

Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS (primer binding site) and extending to the 5’ repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a template switch of the R/U5 DNA with hybridization of the R sequence at the 3’ RNA end. Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions (long terminal repeats) at each end.

HIV-1 enters into quiescent T cells and reverse transcription may result in the accumulation of proviral, non-integrating HIV DNA. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transport of the pre-integration complex into the nucleus. Cellular activation may occur in vitro after stimulation with antigens or mitogens. In vivo, activation of the immune system is observed after antigen contact or vaccination or during an opportunistic infection. In addition, evidence is emerging that HIV-1 gp120 itself may activate the infecting cell to enhance integration. Besides monocytes, macrophages and microglial cells, latently infected quiescent CD4 T cells that contain non-integrated proviral HIV DNA represent important long-lived cellular reservoirs of HIV (Chun 1997), and cellular microRNAs contribute to HIV-1 latency in resting primary CD4 T lymphocytes (Huang 2007). Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4 T cells, viral latency in these resting CD4 T cells likely represents an accidental phenomenon and is not likely to
be important in the pathogenesis of HIV. This small reservoir of latent provirus in quiescent CD4 T cells gains importance, however, in individuals who are treated with ART, since the antivirals are unable to affect non-replicating proviruses – the virus will persist in those cells and be replication-competent to start new rounds of infection if the drugs are stopped. It is the existence of this latent reservoir that has prevented ART from entirely eradicating the virus from infected individuals (Chun 2005).

Until recently it was not clear why HIV replicates poorly in quiescent CD4 T cells. The cellular protein Murr1 that plays a role in copper metabolism is able to inhibit HIV replication in unstimulated CD4 T cells. Murr1 was detected in primary resting CD4 T cells and interferes with activation of the transcription factor NFκB by inhibiting the degradation of IκBα. IκBα prevents NFκB from migrating to the nucleus, especially after cytokine stimulation (e.g., TNFα). Because the HIV LTR region has multiple sites for NFκB, preventing NFκB migration to the nucleus should inhibit HIV replication. Inhibition of Murr-1 by siRNA is associated with HIV replication in quiescent CD4 T cells (Ganesh 2003). Persistence of HIV in quiescent CD4 T cells and other cellular reservoirs seems one of the main reasons why eradication of HIV is not feasible and why current therapies fail to achieve viral eradication (Dinoso 2009, Lewin 2011). If it is ever possible to achieve, a more detailed knowledge of how and when cellular reservoirs of HIV are established and how they may be targeted is of crucial importance for the development of strategies aiming at HIV eradication.

Cellular transcription factors such as NF-kB may also bind to the LTR regions. After stimulation with mitogens or cytokines NF-kB is translocated into the nucleus where it binds to the HIV LTR region, thereby initiating transcription of HIV genes. Transcription initially results in the early synthesis of regulatory HIV-1 proteins such as tat or rev. Tat binds to the TAR site (transactivation response element) at the beginning of the HIV-1 RNA in the nucleus and stimulates transcription and the formation of longer RNA transcripts. Rev activates the expression of structural and enzymatic genes and inhibits the production of regulatory proteins, therefore promoting the formation of mature viral particles. The proteins coded for by pol and gag form the nucleus of the maturing HIV particle, while the gene products coded for by env form the gp120 spikes of the viral envelope. The gp120 spikes are synthesized as large gp160 precursor molecules and are cleaved by the HIV-1 protease into gp120 and gp41. The gag proteins are also derived from a large 53 kD precursor molecule, from which the HIV protease cleaves the p24, p17, p9 and p7 gag proteins. Cleavage of the precursor molecules by the HIV-1 protease is necessary for the generation of infectious viral particles, and therefore the viral protease represents another interesting target for therapeutic blockade. The formation of new viral particles is a step-wise process: a new virus core is formed by HIV-1 RNA, gag proteins and various pol enzymes and moves towards the cell surface. The large precursor molecules are cleaved by the HIV-1 protease, which results in the infectious viral particles budding through the host cell membrane. During the budding process, the virus lipid membranes may incorporate various host cell proteins and become enriched with certain phospholipids and cholesterol. In contrast to T cells, where budding occurs at the cell surface and virions are released into the extracellular space, the budding process in monocytes and macrophages results in the accumulation of virions within cellular vacuoles.

The replication of retroviruses is prone to error and is characterized by a high spontaneous mutation rate. On average, reverse transcription results in 1–10 errors per genome and per round of replication. Mutations can lead to the formation of replication-competent viral species. Mutations that cause drug resistance may also accu-
mulate, which, provided that there is selective pressure due to specific antiretroviral drugs and incomplete suppression of viral replication, may become dominant. In addition, viral replication is dynamic and turns over quickly at an average rate of $10^9$ new virus particles produced and subsequently cleared per day. Thus, within any individual, because of the extensive viral replication and mutation rates, there exists an accumulation of many closely-related virus variants within the population of viruses, referred to as a viral quasispecies. Selection pressure happens not only due to certain drugs, but also due to components of the immune system such as neutralizing antibodies or cytotoxic T cells (CTL).

**HIV and the immune system**

**The role of antigen-presenting cells**

**Dendritic cells as prototypes of antigen-presenting cells**

Dendritic cells, macrophages and B cells represent the main antigen-presenting cells of the immune system. Dendritic cells (DC) are the most potent inducers of specific immune responses and are considered essential for the initiation of primary antigen-specific immune reactions. DC precursors migrate from the bone marrow towards the primary lymphatic organs and into the submucosal tissue of the gut, the genitourinary system and the respiratory tract. They are able to pick up and process soluble antigens and migrate to the secondary lymphatic organs, where they activate antigen-specific T cells. Because DC have a crucial role in adaptive immunity, there is an increasing interest in using dendritic cells to induce or expand HIV-specific T cells. DC from HIV-infected patients have been purified, incubated with inactivated non-infectious HIV particles and subsequently used for vaccination (Lu 2004).

DC represent a heterogeneous family of cells with different functional capacities and expression of phenotypic markers depending on the local microenvironment and the stage of maturation. Immature DC have the capacity to pick up and process foreign antigens, but do not have great T cell stimulatory capacities. Mature DC show a predominant immunostimulatory ability. DC in tissues and Langerhans cells, which are specialized DC in the skin and mucosal areas, represent a more immature phenotype and may take up antigen. Once these DC have taken up the antigen, they migrate to the lymphoid tissues where they develop a mature phenotype. The stimulation of CD8 T lymphocytes and the formation of antigen-specific cytotoxic T cells (CTL) depend on the presentation of a peptide together with MHC class I antigens. DC may become infected with viruses, for instance influenza. Viral proteins are then produced within the cytoplasm of the cell, similar to cellular proteins, then degraded to viral peptides and translocated from the cytosol into the endoplasmic reticulum, where they are bound to MHC class I antigens. Peptide-MHC class I complexes migrate to the DC surface. Alternatively, DC take up antigens for infected cells for presentation via MHC class I (Maranon 2004). Interestingly, the efficacy of this presentation of viral antigens is comparable whether or not DC themselves are productively infected. DC are rather resistant against productive HIV infection and intracellular recognition by DC contributes to innate immune responses following inoculation (Manel 2010, Goldstone 2011).

The number of specific antigen-MHC class I complexes is usually limited and must eventually be recognized by rare T cell clones to a ratio of 1:100,000 or less. The T cell receptor (TCR) may display only a low binding affinity (1 mM or less). The high density of co-stimulatory molecules on the DC surface, however, enhances the TCR-MHC: peptide interaction allows efficient signaling to occur through the T cell
and results in proliferation (clonal expansion) of the T cell. Virus-infected cells or tumor cells often do not express co-stimulatory molecules, and thus may not be able to induce a clonal expansion of effector cells. This underscores the importance of having a highly specialized system of antigen-presenting cells, i.e., DC, to prime T cells to expand and proliferate rapidly.

The interaction of dendritic cells and B/T cells
B and T lymphocytes may be regarded as the principle effector cells of antigen-specific immune responses. However, their function is under the control of dendritic cells. DC are able to pick up antigens in the periphery. These antigens are processed and expressed on the cell surface together with co-stimulatory molecules that initiate T cell activation. B cells may recognize antigen after binding to the B cell receptor. Recognition of antigen by T cells requires previous processing and presentation of antigenic peptides by DC and the intracellular half life time of peptides impacts on the CD8 T cell response (Lazaro 2011). T cells express different T cell receptors (TCR) that may bind to the peptide: MHC class I on the surface of dendritic cells to allow activation of CD8 T cells, or to the peptide: MHC class II molecules, to activate CD4 T cells. The ability of DC to activate T cells also depends on the secretion of stimulatory cytokines such as IL-12, which is a key cytokine for the generation and activation of Th1 and natural killer (NK) cells.

Only a few DC and small amounts of antigen are sufficient to induce a potent antigen-specific T cell response, thus demonstrating the immunostimulatory potency of DC. The expression of adhesion molecules and lectins, such as DC-SIGN, support the aggregation of DC and T cells, promote the engagement of the T cell receptor (TCR) and mutual infection and thereby distribution of the virus within the host (Gringhuis 2010). Classical antiretroviral therapy is probably less efficient in halting cell to cell transmission and this could contribute to persistent low-level replication (Sigal 2011). DC-SIGN is a type C lectin that has also been shown to bind to lentiviruses such as SIV and HIV-1 and -2 by interaction of gp120 with carbohydrates (Geijtenbeek 2000). Mycobacteria and Dengue virus may also bind to DC-SIGN. In vivo, immunohistochemical studies show expression of DC-SIGN on submucosal and intradermal DC, suggesting an implication of DC-SIGN in vertical and mucosal transmission of HIV. The expression of DC-SIGN was shown to enhance the transmission of HIV to T cells and allows utilization of co-receptors if their expression is limited. Thus DC-SIGN may be a mechanism whereby HIV-1 is taken up by DC in the mucosal tissues. It is then transported by the DC to the lymphoid tissues where HIV-1 can then infect all the residing CD4 T cells (Lore 2005).

Lymphatic tissue as the site of viral replication
Viral replication within the lymphatic tissue is extensive in the early stages of the disease even in the hematopoietic system (Pantaleo 1993, Embretson 2003, Carter 2010).

During the initial phase of HIV-1 infection, there is a burst of virus into the plasma, followed by a relative decline in viremia. During this time, a strong HIV-1 specific cytotoxic T cell response is generated, which coincides with the early suppression of plasma viremia in most patients. Virions are trapped by the follicular dendritic cell (FDC) network within the lymphoid tissue. Macrophages and activated and quiescent CD4 T cells are the main targets of infection. Permanent viral reservoirs, mainly in macrophages and latently infected CD4 T cells are established in the early phase of infection and probably represent the major obstacle so far to successful eradication of HIV. During the whole course of infection with HIV-1, the lymphoid tissue
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represents the principle site of HIV-1 replication. The frequency of cells containing proviral DNA is 5–10 times higher in lymphoid tissue than in circulating peripheral mononuclear cells in the blood, and the difference in viral replication in lymphoid tissue exceeds that in the peripheral blood by about 10–100 times.

After entry of HIV-1 into a quiescent CD4 T cell and after completion of reverse transcription, the viral genome is represented by proviral unintegrated HIV DNA. *In vitro* experiments have shown that HIV-1 preferentially integrates into active genes (hot spots) (Schroder 2002). The activation of CD4 T cells is necessary for the integration of the HIV DNA into the host cell genome and is therefore a prerequisite for the synthesis of new virions. In this regard, the micromilieu of the lymphoid tissue represents the optimal environment for viral replication. The close cell-cell contact between CD4 T cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 or TNFα (Stacey 2009), promotes the induction of viral replication in infected cells and augments viral replication in cells already producing the virus. During later stages of the disease, microbial translocation from the gut (Brenchley 2006, Klatt 2010, Estes 2010) contributes to systemic immune activation, which in turn leads to loss of CD4 T cells (Ciccone 2010) and disease progression. It should be noted that both IL-1 and TNFα induce NF-κB which binds to the HIV-1 LTR to promote proviral transcription. The importance of an antigen-induced activation of CD4 T cells is underlined by several *in vivo* and *in vitro* studies that demonstrate an increase in HIV-1 replication in association with tetanus or influenza vaccination or an infection with *Mycobacterium tuberculosis* (O'Brian 1995). Even though the clinical benefit of vaccination against common pathogens (e.g., influenza and tetanus) in HIV-1-infected patients outweighs the potential risk of a temporary increase in viral load, these studies indicate that in every situation where the immune system is activated, enhanced viral replication can also occur.

Patients on ART demonstrate a dramatic decrease in the number of productively infected CD4 T cells within the lymphoid tissue (Tenner-Racz 1998). However, in all patients so far, there persists a pool of latently infected quiescent T cells despite successful suppression of plasma viremia. It is these latently infected cells that may give rise to further rounds of viral replication if the antiviral drugs are stopped.

During the natural course of HIV-1 disease, the number of CD4 T cells slowly decreases while plasma viremia rises in most patients. If sequential analysis of the lymphoid tissue is performed, progression of the disease is reflected by destruction of the lymphoid tissue architecture and a decreased viral trapping. Various immunohistological studies indicate that the paracortex of the lymph nodes represents the primary site where HIV replication is initiated (Embreton 1993, Pantaleo 1993). Infection of the surrounding CD4 T cells, as well as the initiation of T cell activation by DC, contributes to the spreading of HIV-1 within the lymphoid environment. Similar to SIV infection in rhesus macaques, HIV infection at all stages of disease is associated with preferential replication and CD4 T cell destruction in the gut lamina propria and submucosa rather than in lymph nodes (Veazey 1998, Brenchley 2004). This is likely because the gut is predominantly populated by CCR5-expressing effector memory CD4 T cells, which are ideal targets for HIV replication compared to the mixed populations of CD4 T cells found in the lymph nodes. In addition, HIV-1 nef appears to have lost a function which can be found in SIV, where it leads to a down-regulation of CD3 and the T cell receptor, reducing chronic cell activation which would otherwise render them susceptible for apoptosis (Schindler 2006). Several studies have demonstrated that, during acute infection, depletion of CD4+CCR5+ memory cells within the mucosa-associated lymphatic tissue is a hallmark of both HIV and SIV infection. Genome analysis of viral RNA in patients with acute HIV
infection revealed that in about 80% of infected patients, viremia results from infection of a single virus particle (Keele 2008). In the early phase of SIV infection, up to 60% of all CD4 T cells within the intestinal lamina propria were shown to express viral RNA. Most of these cells are destroyed by direct and indirect mechanisms within a few days. Further disease progression seems to depend largely on the capacity of the host to reconstitute the pool of memory cells within the mucosa-associated lymphoid tissue. In view of this data, some researchers argue that initiation of ART during acute HIV infection is crucial in order to limit long-term damage to the immune system. However, in patients with exhaustion of lymphopoiesis despite effective long-term HIV therapy disease progression might occur (Sauce 2011).

Recent studies have also examined the effect of HIV infection on the thymus and its role in CD4 T cell depletion and homeostasis. Recent work has suggested that thymic output of CD4 T cells is decreased during HIV infection, particularly with older patients, and that this defect is due to abnormalities of intra-thymic proliferation of T cells, whose mechanism is still undefined, as thymocytes do not express CCR5 and should not necessarily be targets of HIV (Douek 2001).

**The HLA system and the immune response to HIV**

CD8 T cells recognize specific antigens (peptides) in context with HLA class I molecules on antigen-presenting cells, whereas CD4 T cells require the presentation of antigenic peptides in context with HLA class II molecules. The generation of an HIV-specific immune response is therefore dependent on the individual HLA pattern. Antigen-presenting cells may bind HIV peptides in different ways on the HLA class I molecules. Therefore, CD8 T cells can be activated in an optimal or suboptimal way or may not be activated at all. Using large cohorts of HIV-1 infected patients, in whom the natural course of disease (fast versus slow progression) is known, HLA patterns were identified that were associated with a slow versus fast disease progression (Pereyra 2010). These studies suggest that the HLA type may be responsible for a benign course of disease in about 40% of patients with a long-term non-progressive course of disease. Homozygosity for HLA Bw4 is regarded as being protective. Patients who display heterozygosity at the HLA class I loci characteristically show a slower progression of immunodeficiency than patients with homozygosity at these loci (Carrington 1999). An initial study by Kaslow in 1996 demonstrated that HLA B14, B27, B51, B57 and C8 are associated with a slow disease progression, while the presence of HLA A23, B37 and B49 were associated with a rapid development of immunodeficiency (Kaslow 1996). All patients with HLA B35 had developed symptoms of AIDS after 8 years of infection. More recent studies suggest that discordant couples with a “mismatch” regarding the HLA class I have a protective effect towards heterosexual transmission (Lockett 2001).

*In vitro* studies in HLA B57-positive patients demonstrate that these patients display HLA B57-restricted CTL directed against HIV-1 peptides. There is evidence that the better immune responses in these patients is already determined during thymic selection (Kosmrlj 2010). However, it is possible that the identification of protective HLA alleles or HLA-restricted peptides in HIV-1-infected patients with a benign course of disease does not necessarily indicate that the same alleles or peptides are crucial for the design of a protective vaccine. CD8 T cells from HIV-1-exposed but uninfected African women recognize different epitopes than CD8 T cells from HIV-1-infected African women (Kaul 2001). This suggests that the epitopes that the immune system is directed against during a natural infection might be different from those that are protective against infection. In addition, the individual HLA pattern may affect the adaptive immune response and the evolution of viral escape mutations (Friedrich
CTL from patients with HLA B57 and B58 may force the virus to develop certain mutations in gag that enable the virus to escape the CTL response, but these mutations result in a reduced replicative competence and thus lower viral load (Goepfert 2008). If such a virus is transmitted to another individual with a different HLA background, the virus may back-mutate to the original genotype and regain its full replicative competence because of the absence of CTL-mediated immune pressure.

HLA class II antigens are crucial for the development of an HIV-1-specific CD4 T cell response. Rosenberg (1997) was the first to show that HIV-1-infected patients with a long-term non-progressive course of disease had HIV-1-specific CD4 T cells that could proliferate against HIV-1 antigens. The identification of protective or unfavorable HLA class II alleles is less well elaborated than the knowledge about protective HLA class I alleles. Cohorts of vertically infected children and HIV-infected adults demonstrate a protective effect of HLA DR13 (Keet 1999).

KIR receptors (Killer cell immunoglobulin-like receptors) represent ligands that bind to HLA class I antigens and by functioning as either activating or inhibiting receptors they regulate the activation status of NK cells. Polymorphisms of KIR genes were shown to correlate with slow or rapid progression of HIV disease, especially when the analysis includes known HLA class I polymorphisms (Fauci 2005). During HIV infection NK cells may not only be decreased but may also show a diminished cytolytic activity. Preliminary results suggest that low numbers of NK cells are associated with a more rapid disease progression. NK cells can even build up an immunologic pressure by certain KIRs (e.g. KIR2DL2), which leads to selection of escape HIV mutations. These functional studies argue for a direct impact of NK cells on viral evolution and support the relevance of the innate immune system in antiviral defence (Alter 2011).

In summary, various genetic polymorphisms have been identified that have an impact on the course of HIV disease. However, there is currently no rationale to recommend routine testing of individual patients or to base therapeutic decisions on genetic testing.

The HIV-specific cellular immune response

Cytotoxic T cells (CTL) are able to recognize and eliminate virus-infected cells. A number of studies clearly demonstrate that CTL are crucial for the control of HIV replication and have a substantial impact on disease progression once infection is established. However, there is little evidence to assume that CTL play a major role in primary protection.

In comparison to HIV-1-infected patients with a rapid decline in CD4 T cell numbers, patients with a long-term non-progressive course of disease (LTNP = long-term non-progressors) have high quantities of HIV-1-specific CTL precursors with a broad specificity towards various HIV-1 proteins. The different capacities of certain HLA alleles to present viral particles more or less efficiently and to induce a generally potent immune response may explain why certain HLA alleles are associated with a more rapid or a slower progressive course of disease (see above).

Individuals have been described, who developed CTL escape mutants after years of stable disease and the presence of a strong CTL response. The evolution of CTL escape mutants was associated with a rapid decline in CD4 T cells in these patients, indicating the protective role of CTL (Goulder 1997).

HIV-specific CTL responses have been detected in individuals exposed to, but not infected by HIV-1. Nef-specific CTL have been identified in HIV-1-negative heterosexual partners of HIV-infected patients and env-specific CTL have been found in
seronegative healthcare workers after exposure to HIV-1 by needle stick injuries (Pinto 1995). Unfortunately, patients with a broad and strong CTL response do not seem to be protected from superinfection by a different but closely related HIV isolate (Altfeld 2002).

The presence of a CTL response is not correlated just with the suppression of plasma viremia during the initial phase of HIV infection. Patients who underwent structured therapy interruptions, especially when ART was initiated early following infection, demonstrated the appearance of HIV-specific CTL during the pauses. Goonetilleke (2009) demonstrated that the initial HIV-1 specific CTL response contributes significantly to the control of viremia during acute infection. Novel imaging techniques and animal models enabled for the first time the visualization of the interplay of immune cells with infected target cells and the contribution of this response for the infection control (Li 2009).

However, it is still unclear in most patients who exhibit a potent temporary CTL response why this CTL response diminishes later on (Pantaleo 2004). The appearance of viral escape mutants might explain why previously recognized epitopes are no longer immunodominant.

The nef protein may downregulate HLA class I antigens and therefore counteract the recognition of infected cells by CTL. In addition, the majority of infected individuals show detectable CTL responses. It is unclear why they are unable to control the virus. Interestingly, CTL from HIV-infected patients shows a lack of perforin and an immature phenotype in comparison to anti-CMV-directed effector cells (Harari 2002) even though the ability to secrete chemokines and cytokines is not impaired (Appay 2000). Another study provided evidence that the killing capacity of HIV-specific CTL was associated with the ability to simultaneously produce interferon- and TNFα (Lichtenfeld 2004). Surface molecules such as PD-1 on CTL, which are transiently upregulated upon cell activation, may persist due to prolonged antigen presence. Persistent PD-1 expression, however, can result in CTL and helper cells (Said 2010) dysfunction and this effect can be restored by blockade of PD-1 and PD-1L interaction on DC by administration of anti-PD-1 antibodies. This restores CTL functions such as cytokine production and killing capacity (Trautmann 2006, Velu 2009).

CD8 T cells may also become infected with HIV (Bevan 2004) although this has not been demonstrated for HIV-specific CD8 T cells. It is unclear whether CD8 T cells temporarily express CD4 and which chemokine co-receptors mediate infection of these CD8 T cells.

Proliferation and activation of CTL is dependent on antigen-specific T cell help. Initiation of ART during primary HIV infection was associated with persistence of an HIV-specific CD4 T cell response that was not detected in patients analyzed during the chronic stage of disease (Rosenberg 1997). HIV-specific CD4 T cells are mainly directed against gag and nef-derived epitopes (Kaufmann 2004). HIV preferentially infects pre-activated CD4 T cells and as HIV-specific CD4 T cells are among the first cells to be activated during HIV infection, their preferential infection has been demonstrated (Douek 2002). Therefore, it is currently unclear whether the loss of HIV-specific CTL activity during the course of disease reflects an intrinsic defect of CTL or develops secondary to a loss of specific CD4 T cell help.

Various therapeutic vaccine strategies have been developed during the last few years and mostly tested in SIV-infected rhesus macaques aiming at inducing an SIV-specific CTL response that may alter the natural course of disease (McElrath 2010). Recently, a promising approach was published on a vaccine trial using autologous dendritic cells in SIV-infected rhesus macaques that were pulsed with inactivated SIV (Lu 2003). In contrast to the unvaccinated control group, monkeys that were vaccinated showed a dramatic decrease in viral load, and the development of anti-SIV-
directed humoral and cellular immune responses. Meanwhile, a pilot trial has been initiated in a cohort of 18 HIV-infected antiretroviral-naive patients with stable viral load. The patients were vaccinated with autologous monocyte-derived dendritic cells that were pulsed with inactivated autologous virus. During the following 112 days, a median decrease of 80% of the viral load was observed and maintained for more than one year in 8 patients. In parallel, gag-specific CD8 T cells and HIV-specific CD4 T cells producing IFN and/or interleukin-2 were detected (Lu 2004). Therapeutic vaccination using autologous dendritic cells appears to be a potential immunotherapeutic, but more controlled clinical studies are definitely needed.

In addition to the cytotoxic activities directed against HIV-infected cells, CD8 T cells from HIV-1 infected patients exhibit a remarkable, soluble HIV-1 inhibitory activity that inhibits HIV-1 replication in autologous and allogeneic cell cultures (Walker 1986). Despite multiple efforts, the identity of this inhibitory activity (CAF) has not been clarified, although chemokines such as MIP-1α, MIP-1β or Rantes (Cocchi 1995), IL-16 (Baier 1995), the chemokine MDC (Pal 1997) and defensins may account for at least some of the inhibition.

**The \( T_{H1} \)/\( T_{H2} \) immune response**

Depending on the secretion pattern of cytokines, CD4 T cells may be differentiated into \( T_{H1} \) and \( T_{H2} \) cells. \( T_{H1} \) CD4 T cells primarily produce interleukin-2 (IL-2) and IFN, which represent the cytokines that support the effector functions of the immune system (CTL, NK-cells, macrophages). \( T_{H2} \) cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represent the cytokines that favor the development of a humoral immune response. Since \( T_{H1} \) cytokines are critical for the generation of CTLs, an HIV-1-specific \( T_{H1} \) response is regarded as being a protective immune response. Studies on HIV-exposed but non-infected individuals have shown that following in vitro stimulation with HIV-1 env antigens (gp120/gp160) and peptides, T cells from these individuals secrete IL-2 in contrast to non-exposed controls (Clerici 1991). Similar studies were undertaken in healthcare workers after needlestick injuries and in newborns from HIV-infected mothers. Although these observations may indicate that a \( T_{H1} \)-type immune response is potentially protective, it should be considered that similar immune responses might have been generated after contact with non-infectious viral particles and therefore do not necessarily imply a means of protection against a replication-competent virus.

**HIV-1 specific humoral immune responses**

The association between an HIV-1-specific humoral immune response and the course of disease is less well characterized.

In an SIV model injection of an antibody cocktail consisting of various neutralizing antibodies is able to prevent SIV infection after a mucosal virus challenge (Ferrantelli 2004) indicating that primary protection is mainly dependent on a broad humoral immune response. Additional animal experiments suggest antibody concentrations in mucosal sites required to confer protection (Hessell 2009). This data suggests that HIV-specific antibodies are necessary for a preventive vaccine strategy. In contrast, B cell depletion by a monoclonal antibody directed against B cells in monkeys with already established SIV infection does not affect the course of plasma viremia (Schmitz 2003).

A slow progression of immunodeficiency was observed in patients with high titers of anti-p24 antibodies (Hogervorst 1995), persistence of neutralizing antibodies against primary and autologous viruses (Montefiori 1996) and lack of antibodies against certain gp120 epitopes (Wong 1993).
Long-term non-progressors with HIV tend to have a broad neutralizing activity towards a range of primary isolates and show persistence of neutralizing antibodies against autologous virus. At present, it is unclear whether the presence of neutralizing antibodies in LTNP represents part of the protection or whether it merely reflects the integrity of a relatively intact immune system. Individuals that have a substantial risk for HIV-1 infection, but are considered exposed yet non-infected by definition represent individuals with a lack of a detectable antibody response to HIV-1. This definition implies that a systemic humoral immune response may not represent a crucial protective mechanism. It has been shown that these individuals may demonstrate a local (mucosal) IgA response against HIV-1 proteins that are not detected by the usual antibody testing methods (Saha 2001). Thus, local IgA, rather than systemic IgG, may be associated with protection against HIV-1 infection. There is also some evidence that some anti-HIV-1 antibodies can enhance infection of CD4 T cells.

A number of older as well as recent studies have shown that neutralizing antibodies do exist in HIV-1-infected individuals, although there is a time lag in their appearance. That is, individuals will develop neutralizing antibodies to their own viruses over time, although by the time these antibodies develop the new viruses circulating in the individual's plasma will become resistant to neutralization, even though the older ones are now sensitive to the current antibodies in the patient's serum. Thus, the antibody response appears to be constantly going after a moving target, allowing viruses to escape continuously. Further understanding the mechanisms of humoral escape will likely lead to potential new therapies.

A few years ago, selected patients with advanced HIV infection were treated with plasma from HIV-infected patients at an earlier stage of the disease. No significant effect on the course of disease was notable (Jacobson 1998). The therapeutic application of neutralizing antibodies with defined specificity looked more promising, since a few acute and chronically infected patients were able to control their viral load at least temporarily after stopping antiretroviral therapy (Trkola 2005). Functionally, Fc receptors but not complement binding are important in antibody protection against HIV (Hessell 2007) and some neutralising antibodies recognise the CD4-binding site of gp120 (Li 2007). Neutralizing antibodies frequently recognize conserved epitopes with relevance for viral fitness (Pietzsch 2010) and research during the last years has revealed some of the specific structures and surface glycoproteins, which are targeted by neutralizing antibodies (Wu 2010, Wu 2011, Zhou 2010). More recently, the binding positions of broadly neutralizing antibodies in the V1/V2 loop of gb12 was identified. For the interaction of these antibodies with gp120, glycan-mediated, electrostatic and sequence-independent factors appear to play a role (McLellan 2011). This more detailed understanding is very likely to advance vaccine strategies aiming to treat or to protect against HIV-infection.

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Although great progress has been achieved in the field of treatment and prevention of HIV-1 infection, the HIV-1 pandemic will ultimately be controlled only by an effective HIV-1 vaccine. Unfortunately, despite intense research for over two decades, it has not yet been possible to develop an effective protective HIV-1 vaccine. The following chapter will give a short overview of the current status of HIV-1 vaccine development.

Induction of neutralizing antibodies

Similar to successful vaccination strategies in other infections such as hepatitis B, initial HIV-1 vaccine research focussed on the development of vaccines with the capability of inducing neutralizing antibodies. A variety of studies examined the safety and efficacy of vaccines such as gp120, gp160, parts of gp160 and peptides from gp160 to induce antibodies against HIV-1 envelope proteins. These immunogens stimulated the production of specific antibodies that were able to neutralize HIV-1 strains in vitro, but they failed to induce broadly neutralizing antibodies in HIV-1 variants derived from patients (Mascola 1996).

Two gp120-based vaccines were tested in two large Phase III trials in healthy volunteers: a clade B gp120 from HIV-1 MN and a gp120 from the CRF01_AE HIV-1 isolate were used in the VAX 003 Study in Thailand (Pitisuttithum 2006), while clade B gp120 proteins from HIV-1 MN and HIV-1 GNE8 were tested in the VAX 004 Study in the USA and the Netherlands (Flynn 2005). Despite induction of antibodies against gp120, the incidence of new infections was not lowered in either trial. These studies and others demonstrate that it is difficult to neutralize the biological activity of the envelope molecule gp160 via antibodies. Prior to the binding of gp120 to the CD4 receptor, the conserved and functionally important epitopes are hidden in grooves of the gp120 molecules that are additionally masked by glycan shields and variable sequence loops (Kwong 2002). Therefore, it is difficult for antibodies to block the binding of gp120 to the CD4 molecule.

The binding of the gp120 trimer to CD4 induces a conformational change of the V3 loop that exposes a conserved high-affinity coreceptor binding site on the gp120 molecule. The subsequent binding to the coreceptors CCR5 or CXCR4 triggers structural modifications of the viral transmembrane molecule gp41 and starts the fusion of the virus with the host cell membrane. Antibodies against the V3 loop can neutralize the process, although these activated binding sites on the V3 loop are recognizable by antibodies only for a short period of time. Therefore, high antibody concentrations are required for an efficient neutralization. Another problem for antibody-mediated neutralization is the shielding of the V3 loop-coreceptor interaction site by the gp120 trimer, which also inhibits the binding of antibodies to the V3 loop (Labrijn 2003).

HIV-1 infected patients generate neutralizing antibodies. However, in the majority of patients they are directed against the gp120 variable sequences. Due to the high sequence variability in gp120, HIV-1 can evade antibodies by a rapid generation of escape mutants. Thus, the majority of patients generate antibodies recognizing their own strain of HIV-1, but they neutralize HIV-1 variants from other patients poorly. There are only a few patients able to produce highly effective broadly cross-reacting neutralizing antibodies (bnAbs). These exceptional antibodies recognize the conserved binding site for CD4 in gp120, a particular pattern of glycans in gp120 (2G12...
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antibody), a gp120-V2V3 conformational epitope and the membrane proximal external region (MPER) in gp41 (4E10 and 2F5 antibodies). The majority of the bnAbs show unusual characteristics such as a long complementarity-determining region 3 (CDR3) in the heavy-chain variable (VH) region, a large number of somatic mutations and polyreactivity with non-HIV-1 antigens (McMichael 2012). The requirement of affinity maturation of these antibodies and immune tolerance against polyreactive antibodies are probably important reasons that only approximately 20% of the chronically infected patients are able to generate bnAbs and that these bnAbs emerge usually only after several years of infection.

Vaccination with a recombinant gp120 molecule is not able to induce antibodies against the V3 loop, as the V3 loop epitopes in the native gp120 molecule are not accessible to antibodies. To improve the induction of antibodies targeting the V3 loop, attempts are currently in progress to develop fusion molecules consisting of gp120 and CD4 that simulate the conformational changes in gp120 after binding to the CD4 molecule (Kwong 1998).

An innovative approach is the passive genetic immunization by the transfer of genes encoding highly active neutralizing antibodies or antibody-like immunoadhesins. In Rhesus monkeys, the intramuscular injection of a recombinant adeno-associated virus (AAV) vector encoding such SIV-specific antibody genes could induce the in vivo production of SIV-envelope-specific neutralizing antibody constructs that provided protection from intravenous challenge with SIV (Johnson 2009). Using a new self-complementary AAV (scAAV) vector for transfer of genes coding for neutralizing antibodies, protection from HIV-1 infection could be achieved in a humanized mouse model, too (Balazs 2012). This new exciting development stimulated a worldwide search for those few HIV-1 infected individuals that were able to generate unique highly active neutralizing antibodies that could be used for genetic immunization against HIV-1.

Induction of HIV-1-specific T cells

With all these hurdles regarding the induction of neutralizing antibody responses, the focus of vaccine development turned to vaccines that could elicit HIV-1-specific T cell responses. Cytotoxic T cells (CTL) play an important role in the control of HIV-1 in humans (Koup 1994, Harrer 1996b, Pantaleo 1997) and also for the control of SIV in SIV models. Experimental depletion of CD8 T cells in SIV-infected monkeys abrogated immune control of SIV infection and was associated with a strong increase of viral replication (Schmitz 1999). In contrast to neutralizing antibodies, CTLs do not exert a sterilizing immunity as they can only recognize cells that are already infected.

However, the observation of HIV-1-specific CTLs in HIV-1 exposed but uninfected subjects raised the hope that a T cell-based HIV-1 vaccine could prevent an ongoing HIV-1 infection by containment and eradication of small foci of viral infection (Herr 1998, Rowland-Jones 1998). Even if a T cell-based vaccine could not prevent infection of the host, there is the chance that it could influence the course of infection by reducing the extent of viremia after infection, as seen in the SIV monkey models (Letvin 2006). The viral load four months after infection, also known as the viral setpoint, may be one of the most important prognostic parameters for the course of HIV-1 infection. A vaccine could provide a clinical benefit if it could reduce the viral setpoint by half a log (Johnston 2007). In addition, such a vaccine could possibly exert positive effects on the spread of the HIV epidemic, as a lower viremia probably diminishes the infectivity of the patients. The clinical evaluation of these vaccines that do not prevent infection, but rather influence the course of disease, is dif-
HIV-1 can evade CTL recognition via development of CTL escape mutants in T cell epitopes or in proteasome cleavage sites (Maurer 2008). At least in conserved proteins such as gag or protease CTL-mediated immune selection is a major driving force for the development of polymorphisms (Mueller 2007). Our observations in long-term non-progressors showed that the quality of the CTL response with recognition of conserved CTL epitopes is very important (Harrer 1996a, Wagner 1999). It is essential for an effective vaccine to contain enough highly conserved CTL epitopes for the individual HLA alleles.

CTLs can be induced only by vaccines that are able to load viral peptides on HLA class I molecules of dendritic cells that present these peptides to the CTLs. Live attenuated viruses are effective against several infectious pathogens such as measles and they were protective against SIV in rhesus monkeys, but they are unlikely to be used in humans due to safety concerns. DNA vaccines alone are not very immunogenic in humans, but in DNA prime/vector boost strategies DNA priming could increase the immunogenicity of subsequent vaccinations with viral vectors. Lipopeptides allow the induction of CTL, but they can present only a limited repertoire of epitopes.

A new concept is the genetic immunization by transfer of genes encoding highly effective HIV-1-specific T-cell receptors (TCR) into CD8+ cytotoxic T-cells. In contrast to the transfer of antibody genes, transfer of TCR has to consider the HLA-restriction of the targeted CTL epitope and the HLA-I-type of the recipient. Recently, it could be shown in in-vitro experiments, that it is even possible to transfer two different exogenous HIV-1-specific TCRs into the same cell. If such techniques could be applied also in vivo, this could reduce the risk of selection of CTL escape mutations (Hofmann 2011).

**Recombinant viral vectors**

Recombinant viral vectors can achieve the induction of CTLs without the safety risks of attenuated live viruses. Several vectors have been tested in clinical studies: Adenovirus 5 (Ad5) vectors, ALVAC canarypox viruses, MVA (modified Vaccinia Virus Ankara), NYVAC (Gomez 2007a+b), adenovirus-associated virus and fowlpox vectors.

A great disappointment was the termination of two placebo-controlled Phase IIb trials, the HVTN 502 study (STEP trial) (Buchbinder 2008) and the HVTN 503 study (Phambili Study) (www.stepstudies.com). Both studies were testing Merck's trivalent MRK Ad5 vaccine (V520), a mixture of Ad5 vectors expressing HIV-1 gag, pol and nef. 3000 volunteers from North America, South America, the Caribbean, and Australia participated in the STEP trial that started in December 2004. The vaccine was immunogenic and induced HIV-1-specific CD8+ T cells in 73% and HIV-1-specific CD4+ T cells in 41% of the vaccinees (McElrath 2008). Nevertheless, the study was terminated ahead of schedule in September 2007 because of lack of efficacy. The vaccine neither prevented HIV-1 infection nor did it lower the viral setpoint in those who were infected. 83 volunteers became infected during the trial. As only one female was infected, the post hoc analyses were restricted to the 82 male newly-infected subjects. There was a non-significant trend towards a greater number of infections in the vaccine recipients (49 new infections in 914 subjects) versus the placebo recipients (33 new infections in 922 subjects). Interestingly, subjects with high pre-existing Ad5-specific neutralizing antibody titers (titer of >200) at enrolment showed a higher infection rate in those who got the vaccine (21 infections) versus those in

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the placebo arm (9 infections). In contrast there were no significant differences in subjects with absent or low Ad5-specific neutralizing antibody titers of $\leq 200$ (28 infections in the vaccine arm, 24 infections in the placebo arm). Because of the potential risk of the MRK Ad5 vaccine in subjects with a strong immune response against adenovirus 5, the parallel Phambili trial in South Africa was terminated as well. In Phambili, the MRK Ad5 vaccine showed no efficacy, with 33 new HIV-1 infections (4.54 infections per 100 person-years) in patients receiving at least one vaccination versus 28 HIV-1 infections (3.70 infections per 100 person-years) in the placebo arm (non-significant difference) (Gray 2011).

The STEP trial raises important questions that can be answered only by further examination of infected subjects and transmitted viruses. The fact that the increased infection risk was only seen in subjects with high antibody titers against the Ad5 vector argues against a general risk of immunizing against HIV-1, but it demonstrates the important issue of pre-existing vector immunity. The optimal priming of the immune response by a vaccine seems to be a key element determining the success or failure of a vaccine. More basic research is needed for a better understanding of the mechanisms of HIV-1 immunological control. Because of the unfavourable effects of pre-existing immunity against the adenovirus 5-vector, other adenoviral vectors are currently developed from less frequent adenovirus serotypes. So far, two Phase I studies in healthy volunteers could demonstrate the immunogenicity of new HIV-1 vaccines based on the adenovirus serotypes AD26 (AD26.ENVA.01) and AD35 (AD35-GRIN/ENV) (Keefer MC 2010; Barouch D 2010).

In contrast to the STEP trial, the RV144 study (Rerks-Ngarm 2009) involving more than 16,000 volunteers in Thailand showed a modest protective effect with a significant reduction of new HIV-1 infections by about 31%. The vaccine was a Sanofi Pasteur’s canarypox-vector-based ALVAC HIV (vCP1521) expressing HIV-1 subtype B gag and protease and subtype E envelope in combination with AIDSVAX B/E gp120 proteins (MN rgp120/HIV-1 plus A244 rgp120/HIV-1). Among the 8,198 subjects receiving placebo, 74 new HIV-1 infections were observed during the three years follow-up compared to 51 infections among the other half of volunteers that had received four immunizations with the ALVAC HIV and two immunizations with AIDSVAX B/E gp120 glycoproteins within a six months period. The vaccine had no effect on viral setpoints and the clinical course of HIV-1 infection in the subjects infected (Rerks-Ngarm 2012). This was probably due to the fact that the vaccine induced only gp120-specific CD4 T cells (in 33% of the vaccinees), but almost no gag-specific CD4 T cells (in 1% of vaccines) and no HIV-1-specific CD8 T cells (measured by intracellular cytokine staining ICS). In contrast, almost every vaccinee developed high titer antibodies, although these antibodies only had a weak to moderate capacity to neutralize various HIV-1 strains. The mechanisms of the protective effect of the vaccine are still unresolved. It has been hypothesized that antibody-dependent cellular cytotoxicity (ADCC) may have played a role. Recent data indicate a protective role of IgG antibodies to variable regions 1 and 2 (V1V2) of HIV-1 envelope proteins, whereas plasma IgA antibodies to gp120 were associated with higher rates of infections, presumably due to interference with epitope recognition by the protective IgG antibodies (Haynes 2012). Another efficacy trial, the HVTN 505 study, started enrolment in 2009. This study is testing a prime boost vaccination regimen using DNA and a rAd5 vector containing env/gag/pol/nef.

A promising approach for the development of more effective HIV-1 vaccines is the therapeutic immunization of HIV-1-infected patients on ART who then undergo a treatment interruption (Harrer 2005). The analysis of a vaccine’s ability to control HIV-1 replication during treatment interruption may be a good instrument in identifying vaccines that are also effective in prevention.
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5. Acute HIV-1 Infection

HENDRIK STREECK AND MARCUS ALTFELD

Introduction

Within days of HIV-1 acquisition, a transient symptomatic illness associated with high levels of HIV-1 replication and rapid loss of CD4 T cells occurs. This highly dynamic phase of the infection is accompanied by clinical symptoms similar to mononucleosis. However, despite an estimate of 7,000 new HIV-1 transmissions per day (UNAIDS 2010 Global Report), the diagnosis is missed in the majority of cases. Most commonly other viral illnesses (i.e., flu) are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of awareness and clinical knowledge based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

An accurate diagnosis of HIV-1 infection during this early stage of infection is particularly important as about 50% of new sexual transmissions are estimated to happen while a person is in this primary phase of infection (Brenner 2007). Indeed, phylogenetic analyses demonstrate a clustering of infections during primary HIV-1 infection, and the catalytic effect of acute HIV-1 infection on the HIV pandemic could be prevented or at least slowed by early diagnosis and immediate antiretroviral therapy intervention (see below). The potentially beneficial use of antiretroviral therapy as pre-exposure prophylaxis might change the face of acute HIV-1 infection in the future. Recent studies conducted in South Africa and USA have demonstrated that the use of tenofovir or tenofovir-gel might significantly protect from HIV infection (Cohen 2011, Karim 2011). However, it is currently unknown how such practice might bear the risk for increased viral resistance due to the monotherapeutic use of antiretroviral medication. This will need to be evaluated in future studies.

Definition and classification

Acute HIV-1 infection (AHI) is defined by high levels of plasma HIV-1 RNA in the presence of a negative anti-HIV-1 ELISA and/or negative/indeterminant Western Blot (<3 bands positive) documenting the evolving humoral immune response; whereas early HIV-1 infection (EHI) includes anyone with documentation of being HIV-1 antibody negative in the preceding 6 months and is therefore broader than the definition of acute HIV-1 infection. Both are included in the term primary HIV-1 infection (PHI) (see Figure 1). Recently, a more detailed classification system of the early phases of HIV infection has been implemented (Fiebig 2003), which has rather little relevance for clinical decisions but is more important for scientific purposes. The definition used influences the methods needed to make the diagnosis and any considerations regarding the pathogenic implications of this stage of disease. Acute HIV-1 infection is often associated with an acute “retroviral syndrome” that usually includes fever with a variety of nonspecific clinical and laboratory abnormalities. In contrast, subjects with early HIV-1 infection can be asymptomatic. The time from exposure to symptomatic disease is typically 2 to 4 weeks, and the duration of illness is generally days to weeks. Identifying patients with this syndrome requires a thorough risk assessment, recognition of the variable clinical and laboratory manifestations, and understanding what tests need to be performed in order to make the diagnosis.
After an incubation period ranging from a few days to a few weeks after exposure to HIV, most infected individuals present with an acute flu-like illness. Acute HIV-1 infection is a very heterogeneous syndrome and individuals presenting with more severe symptoms during acute infection and a longer duration of the acute infection syndrome tend to progress more rapidly to AIDS (Vanhems 1998, Pedersen 1989, Keet 1993). The clinical symptoms of acute HIV-1 infection were first described in 1985 as an illness resembling infectious mononucleosis (Cooper 1985). Several non-specific signs and symptoms have been reported in association with acute infection. Fever in the range of 38 to 40°C is almost always present; in addition lymphadenopathy concomitant with the emergence of a specific immune response to HIV occurs. A generalized rash is also common in symptomatic acute HIV infection. The eruption typically occurs 48 to 72 hours after the onset of fever and persists for five to eight days. The upper thorax, collar region, and face are most affected with well-circumscribed, red colored macules or maculopapules. In addition, painful mucocutaneous oral, vaginal, anal or penile ulcerations are one of the most distinctive manifestations of the syndrome. Further common symptoms (see Table 1) are arthralgia, pharyngitis, malaise, weight loss, aseptic meningitis and myalgia (Kahn 1998). Although none of these findings are specific, several features, combinations of symptoms and prolonged duration are suggestive of HIV. The highest sensitivity for a clinical diagnosis of acute HIV-1 infection are fever (80%) and malaise (68%), whereas weight loss (86%) and oral ulcers (85%) had the highest specificity (Hecht 2002). In this study, the symptoms of fever and rash (especially in combination), followed by oral ulcers and pharyngitis had the highest positive predictive value for diagnosis of acute HIV-1 infection. In another study, fever, rash, myalgia, arthralgia and night sweats were the best predictors of acute infection (Daar 2001).
Table 1: Main symptoms of acute HIV-1 infection (from Hecht 2002).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>80%</td>
<td>5.2 (2.3-11.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>51%</td>
<td>4.8 (2.4-9.8)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>37%</td>
<td>3.1 (1.5-6.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>54%</td>
<td>2.6 (1.3-5.1)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>44%</td>
<td>2.6 (1.3-5.1)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>54%</td>
<td>2.5 (1.2-4.8)</td>
</tr>
<tr>
<td>Weight loss &gt;2.5 kg</td>
<td>32%</td>
<td>2.8 (1.3-6.0)</td>
</tr>
<tr>
<td>Malaise</td>
<td>68%</td>
<td>2.2 (1.1-4.5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>49%</td>
<td>2.1 (1.1-4.2)</td>
</tr>
<tr>
<td>Fever and rash</td>
<td>46%</td>
<td>8.3 (3.6-19.3)</td>
</tr>
</tbody>
</table>

Diagnosis

Currently, four different HIV tests are commercially available, but they have limited sensitivity in detecting acute HIV-1 infection. In order to be able to correctly interpret a positive or negative result in the presence (or absence) of acute HIV infection symptoms and corresponding history, it is important to understand differences in the sensitivities of the available tests.

The 1st and 2nd generation EIA tests are able to detect HIV-1 infection with both high specificity and sensitivity, but only after HIV-1 seroconversion, as decent levels of anti-p24 IgG antibodies need to be present to give a positive result (see Figure 1). 3rd generation EIA tests can now detect IgM antibodies and therefore are able to detect a recent infection with HIV earlier than the 1st or 2nd generation tests (Hecht 2002). The newly developed 4th generation EIA test now combines the detection of p24 antigen and p24 antibodies and therefore is able to detect HIV infection prior to seroconversion (Ly 2007). However, although this test is able to detect HIV-1 infection much earlier than all previously developed tests, a second diagnostic false negative window can occur when equal levels of p24 antigen and anti-p24 antibody are present. The most substantiated diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies (pre-seroconversion). The most sensitive test is therefore based on detection of plasma HIV-1 RNA. All assays for HIV-1 RNA that have been compared (branched chain DNA, PCR and GenProbe) have a sensitivity of 100%, but occasionally (in 2–5% of cases) lead to false positive results (Hecht 2002). False positive results from these tests are usually below 2,000 copies HIV-1 RNA per ml, and therefore are far below the high titers of viral load normally seen during acute HIV-1 infection (in our own studies subjects average 13 x 10^6 copies HIV-1 RNA/ml with a range of 0.25–95.5 x 10^6 copies HIV-1 RNA/ml). Repetition of the assay for HIV-1 RNA from the same sample with the same test led to a negative result in all false positive cases. Measurement of HIV-1 RNA from duplicate samples therefore results in a sensitivity of 100% with 100% specificity. In contrast, detection of p24 antigen has a sensitivity of only 79% with a specificity of 99.5–99.96%. The diagnosis of acute infection must be subsequently confirmed with a positive HIV-1 antibody test (seroconversion) within the following weeks.

During acute HIV-1 infection, there is frequently a marked decrease of the CD4 cell count, which later increases again, but usually does not normalize to initial levels. In contrast, the CD8 cell count rises initially, which may result in a CD4/CD8 ratio of <1. Infectious mononucleosis is the most important diagnosis to be aware of, but the differential diagnosis also includes cytomegalovirus, toxoplasmosis, rubella,
syphilis, viral hepatitis, disseminated gonococcal infection, other viral infections and side effects of medications.

In summary, the most important step in the diagnosis of acute HIV-1 infection is to keep it in mind during diagnosis. The clinical hypothesis of acute infection requires performance of an HIV-1 antibody test and possibly repeated testing of HIV-1 viral load, as shown in the algorithm in Figure 1 (adapted from Hecht 2002).

**Immunological and virological events during AHI**

Transmission of HIV-1 generally results from viral exposure at mucosal surfaces followed by viral replication in submucosal and locoregional lymphoid tissues, and subsequently through overt systemic infection. The virus exponentially replicates in the absence of any detectable adaptive immune response, reaching levels of more than 100 million copies HIV-1 RNA/ml. It is during this initial cycle of viral replication that important pathogenic processes are thought to occur. These include the seeding of virus to a range of tissue reservoirs and the destruction of CD4+ T lymphocytes, in particular within the lymphoid tissues of the gut. Early on in infection, the very high levels of HIV-1 viremia are normally short-lived, indicating that the host is able to generate an immune response that can control viral replication. Over the following weeks, viremia declines by several orders of magnitude before reaching a viral setpoint. This setpoint following resolution of the acute infection is a strong predictor of long-term disease progression rates (Mellors 1995, 2007). It is therefore of critical importance to characterize and understand the immune
responses induced in the initial stages of HIV-1 infection as these first responses appear responsible for the initial control of viral replication. In contrast to hepatitis B and C infection, acute-phase HIV replication is associated with the activation of a dramatic cytokine cascade, with plasma levels of some of the most rapidly induced innate cytokines peaking 7 days after the first detection of plasma viremia and many other cytokines being upregulated as viral titers increase to their peak. Although some of the cytokines/chemokines produced in acute HIV infection may contribute to the control of viral replication, the exaggerated cytokine response likely also contributes to the early immunopathology of the infection and associated long-term consequences (Stacey 2009). Also, a specific activation and expansion of natural killer (NK) cells has been noted during the acute phase of infection (Alter 2007). Indeed, a recent study demonstrated that NK cells can recognize and kill HIV infected cells (Alter 2011). Moreover, recent studies suggest that NK cells can form memory (Paust 2010) suggesting a potential new avenue for vaccine research.

Several factors can influence viral replication during acute infection and the establishment of a viral setpoint. These include the fitness of the infecting virus, host genetic factors and host immune responses. While it has been shown that the transmitted/founder virus population has intact principal gene open reading frames and encodes replication-competent viruses (Salazar-Gonzalez 2009), the envelope (env) gene of elite controllers has been demonstrated to mediate less efficient entry than the envelope protein of chronic progressors (Troyer 2009). Interestingly, acute infection envs exhibit an intermediate phenotypic pattern not distinctly different from chronic progressor envs. These findings imply that lower env fitness may be established early and may directly contribute to viral suppression in elite controllers. Antibodies against HIV-1 with neutralizing capacities are rarely detectable during primary HIV-1 infection and are therefore less likely to be major contributors to the initial control of viral replication. However, broadly neutralizing antibodies develop over time in a rare subset of HIV-infected individuals and the expression of specific markers on CD4 T cells is modestly associated with the development of these responses (Mikell 2011). In addition, several studies have demonstrated a crucial role of HIV-1-specific cellular immune responses for the initial control of viral replication. A massive, oligoclonal expansion of CD8 T cell responses has been described during acute HIV-1 infection (Pantaleo 1994), and the appearance of HIV-1-specific CD8 T cells has been temporally associated with the initial decline of viremia (Koup 1994, Borrow 1994). These CD8 T cells have the ability to eliminate HIV-1-infected cells directly by MHC class I-restricted cytolysis or indirectly by producing cytokines, chemokines or other soluble factors, thus curtailing the generation of new viral progeny (Yang 1997). The biological relevance of HIV-1-specific cytotoxic T cells (CTL) in acute HIV-1 infection was highlighted in recent in vivo studies demonstrating a dramatic rise of SIV viremia and an accelerated clinical disease progression in macaques after the artificial depletion of CD8 T cells (Schmitz 1999, Jin 1999). Additional evidence for the antiviral pressure of HIV-1-specific CTLs during primary HIV-1 infection was provided by the rapid selection of viral species with CTL epitope mutations that were detected within a few weeks of HIV-1 infection (Price 1997). A study assessing the impact of early HIV-1-specific CD8 T cell responses on the early viral set point in a cohort of over 420 subjects was able to demonstrate that the ability to mount a strong early CD8 T cell response during primary HIV-1 infection is moderately associated with a lower viral setpoint (Streeck 2009). Furthermore, the assessment of the CD8 T cell responses against autologous patient-virus-derived peptides in three subjects suggest that even more, yet undetectable, responses are present during the acute phase of the infection contributing up to 15% each to the initial control of viral replication (Goonetilleke 2009).
Many of the early immunodominant CD8 T cell responses have been shown to be restricted by HLA class I alleles, which have been previously associated with slower disease progression such as HLA-B57 or -B27. Moreover, these HLA-restricted responses preferentially target epitopes within a short highly conserved region of p24/Gag (Streeck 2007). This region encodes the HIV-1 capsid, which has been shown to be crucial for the stability of HIV-1 (Schneidewind 2007). The preservation of the early CD8 T cell responses has been associated with slower disease progression (Streeck 2009), which might be linked by the presence of HIV-1-specific CD4 T helper responses during the CTL priming process. During acute infection, the number of CD4 T cells decline, occasionally to levels that allow the development of opportunistic infections (Gupta 1993, Vento 1993). Even though the CD4 T cell count rebounds with the resolution of primary infection, it rarely returns to baseline levels in the absence of antiretroviral therapy. In addition to the decline in CD4 T cell counts, qualitative impairments of CD4 T cell function are perhaps the most characteristic abnormalities detected in HIV-1 infection. The impairment of HIV-1-specific CD4 T cell function occurs very early in acute infection (Rosenberg 1997, Lichterfeld 2004), potentially due to the preferential infection of virus-specific CD4 T cells by HIV (Douek 2002). This is followed by a functional impairment of CD4 T cell responses to other recall antigens, as well as a reduced responsiveness to novel antigens (Lange 2003). The impairment of HIV-1-specific CD4 T helper cell function in acute HIV-1 infection subsequently results in a functional impairment of HIV-1-specific CD8 T cells (Lichterfeld 2004). The antiviral contribution of CD4 T helper response against HIV-1 not been well studied. A recent study demonstrated that a specific CD4 T cell subset with cytolytic properties expands during acute infection only in those patients that can subsequently control viral replication (Soghoian 2012). Moreover, the Granzyme A levels in those cells, unlike any other factor, can actually predict disease outcome. The relevance of this association is currently still under investigation.

However, CD4 T cells most likely contribute indirectly through the modulation of HIV-specific CD8 T cell responses or B cell responses to the control of viral replication (Lindqvist 2012). It has been demonstrated in the lymphocytic choriomeningitis virus (LCMV-) mouse model that an efficacious CD8 T cell memory response is dependent on the presence of a CD4 T cell response (Janssen 2003, Williams 2006). However, the CD4 T cell signals involved in this interaction are not fully understood. Lack of CD4 T helper cells and chronic antigenic stimulation have been described to be the major cause of the functional deficits CD8 T cells undergo soon after the early phase of infection. It has been demonstrated that IL21-secreting HIV-specific CD4 T cells can preserve and maintain the effector function of HIV-specific CD8 T cells and indeed these responses are mainly found in HIV elite controllers (Chevalier 2011).

The hierarchical loss of CD8 T cell function has been linked to the expression of inhibitory molecules on the cell surface of HIV-1-specific CD8 T cells such as PD-1 and several others (Day 2006, Blackburn 2009). The identification of such receptors might help in the generation of potential immune therapeutics to boost HIV-1-specific CD8 T cell function.

In addition to host immune responses, host genetic factors play an important role in both susceptibility and resistance to HIV-1 infection and speed of disease progression following infection. The most important of these is a deletion in the major co-receptor for entry of HIV-1 into CD4 T cells, a chemokine receptor called CCR5 (Samson 1996). Homozygotes for this 32 base pair deletion (CCR5delta32) do not express the receptor at the cell surface and can only be infected with HIV strains that are able to use other co-receptors such as CXCR4. Thus, although CCR5delta32
homozygotic individuals show a significant degree of resistance to HIV-1 infection (Samson 1996), a number of cases of infection with CXCR4-using HIV-1 strains have been described (O’Brien 1997, Biti 1997). Heterozygotes for this deletion exhibit significantly lower viral setpoints and slower progression to AIDS. In addition to mutations in the chemokine receptor genes, a number of HLA class I alleles, including HLA-B27 and -B57, have been described to be associated with both lower viral setpoints and slower disease progression (O’Brien 2001, Kaslow 1996). Studies demonstrate that individuals expressing HLA-B57 present significantly less frequently with symptomatic acute HIV-1 infection and exhibit a better control of viral replication following acute infection (Altfeld 2003). A number of further polymorphisms have been identified that have a potential impact on HIV-1 disease progression. Here especially, the axis between detrimental immune activation and beneficial immune responses is largely unknown and part of ongoing research. For example, it has been demonstrated that polymorphisms in the IL-10 promotor region directly inhibit HIV replication, but may also promote viral persistence through the inactivation of effector immune function (Naicker 2009). These data demonstrate that host genetic factors can influence the clinical manifestations of acute HIV-1 infection and can have an important impact on the subsequent viral setpoint and the speed of disease progression.

Treatment

The hypothesis of antiretroviral therapy during acute HIV-1 infection is to shorten the symptomatic viral illness, reduce the number of infected cells, preserve HIV-1-specific immune responses and possibly lower the viral setpoint in the long term. Several studies have suggested that treatment of acute HIV-1 infection allows long-term viral suppression and might lead to a preservation and even increase of HIV-1-specific T helper cell responses.

Pilot studies in patients who are treated during acute HIV-1 infection and subsequently start treatment interruptions show that the HIV-1-specific immune response can be boosted (Rosenberg 2000, Vogel 2006, Grijsen 2011), and they experience at least temporal control of viral replication. However, other studies were not able to confirm this theoretic benefit (Markowitz 1999, Streeck 2006) and viral load rebounded during longer follow-up, requiring the eventual initiation of therapy. The theoretic benefits of early treatment must be balanced against the possible and known risks of prolonged antiretroviral therapy. These include a higher risk of accumulated long-term antiretroviral drug toxicities due to a considerable increase in the duration of antiretroviral exposure and the possibility of drug resistance if therapy fails to completely suppress viral replication. The long-term clinical benefit of early initiation of therapy has not been demonstrated. It is also not known how long the period between acute infection and initiation of therapy can be without losing immunological, virological and clinical benefit. Thus, no recommendation for or against the initiation of antiretroviral therapy during primary HIV-1 infection can be given and needs to be decided case by case. In view of all these unanswered questions, it would be beneficial to design and enroll patients with acute HIV-1 infection in a controlled clinical trial. As a treatment option, a standard first-line treatment could be considered. It is important during counseling to clearly indicate the lack of definitive data on the clinical benefit of early initiation of antiretroviral therapy and to address the risks of antiretroviral therapy and treatment interruptions, including drug toxicity, development of resistance, acute retroviral syndrome during viral rebound and HIV-1 transmission and superinfection during treatment interruptions.
References


PART 2

Antiretroviral Therapy
6. ART 2012

6.1. Perspective

CHRISTIAN Hoffmann

The development of antiretroviral therapy has been one of the most dramatic evolutions in the history of medicine. Few other areas have been subject to such fast progress, along with some short-lived trends. Those who have experienced the rapid developments of the last few years have been through quite a ride.

The early years, from 1987–1990, brought great hope and the first modest advances with monotherapy (Volberding 1990, Fischl 1990). But when the results of the Concorde Study arrived (Hamilton 1992, Concorde 1994) both patients and clinicians plunged into a depression that lasted several years. AZT (zidovudine) was first tested on humans in 1985, and was introduced as a treatment in March 1987 with great expectations. Although quickly approved after rapid study, as monotherapy it was actually very limited. The same was true for the nucleoside analogs ddC (zalcitabine), ddI (didanosine) and d4T (stavudine), all introduced between 1991 and 1994. The lack of substantial treatment options led to a debate that lasted for several years about which nucleoside analog should be used, when, and at what dose. A typical question was, “Should the alarm clock be set to go off during the night for a sixth dose of AZT?”

Patients infected during the early and mid-80s were dying, and quickly. Hospices were established as well as support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. There was, however, definite progress in the field of opportunistic infections (OI) – cotrimoxazole, pentamidine, gancyclovir, foscarnet and fluconazole saved many patients’ lives, at least in the short-term. Some clinicians started to dream of a kind of “mega-prophylaxis”. But the general picture was still tainted by an overall lack of hope. Many remember the somber, still mood of the IXth World AIDS Conference in Berlin in June 1993. Between 1989 and 1994 not much improved.

Then in September 1995, the preliminary results of the European-Australian DELTA Study (Delta 1995) and the American ACTG 175 Study (Hammer 1996) attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than monotherapy. Indeed, the differences made in the clinical endpoints (AIDS and death) were highly significant. Both studies demonstrated that it was of great importance to start treatment with two nucleoside analogs, as opposed to using the drugs sequentially.

This turned out to be the beginning of many breakthroughs. The first studies with protease inhibitors (PIs), a completely new class of drugs, had been under way for several months. PIs had been designed in the lab using the knowledge of the molecular structure of HIV and protease, but their clinical value remained uncertain. Preliminary data, along with many rumors, were circulating. Great impatience pervaded the patients and clinician communities. By the fall of 1995, a fierce competition had started up between three companies: Abbott, Roche and MSD. The licensing studies for the three PIs, ritonavir, saquinavir and indinavir, were pursued with intense effort. The monitors of these studies lived for weeks at the participating clinical sites. Deep into the night, case report files were written up and thousands of queries were answered. These efforts led to fast track approval for all three PIs between December 1995 and March 1996 – first saquinavir, followed by ritonavir and indinavir – for the treatment of HIV.

Many clinicians (including this author) were not really aware of what was happen-
ing during these months. AIDS remained ever-present. Although the incidence of AIDS had dropped by half between 1992 and 1996, many were still dying. Doubts remained. Hopes had already been raised too many times in the previous years by supposed miracles. Early in January 1996, during the 5th AIDS conference in Munich, other topics were higher on the agenda: palliative medicine, pain management, even euthanasia. Here and there a few speeches on “new approaches”, nothing much. Faint and latent optimism was the highest of emotions anyone dared show. No one dared to proclaim a breakthrough.

In February 1996, during the 3rd Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from the ABT-247 Study during the late breaker session. The auditorium was absolutely silent. Riveted, listeners heard that the mere addition of ritonavir oral solution decreased the frequency of death and AIDS from 38% to 22% (Cameron 1998). These results were sensational in comparison to everything else that had been previously published.

The World AIDS Conference in Vancouver a few months later in June 1996, where the great potential of PIs became fully apparent, developed into a celebration. Even regular news channels reported in great depth on the new “AIDS cocktails”. The strangely unscientific expression “highly active antiretroviral therapy” (HAART) began to spread irreversibly.

By this time, David Ho, Time magazine’s “Man of the Year” in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his breakthrough research (Ho 1995, Perelson 1996). A year earlier, Ho had already initiated the slogan “hit hard, hit early”, and almost all clinicians were now taking him at his word. With the new knowledge of the incredibly high turnover of the virus and the relentless daily destruction of CD4 T cells, there was no longer any consideration of a latent phase – and no life without antiretroviral therapy. In many centers almost every patient was treated with HAART. Within only three years, 1994–1997, the proportion of untreated patients in Europe decreased from 37% to barely 9%, whilst the proportion of patients on HAART rose from 2% to 64% (Kirk 1998).

Things were looking good. By June 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs. In February 1998, CROI in Chicago finally brought home the realization among clinicians that PIs were perhaps not as
selective as had long been believed. One poster after another, indeed whole walls of pictures, showed fat abdomens, buffalo humps, thin legs and faces. What was almost immediately coined “crix belly” by those taking the new PIs in early 1997 – and there were internet listservs and chats about it – was given a more medical definition new term at the beginning of 1998, and would influence ART for years to come: lipodystrophy. And so the old medical saying was shown to hold true for ART as well: all effective drugs have side effects. The actual cause of lipodystrophy remained completely unclear. Then, in early 1999, a plausible hypothesis emerged from the Netherlands, mitochondrial toxicity (Brinkmann 1999). It has become an ubiquitous term in HIV medicine today.

The dream of eradication (and cure), widely hoped for in the beginning, was eventually abandoned. Mathematical models were evidently not real life. In 1997, it was estimated that viral suppression with a maximum duration of three years was necessary; it was predicted that all infected cells would die in this time. Since then, the duration has constantly been adjusted upwards. Estimates evolved upwards to around 60 to 70 years (Silicano 2003). These numbers show one thing: HIV will not be cured with standard ART. More recent studies have come to the sobering conclusion that HIV remains detectable in latent infected cells, even after long-term suppression. In any case, we do talk about being able to cure the disease someday, however utopian it may seem. We will never get there without a vision.

In fact, today’s reality seemed impossible ten years ago: HIV infection is a chronic disease which, although incurable, is manageable lifelong with therapy, even in patients with resistant virus. CCR5 antagonists as well as integrase inhibitors have opened up new possibilities of treatment. It has become increasingly possible to lower viral loads to below detection in most patients. The newer drugs maraviroc and raltegravir have been shown to be extremely well-tolerated. These new drug classes will bring about fundamental changes to current ART. The dogma of always using two nucleoside analogs as the backbone of every therapy may start to change. Many of the currently widespread drugs will disappear over the next few years. The end of HIVID®, Agenerase®, Fortovase® or Viracept® is just the beginning. Veteran agents like AZT, d4T, ddI, nelfinavir or indinavir are not recommended by guidelines anymore although they served us in HIV management in the nineties. Will we be needing saquinavir, fosampranavir, nevirapine or even efavirenz and lopinavir as much as we do today five years from now?

A normal life expectancy seems realistic today with treatment. Therapy is likely to be permanent. This will pose a tremendous challenge for patients, physicians and for the pharmaceutical industry and payors. The comfortable situation at present does not mean one can relax. New drugs are urgently needed. There is uncertainty about whether our drugs can stand the test of time over decades. Effects on the heart, kidney, bones and other organs in an aging HIV population are difficult to foresee. If the cure is delayed, over the decades one will need a wider breadth and range of available drugs. It will not be easy for new drugs to be approved, as vicriviroc has shown. How do you show the advantages of a new drug over other successful therapies today? Approval for new drugs is becoming more strict and the market is tightening. Already one can observe the pharmaceutical industry’s caution. The days may be over when an HIV drug got from the laboratory to the market within five years. Compared to the previous decade, the HIV ARV pipeline is now drying up. New strategies are needed.

At the same time, the simple question of “when to start” with ART remains unanswered. Instead of David Ho’s recommendation from the nineties “hit hard, hit early”, we often hear “hit HIV hard, but only when necessary” (Harrington 2000). This sounds sensible. However, when is it actually necessary? At a count of 350 CD4 T
cells? What roles do the following play: viral load, CD4 T cell changes, CD4 percentages, age, gender, host elements and viral tropism? What about acutely infected patients? These strategically important questions will hopefully find some answers through big studies like START that are underway now. Until then, this issue requires keen sensitivity.

HIV clinicians are well-advised to keep an open mind to new approaches. Those who do not make an effort to constantly expand their knowledge at conferences will not be able to provide adequate treatment for their patients in a field that is still growing and learning and changing direction every two to three years. Those who adhere strictly to evidence-based medicine and only treat according to guidelines are quickly outdated. HIV medicine is ever-changing. Treatment guidelines remain just that, and are often out of date by the time of publication. There are no laws set in stone. However, those who confuse therapeutic freedom with random choices, and assume that data and results coming from basic research can be ignored are also missing the point. Individualized treatment is not random treatment. It cannot be stressed enough that clinicians are also responsible for the problem of poor adherence. Even if many experienced clinicians have come to disregard this, every patient has the right to know why they are taking the therapy they are on or, indeed, why certain therapies are not an option. The more they understand their therapies, the better the long-term results.

HIV remains a dangerous opponent. Patients and clinicians must tackle it together. The following chapters describe how this can be done.

References
6.2. Overview of Antiretroviral Agents

CHRISTIAN HOFFMANN

Preliminary remark

As of now (March 2012) there are 30 individual or combination agents licensed for treatment of HIV infection. These drugs are from five different classes:

1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Entry inhibitors (co-receptor antagonists and fusion inhibitors)
5. Integrase inhibitors

The FDA in the US and the European EMA do not always agree on the granting of brand names with the result that, in some cases, names differ from country to country. Sometimes a pharmaceutical company does not hold authorization for production worldwide. The NNRTI efavirenz, for example, is produced by BMS in Germany under the brand name Sustiva® and in Austria by MSD under the name of Stocrin®. The situation will not improve when patents and rights for some agents, including blockbuster drugs such as nevirapine or efavirenz, run out in industrial countries and several generics start arriving in the near future.

Moreover, definitions for indication areas vary widely. Some agents are specifically not licensed for primary (first line) therapy, such as entry inhibitors, the PI tipranavir and the NNRTI etravirine, as well as combination agents such as Atripla® in Europe. The new NNRTI rilpivirine is limited to patients with a plasma viremia of less than 100,000 HIV RNA copies/ml. Other limitations concern pregnant women and children (see the chapters in part 4). Complex dosing instructions have to be considered for some drugs, due to drug-drug interactions or due to renal or hepatic insufficiency. More details can also be found in the chapter “Drugs” at the end of this book.

In the face of cost pressures suffered by health systems, it is advisable for clinicians to adhere to the specific indication areas of the individual agents. Due to such a wide range of choices, this is possible in most cases, although not in all. Clinicians should have good reason when using an agent outside the stated indication area. A thorough documentation should be kept in case of disagreement from payors.

In this chapter, individual agents listed by class are discussed with reference to their specific benefits and problems. Discussion on common primary therapy can be found in the chapter “What to start with?”. Other chapters talk about adjusting ART and therapy interruptions. Salvage therapy as well as new and experimental agents are discussed in other chapters.
Table 2.1: Overview of antiretroviral drugs. *USA only, approval in Europe pending

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Abbrev.</th>
<th>Drug</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td><strong>Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
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<tr>
<td>Emtriva®</td>
<td>FTC</td>
<td>Emtricitabine</td>
<td>Gilead Sciences</td>
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<tr>
<td>Epivir®</td>
<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>Retrovir®</td>
<td>AZT</td>
<td>Zidovudine</td>
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<td>Bristol Myers-Squibb</td>
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<td>Viread®</td>
<td>TDF</td>
<td>Tenofovir</td>
<td>Gilead Sciences</td>
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<td>Zerit®</td>
<td>d4T</td>
<td>Stavudine</td>
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<tr>
<td>Ziagen®</td>
<td>ABC</td>
<td>Abacavir</td>
<td>ViiV Healthcare</td>
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<tr>
<td><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
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<td>Sustiva®, Stocrin®</td>
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<td>BMS/MSD</td>
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<td>Nevirapine</td>
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<td>Rilpivirine</td>
<td>Janssen-Cilag</td>
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<td>Etravirine</td>
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<td>Delavirdine</td>
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<td>Nelfinavir</td>
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<td><strong>Entry Inhibitors</strong></td>
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<td>MVC</td>
<td>Maraviroc</td>
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<td>Fuzeon®</td>
<td>T-20</td>
<td>Enfuvirtide</td>
<td>Roche</td>
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<td><strong>Integrase Inhibitors</strong></td>
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<td>Isentress®</td>
<td>RAL</td>
<td>Raltegravir</td>
<td>MSD</td>
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<td><strong>Combination Drugs</strong></td>
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<td>TDF+FTC+EFV</td>
<td>Gilead+BMS+MSD</td>
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<td>AZT+3TC</td>
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<td>TDF+FTC+RPV</td>
<td>Gilead+Janssen-Cilag</td>
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<td>Kivexa®, Epzicom®</td>
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<td>Trizivir®</td>
<td>TZV</td>
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<tr>
<td>Truvada®</td>
<td>TVD</td>
<td>TDF+FTC</td>
<td>Gilead Sciences</td>
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*The single tablet regimen of TDF+FTC, the integrase inhibitor elvitegravir and the pharmacokinetic enhancer cobicistat was approved by the FDA in August 2012. Approval in Europe is expected for 2013.

**Costs**

Antiretroviral treatment is expensive. A health provider needs to be aware of drug costs. Even within drug classes, there are astonishing differences. For example, the PI indinavir (Crixivan®, hardly used today) is relatively cheap in most countries, while the PI tipranavir (Aptivus®) is more than three times the price. Even in recommended first-line therapies in guidelines there are great price variations: PIs are
almost double the price of NNRTIs in many countries. A salvage therapy for a patient with multiresistant virus can amount to as much as €30,000–€50,000 and more per year. For pricing in low- or middle-income countries, please refer to the chapter Global Access to HIV Treatment.

It is difficult to comprehend the pricing policies of pharmaceutical companies. The reason why prices for directly competing agents (3TC and FTC) are almost exactly the same, whilst prices for other agents of the same drug class differ by 200–300%, cannot be explained by development costs alone. There is no doubt that ART is a money-maker and the market is full of competitors – monopolies and patents are being protected. Despite all the criticism and price discussions, two facts cannot be forgotten:

First, the high development costs for new medicines can rise to a billion dollars or more. Most agents never make it to the market. Even a licensed drug such as T-20 may never recoup its development costs. According to Roche, research and development alone chewed up 600 million dollars. To cover such production costs, thousands of patients worldwide would have to be treated with T-20 for several years – a very unrealistic scenario.

Second, there is hardly a more effective therapy than antiretroviral therapy. US estimations assume an expenditure of between $13,000 and $23,000 per additional QALY (quality-adjusted life year) (Freedberg 2001). Compared to many other therapies this is relatively cheap. ART reduces the cost of expensive treatment of opportunistic infections, inpatient and outpatient care. In one German study, between 1997 and 2001 total annual spending per patient decreased from €35,865 to €24,482 (Stoll 2002). Many patients return to work, resulting in an overall economic gain for society (Sendi 1999).

Nevertheless, ART is expensive. Therefore, it should be expected from patients to use up remaining packets of drugs, etc. if the reasons for a change in therapy are not urgent. Concerns of pill reduction or doubts about long-term toxicity should be part of an ongoing discussion with patients. All patients need to be made aware of the costs of medication so they can better understand the value of the therapy.

Initially, ART should be prescribed for a month. This way, mountains of unused pills will not be wasted if signs of intolerability or complicated adverse events occur. If response to ART is positive and its effects constant, prescriptions can then be done for periods of three months.

Many companies now offer three-month supply packages. This practice has not been without criticism. In any case, prescriptions of longer than a three month’s supply should be avoided.

In the future, we all need to be more aware of the costs of ART. The patents for AZT, ddi, 3TC, d4T and abacavir, but also saquinavir will disappear or have already gone. Efavirenz and nevirapine are soon to follow. It will be interesting to watch price developments when generics come to the market, as has happened in resource-limited settings.

**Nucleoside Analogs (NRTIs)**

**Mechanism of action**

Nucleoside analogs (“nukes”) are also referred to as nucleoside reverse transcriptase inhibitors (NRTIs). Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates, they compete with physiological nucleosides, differing from them only by a minor modification in the ribose molecule. The incorporation of nucleoside analogs induces the abortion of DNA synthesis because phosphodiester bridges can no longer be built to stabilize the double strand.
Nucleoside analogs are pro-drugs. They are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to the effective triphosphate derivatives.

Nucleoside analogs were the first antiretroviral agents on the market. AZT (zidovudine, Retrovir®) was approved for the treatment of HIV infection in 1987. Once-daily dosing is sufficient for many nukes. Overall tolerability is fairly good. However, frequent complaints during the first weeks are fatigue, headache and gastrointestinal problems, which range from mild abdominal discomfort to nausea, vomiting and diarrhea. The gastrointestinal complaints are easily treated symptomatically (see chapter on Management of Side Effects).

Nucleoside analogs can cause a wide variety of long-term side effects, including myelotoxicity, lactate acidosis, polyneuropathy and pancreatitis. Many metabolic disorders, especially lipodystrophy, are also attributed to nucleoside analogs (Galli 2002). Long-term side effects that are probably related to mitochondrial toxicity were first described in 1999 (Brinkmann 1999). Mitochondrial function requires nucleosides. The metabolism of these important organelles is disrupted by the incorporation of false nucleosides (the drugs) leading to mitochondrial degeneration. More recent clinical and scientific data indicate that there are probably considerable differences between individual drugs with regard to mitochondrial toxicity. Agents like d4T or ddl are more toxic than abacavir or 3TC and are therefore not used in HIV treatment today and ddC has disappeared entirely. For further details see chapter on Mitochondrial Toxicity of Nucleoside Analogs.

Nucleoside analogs are eliminated mainly by renal excretion and do not interact with drugs that are metabolized by hepatic enzymes. There is therefore little potential for interaction. However, ribavirin, used in the treatment of hepatitis C, can reduce intracellular phosphorylation of AZT or d4T (Piscitelli 2001). In patients with renal failure, the dosage of nucleoside analogs has to be adjusted. AZT and d4T are thymidine analogs, while FTC and 3TC are cytidine analogs. Combinations containing AZT plus d4T or FTC plus 3TC are therefore pointless since these drugs compete for the same attachment pocket. There is a high degree of cross-resistance between NRTIs (see chapter on Resistance).

Individual agents

Abacavir (ABC, Ziagen®) is a guanosine analog. Monotherapy studies showed this drug to lower viral load by approximately 1.4 logs within 4 weeks, but that resistance develops rapidly (Harrigan 2000). Abacavir is phosphorylated intracellularly to carbovir triphosphate, which has a long half-life (Harris 2002). In October 2004, following larger studies, abacavir was licensed for once-daily therapy (Clumeck 2004, Moyle 2005, Sosa 2005).

ABC+3TC is comparable in efficacy to either AZT+3TC (DeJesus 2004) or d4T+3TC (Podzamczer 2006). In combination with AZT+3TC (Trizivir®, see section on Triple Nukes), abacavir was less effective than efavirenz (Gulick 2004) or indinavir (Staszewski 2001). In randomized studies, a switch from a successful PI- or NNRTI-containing therapy to abacavir plus two NRTIs proved relatively safe (Clumeck 2001, Katlama 2003, Martinez 2003, Bonjoch 2005) although there is an increased risk of virological failure, especially in extensively pretreated patients (Opravil 2002, Martinez 2003, Bommenell 2011). Resistance can also develop rapidly with the combination ABC+TDF+3TC (see section on Triple Nukes).

With respect to mitochondrial toxicity, abacavir seems to compare favorably to other NRTIs. In comparison with d4T, the risk of lipodystrophy is lower (Podzamczer 2006). Moreover, switching from d4T to abacavir led to improvements in subjects with existing lipodystrophy (Carr 2002, John 2003, Moyle 2003, McComsey 2005). Improve-
ment was associated with an increase in mitochondrial DNA as shown in *in vitro* studies (Hoy 2004, Martin 2004, McComsey 2004+2005).

One drawback to the use of abacavir is the risk of hypersensitivity reaction (HSR). HSR occurs in 7–11% of patients. On re-exposure after stopping ABC due to HSR, it can be fatal. Cases of severe HSR have been reported after only a single abacavir dose (De la Rosa 2004) or after treatment re-initiation despite prior tolerability (El-Sahly 2004). A genetic predisposition exists. 80% of cases of HSR occurs in patients with the HLA B*5701 allele (Mallal 2002, Hetherington 2002). The predictive value of the HLA test was proven in the large PREDICT trial with approximately 2000 patients (Mallal 2008), and the assay is now obligatory prior to starting abacavir. However, clinical HSR cases without the HLA B*5701 allele have been observed on rare occasions. Once the problem with HSR was largely resolved, abacavir came under pressure again in 2008. Cohort studies reported an association between recent use of abacavir and an increased risk of myocardial infarction (Sabin 2008, SMART 2008). However, this was not found by two recent meta-analyses (Cruciani 2011, Ribaudo 2011). Thus, the opinion some experts hold that alternative regimens should be considered for patients with underlying high cardiovascular disease risk (Behrens 2010) may no longer be supportable.

Today, abacavir is mainly used in the combination tablet Kivexa® (US: Epzicom®, see below). The individual agent Ziagen® or the triple nuke Trizivir® (see below) are not frequently used today.

AZT (zidovudine, Retrovir®) was the first antiretroviral agent in 1987 to make it to market. Very early studies that tested AZT monotherapy were able to show a significant survival benefit – in very immunocompromised patients (Fischl 1987). In contrast, two other very large early studies, ACTG 016 and ACTG 019, were not able to demonstrate significant survival benefit in asymptomatic patients, although the risk for progression was significantly reduced in both (Fischl 1990b, Volberding 1990). Even at that time, it was becoming apparent that the success of AZT monotherapy was likely to be limited. The Concorde Study brought AZT into disrepute by showing that there was no long-term benefit of AZT treatment. The higher doses (1500 mg/day) led to considerable myelotoxicity (Fischl 1990). Myelotoxicity should also not be underestimated with the current dosages of 500–600 mg/day; monitoring of the blood is obligatory. Long-term treatment almost always increases the mean corpuscular volume of erythrocytes, which is to some extent a measure of monitoring adherence. AZT is very effective in combination with other ARV drugs. In the nineties, the combination of AZT and 3TC was one of the most frequently used backbones in HIV therapy. AZT has been tested in numerous clinical studies and offers more experience than any other agent (over 20 years).

AZT came under heightened scrutiny when it performed significantly worse than tenofovir in the Gilead 934 study. In this large-scale randomized study, ART-naïve patients were treated with efavirenz plus either AZT+3TC or TDF+FTC. In particular, severe anemia was more frequent on AZT, leading to withdrawal in 5.5% of the cases (Gallant 2006). After 144 weeks, fewer patients on AZT had a viral load of less than 400 copies/ml than on TDF (58% vs 71%). This difference was due in large part to the fact that more patients on AZT withdrew due to adverse events (11% vs 5%). Apart from myelotoxicity including anemia and neutropenia, side effects leading to discontinuation were mainly gastrointestinal complaints such as nausea, usually occurring within the first few weeks of treatment. Moreover, a significant reduction in fat tissue of the extremities while on AZT was observed (Arribas 2009). Many studies have confirmed an improvement of lipoatrophy after switching from AZT to other drugs (see below).
Consequently, in many guidelines AZT is now no longer listed as a preferred first-line drug in treatment naïve patients. Another disadvantage is that AZT needs to be taken twice daily as opposed to most HIV compounds, thereby disqualifying it as being part of once-daily combinations. However, AZT currently remains a component of some ART regimens and transmission prophylaxes as it proves to be valuable especially with regard to resistance. For example, a hypersensitivity to AZT is seen in viral isolates with mutations K65R or M184V. Lack of neurotoxicity and a good CNS penetration are additional advantages.

**ddC (zalcitabine, HIVID®)** was the third NRTI to reach the market in 1992. Limited efficacy, unfavorable pharmacokinetics and side effects led to its withdrawal from the market in June 2006 – a first in HIV therapy.

**ddl (didanosine, Videx®)** was, in 1991, the second NRTI to be licensed. Antiretroviral efficacy of ddl is comparable to AZT as part of triple ART (Berenguer 2008). The introduction of acid-resistant tablets in 2000 improved tolerability significantly. However, ddl is currently used only in very limited situations (Molina 2005) due to toxicity. Gastrointestinal complaints and polyneuropathy are the main side effects. Pancreatitis occurs in up to 10%, and can be fatal. This toxicity is probably dose-dependent. The cause for this is unclear, but could possibly be related to disorders of purine metabolism (Moyle 2004). Special caution should be given to combinations with ribavirin, d4T, hydroxyurea or tenofovir (Havlir 2001, Martinez 2004). Mitochondrial toxicity is greater than with other NRTIs (see chapter on Mitochondrial Toxicity). The dosage needs to be adjusted according to the patient’s weight. If body weight is less than 60 kg, the dose should be reduced from 400 mg to 250 mg. Of note, ddl has to always be taken on an empty stomach.

**d4T (stavudine, Zerit®)** was the second thymidine analog to be introduced after AZT. Although better tolerated (less gastrointestinal complaints) and just as effective as AZT, d4T is hardly ever used nowadays in western industrialized countries. This is mainly due to its long-term toxicities in comparison to other NRTIs, shown in large randomized studies (Gallant 2004, Saag 2004). Use of d4T is associated with lactic acidosis and Guillain-Barré-like syndromes (Mokrzycki 2000, Shah 2003), as well as for lipoatrophy (Mallal 2000, Mauss 2002). Numerous studies have now been published in which substitution of d4T by other NRTIs, particularly abacavir or tenofovir, had positive effects on lipoatrophy and other metabolic disorders (see chapter 6.7). In March 2011, a warning letter was distributed to physicians according that clarified that d4T was indicated only if there were no other options. Duration was to be limited to the shortest possible time and whenever possible switched to other suitable therapy alternatives. There is nothing else to be said.

**3TC (lamivudine, Epivir®)** was licensed in Europe in August 1996 as the fifth NRTI. It is a well-tolerated cytidine analog and part of various fixed-dose combinations such as Combivir®, Kivexa® (US: Epzicom®) and Trizivir®. Its main disadvantage is its rapid development of resistance, and a single point mutation (M184V) is sufficient for compromising its effectiveness. Resistance is likely to develop after only a few weeks (Éron 1995). The full effect of 3TC only emerges in combination with other nucleoside analogs. Large studies such as NUCB 3002 or CAESAR showed a significant clinical benefit when 3TC was added to nucleoside therapy (Staszewski 1997). The M184V point mutation does have advantages: not only does it improve the susceptibility of certain AZT-resistant viruses in some patients but it also impairs viral fitness (Miller 2002). This was demonstrated in a study with monotherapy in patients with the M184V mutation: maintaining 3TC monotherapy was associated with a lower increase in viral load and slower CD4 decline compared to completely stopping ART (see chapter on Salvage). Keeping 3TC as part of a combination despite
proven resistance is therefore sensible in order to conserve the M184V mutation and thus reduce the replicative capacity of HIV, especially when not all the other agents in the regimen are active. The antiviral efficacy of 3TC is the same as that for FTC (Rousseau 2003, Benson 2004). Once-daily dosing is possible although the half-life of 3TC is less than that of FTC (DeJesus 2004). 3TC has also efficacy against hepatitis B viruses, useful in coinfected patients. However, resistance mutations may occur rapidly. In coinfected patients, 3TC should be combined with other HBV drugs.

**FTC (emtricitabine, Emtriva®)** is a cytidine analog. It is biochemically very similar to 3TC, but has a longer half-life. Once-daily dosing is possible, and the drug also has efficacy against HBV. Tolerability is good, while the potential for interactions is minimal (Frampton 2005). FTC seems to have a low affinity for the mitochondrial polymerase so the risk of mitochondrial toxicity is likely to be relatively low. FTC was as effective as 3TC both as monotherapy as well as in combination with AZT (Rousseau 2003, Benson 2004). However, as with 3TC, efficacy is limited by the M184V point mutation. The drug was licensed in 2003 when a randomized, double-blind trial (FTC-301) showed that FTC was clearly more effective and tolerable than d4T (Saag 2004). The combination of TDF+FTC was superior to AZT+3TC in the large GS-934 study, notably in terms of tolerability (Gallant 2006, Arribas 2008). Tolerability was probably in most part due to the second agent (AZT or d4T) and not FTC or 3TC. Post-approval, the ALIZE study confirmed the good long-term tolerability and efficacy of a once-daily combination of FTC+ddI plus efavirenz (Molina 2005). FTC is currently an important component in combination therapy particularly as a fixed partner of tenofovir (Truvada®), with tenofovir and efavirenz (Atripla®) or with tenofovir and rilpivirine (Complera® or Eviplera®). Like with 3TC, the individual agent (Emtriva®) no longer plays a role. Due to the fact that no clinical differences have yet been established between 3TC and FTC, the choice between the two is usually determined by its co-medication (abacavir, tenofovir, AZT).

**TDF (tenofovir, Viread®)** acts as a false building block similar to nucleoside analogs, targeting the enzyme reverse transcriptase. However, in addition to the pentose and nucleic base, it is monophosphorylated and therefore referred to as a nucleotide analog. A more accurate description of the agent is tenofovir DF (disoproxil fumarate), which refers to the phosphonate form from which the phosphonate component is only removed by a serum esterase, and which is activated intracellularly in two phosphorylation steps (Robbins 1998).

Tenofovir is available as a single agent, but is most often administered in fixed-dose combinations within Truvada®, Atripla® and Complera®. Tenofovir is well tolerated. Side effects in these studies were comparable to the placebo arms. The 903 Study was a double-blind study in which ART-naïve patients were given either tenofovir or d4T (both arms received 3TC and efavirenz). Results showed at least equivalent potency with a significantly reduced incidence of polyneuropathy and lipid changes compared to d4T (Gallant 2004). It has been shown that phosphorylated tenofovir has a low affinity for mitochondrial polymerase (Su 1998). As a result of this convincing clinical data and its licensing in 2001, the drug is now very widely used in antiretroviral therapies. In the 934 study, TDF+FTC were significantly better than AZT+3TC (Gallant 2006, Arribas 2008), particularly due to improved tolerability. Furthermore, tenofovir can help improve lipoatrophy and dyslipidemia (see chapter 6.7). Another advantage is its efficacy against the hepatitis B virus, which resulted in the licensing of this drug for HBV monoinfection. Other areas of use are in vertical prevention and pre-exposure prophylaxis (see appropriate chapters). Some problems have come to light with the more extensive use of TDF. The combination with ddI should be avoided. An unfavorable interaction with atazanavir exists...
that calls for being boosted with ritonavir (Taburet 2004). Efficacy may also be limited in some triple nuke regimens (see section on Triple Nukes).

However, the main problem today with tenofovir is its potential risk of nephrotoxicity (see chapter on HIV and the Kidneys). Nephrotoxicity is reflected by a mostly mild disturbance of renal function (Review: Hall 2011). Fortunately, severe dysfunctions are very rare (Gallant 2008, Scherzer 2012). In a Swiss cohort trial, 46 out of 2,592 patients (1.6%) had to discontinue tenofovir due to renal toxicity, on average within 442 days (Fux 2007). The risk of renal toxicity seems to be higher when tenofovir is combined with boosted PIs (Young 2012). Renal failure can also be observed in the setting of Fanconi syndrome, a defect of the proximal tubular transport (Schaaf 2003, Hall 2011). Patients with renal disease should either not be treated with tenofovir, or receive a lower dose (see chapter on Drugs). Elderly patients and patients with low body weight are particularly at risk (Crane 2006). However, it is so far impossible to predict who is at risk of developing renal dysfunction. According to current data, because it is taken by such a large number of patients, it is important to remain alert and to regularly check renal function of patients on tenofovir, especially of those on long-term therapy. Tenofovir is also associated with bone damage such as osteomalacia (see HIV and Rheumatology).

The choice of nuke backbones

Until now, all classical ART regimens have contained two nucleoside or nucleotide analogs (the “nuke backbone”). This is mainly historical: nucleoside analogs were the first HIV drugs, and when PIs appeared years later, treatment with two nukes was standard. As knowledge has grown about the mitochondrial toxicity of some NRTIs, this concept is now being questioned by an increasing number of experts (see section on Nuke-Sparing). However, data on combinations without NRTIs are still limited, and there are currently no recommendations for such strategies. The most frequently used backbones are TDF+FTC, and with some limitations, ABC+3TC. Both are available in fixed-dose combinations that can be taken once daily. AZT+3TC, the long-standing standard backbone in the nineties, is now considered an alternative.

Table 2.2: NRTI combinations.

<table>
<thead>
<tr>
<th></th>
<th>3TC</th>
<th>ABC</th>
<th>ddl</th>
<th>d4T</th>
<th>FTC</th>
<th>TDF</th>
<th>AZT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ABC</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>ddl</td>
<td>+</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>d4T*</td>
<td>+</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>0</td>
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<tr>
<td>FTC</td>
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<td>0</td>
<td>0</td>
<td>+++</td>
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<tr>
<td>TDF</td>
<td>++</td>
<td>0</td>
<td>–</td>
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<td>+++</td>
<td>0</td>
<td>0</td>
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<tr>
<td>AZT</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

+++ preferred backbones, ++ recommended as alternative, + other alternative, 0 insufficient data, – should be avoided. d4T is only indicated “if other antiretroviral drugs can not be used.” (see above).

TDF+FTC

There is convincing data for the combination of TDF plus FTC (or initially 3TC). In the Gilead 903 Study, the combination TDF+3TC was not only as virologically effective as d4T+3TC, but was also much better tolerated (Gallant 2004). Since the introduction of FTC and the fixed-dose combination tablets of Truvada®, Atripla®, and, more recently, Complera®, tenofovir is almost always co-administered with FTC, and
TDF+FTC is the most frequently-used NRTI backbone. In the Gilead 934 Study (Gallant 2006), enrolling 509 ART-naïve patients, TDF+FTC was tested against AZT+3TC in an open-label design (all patients also received efavirenz). At 48 weeks, a larger proportion of patients in the TDF+FTC arm reached less than 50 copies/ml (80% versus 70%). This was even true for patients with a higher baseline viral load. The significant differences were primarily related to the poorer tolerability of Combivir®, which often resulted in the discontinuation of therapy (9% versus 4%). Virological failure and resistance mutations were approximately equal in both arms and were infrequent. After 144 weeks, lipoatrophy was less frequent in the TDF+FTC arm (Arribas 2008). Providing no further surprises with regard to nephrotoxicity or bone toxicity in the longer term, TDF+FTC should remain the most frequently used backbone.

ABC+3TC

Another frequent backbone is ABC+3TC, which is also available in a fixed-dose combination known either as Kivexa® or Epzicom®. The double-blind randomized CNA30024 Study showed the non-inferiority of ABC+3TC in comparison to Combivir® (DeJesus 2004). In the ABCDE Study, ABC+3TC had the same efficacy as d4T+3TC, but had less toxicity (Podzamczer 2006).

Over the last few years, ABC+3TC has been compared to TDF+FTC in several randomized studies of therapy-naïve patients (Assert, ACTG 5202, HEAT), as well as in treatment-experienced patients (BICOMBO, STEAL) (see following Table).

<table>
<thead>
<tr>
<th>Study Setting, 3rd agent</th>
<th>Major results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART naïve patients</td>
<td></td>
</tr>
<tr>
<td>HEAT</td>
<td>Double-blind (n=688) plus LPV/r</td>
</tr>
<tr>
<td>ACTG 5202 (Sax 2011)</td>
<td>Double-blind (n=1858) plus EFV or ATV/r</td>
</tr>
<tr>
<td>Assert (Stellbrink 2010)</td>
<td>Open label (n=385) plus EFV</td>
</tr>
<tr>
<td>Pretreated patients</td>
<td></td>
</tr>
<tr>
<td>STEAL (Martin 2009)</td>
<td>Open label (n=357) VL &lt;50</td>
</tr>
<tr>
<td>BICOMBO (Martinez 2009)</td>
<td>Open label (n=333) VL &lt;200 &gt;6 months</td>
</tr>
</tbody>
</table>

The table shows that data is not consistent. ABC+3TC were equivalent to TDF+FTC in HEAT and STEAL. In contrast, ACTG 5202, ASSERT and BICOMBO showed some differences to the disadvantage of ABC+3TC. Possibly the virological efficacy of TDF+FTC is better under certain conditions (Sax 2011). Moreover, severe side effects are slightly more frequent under ABC+3TC. However, in studies like BICOMBO and ACTG 5202, HLA testing was not performed, which significantly reduces abacavir HSR. It must be stressed that overall, results of TDF+FTC and ABC+3TC do not vary greatly despite the very different settings. This applies also to the risk of lipoatrophy. At least two studies did not see significant differences between backbones (Curran 2011, McComsey 2011).
AZT+3TC
In the past, international guidelines recommended AZT+3TC as the standard backbone for first-line therapy. There is more experience with this combination than with any other. The resistance profile is favorable: the M184V mutation that frequently develops during 3TC treatment increases sensitivity to AZT. AZT+3TC are usually given as Combivir®. Although the licensing study for Combivir® showed no difference in toxicity (Eron 2000), in our experience the 300 mg AZT dose in Combivir® is too high for some patients and can lead to anemia. In such cases, it is worth trying AZT+3TC as individual components, so that the dose of AZT can be reduced to 250 mg BID.
AZT+3TC has comparable efficacy to d4T+3TC or to AZT+FTC (Benson 2004). The ACTG 384 Study showed superiority of AZT+3TC over d4T+ddI (Robbins 2003, Shafer 2003). This notion did change over time: while early results suggested a lower rate of lipoatrophy (Molina 1999), the development of lipoatrophy with AZT+3TC occurred only slightly later than with d4T+ddI. AZT+3TC was shown to be less effective and less well-tolerated than TDF+FTC in the GS-934 study (Gallant 2006, Pozniak 2006). Another large ACTG study also showed that it was less well-tolerated (Campbell 2011). Compared to ABC+3TC, immune reconstitution may be less impressive (DeJesus 2004). Facing these potential disadvantages and the fact that once daily dosing is not possible, most guidelines no longer recommend AZT+3TC as a preferred backbone in treatment-naive patients.

ddi+3TC (FTC)
In some treatment guidelines, this combination is listed as an alternate for ART naïve patients. Of note, data is limited. Some studies suggest a comparable efficacy (and better tolerability) versus AZT+3TC (Berenguer 2008). However, keeping in mind the long-term toxicity of ddi, we would only recommend ddi+3TC when there are significant reasons to not use TDF+FTC or ABC+3TC.

Poor and not-recommended backbones
It should be noted that the majority of the clinical trials cited above were conducted in treatment-naive patients. In pretreated patients, other backbones may be necessary due to resistance or lack of tolerability. But the following backbones should be avoided whenever possible:
Guidelines explicitly recommend avoiding the previously very popular combination of d4T+ddI. Mitochondrial toxicity is high with both individual agents, and it performs less well than AZT+3TC (Robbins 2003). Considering the choice of NRTIs given today, its use can no longer be justified.

Increased gastrointestinal side effects and the necessity of taking ddi on an empty stomach (AZT is better tolerated taken with a meal) speak against the combination AZT+ddI. Due to their divergent resistance pathways AZT+TDF is not recommended for primary therapy and should be restricted to treatment-experienced patients only. The combination TDF+ddI is relatively toxic and over the years many studies have shown less virologic and immunologic efficacy (see section on Inappropriate Initial Therapies). TDF+ABC are likely to be problematic due to rapid development of resistance. AZT+d4T and FTC+3TC are antagonistic (competitive, as noted above) and should not be employed.
Alternating backbones with regular changes from one backbone to another can not currently be recommended, although initial studies indicate that this strategy is at least not harmful (Molina 1999, Martinez-Picado 2003).

References


Cooper D, Bloch M, Humphries, et al. Simplification with fixed-dosed tenofovir/emtricitabine or abacavir/lamivudine in adults with suppressed HIV replication: the STEAL study, a randomized, open-label, 96-week, non-inferiority trial. Abstract 576, 16th CROI 2009 Montreal.


Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Mechanism of action and efficacy

NNRTIs were first described in 1990. As with the nucleoside analogs, the target enzyme is reverse transcriptase. However, NNRTIs bind directly and non-competitively to the enzyme at a position near but distinct from the substrate binding site for nucleosides. The resulting complex blocks the catalyst-activated binding site of the reverse transcriptase. This in turn can bind fewer nucleosides, slowing down polymerization significantly. In contrast to NRTIs, NNRTIs do not require activation within the cell.

Three first-generation NNRTIs – nevirapine, delavirdine and efavirenz – were introduced between 1996 and 1998. Although studies such as ACTG 241 or INCAS had already clearly demonstrated the superiority of triple therapy compared to double nukes (D’Aquila 1996, Raboud 1999, Conway 2000), the acceptance and use of NNRTIs was rather slow and did not receive the media attention given to the PIs. This was due to the early observation that functional monotherapy with NNRTIs, i.e., the addition of an NNRTI to a failing NRTI regimen, showed practically no effect. There were also initial difficulties in dealing with the development of resistance: the risk of resistance is not only very high, but it can develop very rapidly. Once it occurs, it almost always indicates cross-resistance to the entire class. Waiting too long when there is insufficient suppression of viral load can lead to a point mutation at position 103 (K103N) of the hydrophobic binding site, which is enough to eliminate the entire drug class.

Resistance has even been described in mothers who took a single dose of nevirapine as transmission prophylaxis. In large studies, the frequency of NNRTI mutations following a single perinatal nevirapine dose was between 14% and a worrying 65% (Cunningham 2002, Jourdain 2004, Johnson 2005), which can impair the success of later NNRTI therapies (Lockman 2010, Boltz 2012).

NNRTI resistance appears faster than you might expect, possibly due to their long half-life (Muro 2005). This is why NNRTIs should always be stopped some days before the other drugs if a break in therapy is planned (see chapter on Treatment Interruption). If resistance develops, the drug should be stopped, because the replication capacity of HIV is not reduced as much by NNRTI mutations as by some PI or NRTI mutations (Piketty 2004). In Europe, the prevalence of NNRTI resistance mutations in untreated patients is currently 2–3% (Vercauteren 2009).

Despite the problems with resistance, both randomized and large cohort studies have demonstrated that NNRTIs are extremely effective when combined with nucleoside analogs. The immunologic and virologic potency of NNRTIs in treatment-naïve patients is at least equivalent to that of PIs (Torre 2001, Robbins 2003, MacArthur 2006, Riddler 2008, Daar 2011, DeJesus 2011, Soriano 2011). However, the efficacy of NNRTIs in treatment-experienced patients is probably weaker in comparison to PIs (Yazdanpanah 2004).

The simple dosing and overall tolerability have enabled nevirapine and efavirenz to become important components of ART regimens, which are often ranked higher than those containing PIs. Over the last few years, many randomized studies have demonstrated that it is possible to switch from a PI to an NNRTI if good virological suppression has already been achieved. The efficacy was sometimes even better on NNRTIs than on the continued PI regimen (see chapter When to Switch).

All NNRTIs are metabolized by the cytochrome p450 system (Miller 1997). Nevirapine is an inducer, whereas efavirenz is an inducer and an inhibitor of p450. In the combination of efavirenz plus lopinavir the effects are so strong that dose adjustment is necessary.
So far, no study has provided definitive evidence that one NNRTI is more potent than another. Whereas delavirdine no longer has any significant role (see below) and etravirine merely serves as a salvage drug, nevirapine and efavirenz have a similar standing in most countries (Mbuagbaw 2010). In the 2NN Study (The Double Non-Nucleoside Study), both agents were compared in a large-scale randomized study (Van Leth 2004). A total of 1216 patients received a nuke backbone of d4T+3TC with either nevirapine 1 x 400 mg, nevirapine 2 x 200 mg, efavirenz 1 x 600 mg or efavirenz 1 x 800 mg plus nevirapine 1 x 400 mg. The only significant virological difference was an advantage of the efavirenz arm over the double NNRTI arm, mainly due to higher toxicity in the latter. In the nevirapine arm with 1 x 400 mg, severe hepatic side effects occurred more frequently than in the efavirenz arm; on the other hand, lipids were more favorably influenced in the nevirapine group. Sub-analyses of 2NN have shown that the hepatic toxicity associated with once-daily doses of nevirapine was observed in a single center in Thailand (Storfer 2005). In another randomized trial no increased risk for hepatotoxicity was observed in patients on once-daily nevirapine (Podzamczer 2008). In a subanalysis of the FIRST trial there were no differences with regard to efficacy between nevirapine and efavirenz (van den Berg 2008). In a small study more patients in ultrasensitive assays were below the detection level of 1 copy/ml with nevirapine than with efavirenz (Haim-Boukobza 2011).

2NN, FIRST, as well as switch studies, such as the Spanish Nefa trial (Martinez 2003), demonstrate that the choice of NNRTI should be based mainly on the side effect profiles (see below). Patient-specific factors should be taken into account (Reviews: Mbuagbaw 2010).

Since 2008, etravirine, a second-generation NNRTI can be an option for patients with NNRTI resistance mutations from nevirapine or efavirenz. Another second-generation NNRTI, rilpivirine, was approved in 2011. In large studies comparable efficacy of rilpivirine and efavirenz was shown, however, limited to patients with a baseline viremia of less than 100,000 HIV RNA copies/ml (see below).

**Individual agents: Special features and problems**

**Nevirapine (NVP, Viramune®)** was the first licensed NNRTI in 1997. The combination of nevirapine with AZT+ddl is probably the oldest triple combination of all (D’Aquila 1996). In early randomized studies nevirapine performed comparably to indinavir (van Leeuwen 2003) and better than nelfinavir (Podzamczer 2002). Studies such as ARTEN or NEWART showed that the virological efficacy of nevirapine was comparable to boosted atazanavir (DeJesus 2011, Soriano 2011). However, some studies reported on a higher risk for virological failure with nevirapine compared to lopinavir. This was mainly observed in special situations such as in the setting of concurrent TB therapy or in women who had received single-dose nevirapine transmission prophylaxis (Boltz 2011, Swaminathan 2011, Clumeck 2012).

Over the long term nevirapine is usually well-tolerated. Studies such as Atlantic, 2NN or ARTEN showed favorable lipid changes compared to other drugs (Van der Valk 2001, Van Leth 2004, Podzamczer 2011). In one small randomized trial, lipid profiles improved when efavirenz was replaced by nevirapine (Parienti 2007). Whether these positive effects will have clinical relevance over time and really help prevent cardiovascular events remains to be seen.

Nevirapine causes elevation of liver enzymes in up to 20% of people, which may occasionally be severe. Lead-in dosing is always required. During the first eight weeks on nevirapine, biweekly monitoring of transaminases is recommended. A rash develops in 15–20% and leads to discontinuation in up to 7% of patients (Miller 1997). Prophylactic administration of antihistamines or steroids does not prevent the rash (GESIDA 2004, Launay 2004). In the case of an isolated rash or elevation of trans-
aminases (up to five times the upper limit of normal), treatment can usually be continued but use caution if both occur simultaneously. It is recommended to stop treatment if a rash occurs together with even a slight elevation of transaminases (>2-fold ULN). It is important to note that hepatic toxicity may occur even after several months (Sulkowski 2002). Patients with chronic hepatitis are at higher risk, as are women with low body weight (Sulkowski 2000, Sanne 2005, Kappelhoff 2005). An increased risk has also been reported for patients with good immune status. Women with CD4 T cell counts above 250/µl have a 12-fold elevated risk (11% versus 0.9%) of hepatic toxicity. In men there is an increased risk above 400 cells/µl (6.3% versus 1.2%). Although other studies failed to reveal an association between toxicity and immune status (Manfredi 2006, Wolf 2006, Chu 2010), it is recommended not to use nevirapine in treatment-naïve patients with higher CD4 T cell counts. In contrast, in ART-experienced patients with higher CD4 T cell counts at time of initiation of nevirapine, the risk is not elevated (Mocroft 2007, De Lazzari 2008, Wit 2008). In 2010 the EMA altered the health warning in their publications – a switch to nevapirine is possible at a viral load of <50 copies/ml regardless of CD4 T cell count. There is some evidence for an association between nevirapine-associated hypersensitivity and specific alleles at the HLA-DRB1 (Martin 2005) and polymorphisms in the p-glycoprotein drug transporter MDR1 gene (Haas 2006, Ritchie 2006). However, there is currently no test available to predict hypersensitivity (Yuan 2011). Gamma-glutamyl transpeptidase (GGT) elevations are very common, which may subject patients to false appearances of excess alcohol consumption.

After several studies in both treatment-naïve and -experienced patients (Arasteh 2011, Gathe 2011), a nevirapine extended-release (NVP XR) formulation was approved in 2011. This now allows once-daily dosing. Of note, patients should know that the XR tablets are formulated in a non-digestible cellulose-based matrix, which may be seen in the feces. These softened tablet remnants may sometimes resemble whole tablets, but lab testing had shown that the remnants are inactive ingredients. Thus, there is no need to worry when patients observe tablets in their stool.

**Delavirdine (DLV, Rescriptor®)** was, in April 1997, the second NNRTI to be licensed by the FDA. Due to the pill burden and the required three times daily dosing, delavirdine is currently rarely prescribed. Delavirdine is not licensed in Europe where, in 1999, an application for licensure was rejected due to insufficient efficacy data. Although delavirdine may be as effective as other NNRTIs (Conway 2000), rash probably occurs more frequently (30%) than with other NNRTIs. Delavirdine increases plasma levels of various PIs, including saquinavir (Harris 2002). However, use of DLV as a strategy for boosting has not been widely explored. Even in the US where it is approved, use (and helpful real life data) is almost non-existent.

**Efavirenz (EFV, Sustiva®, Stocrin®, also in Atripla®)** was the third NNRTI to be approved, and the first for which it could be shown that NNRTIs were at least as effective and maybe better than PIs in untreated or only slightly treatment-experienced patients. In particular, the 006 Study showed superiority of efavirenz over indinavir (Staszewski 1999). Since then efavirenz has often been compared to other drugs and has usually done well. In ACTG 5095, efavirenz in combination with AZT+3TC was better than abacavir (Gulick 2004); in ACTG 384 it was better than nelfinavir (Robbins 2003, Shafter 2003); and in AI424-034 and ACTG 5202 it was at least as effective as atazanavir and atazanavir/r respectively (Squires 2004, Daar 2011). In ACTG 5142, efavirenz appeared to be superior to lopinavir/r although resistance mutations were more frequently observed in the efavirenz arm (Riddler 2008).

In many guidelines, efavirenz is among the preferred drugs for treatment-naïve patients. However, there are some problems with its use: CNS side effects are typical...
for efavirenz, which is recommended to be taken in the evening before going to sleep. Patients should be warned about these side effects, which usually include dizziness and numbness, but when taken before bed may also manifest as vivid dreams or even nightmares. In addition, patients should be warned about potentially hazardous tasks such as driving or operating machinery. The side effects probably correlate with high plasma levels (Marzolini 2001). Black patients in particular seem to have a genetic predisposition to the CNS effects (Haas 2004, Wyen 2008). Efavirenz disrupts sleep architecture (Gallego 2004). In one study, after four weeks of treatment with efavirenz, 66% of patients complained of dizziness, 48% of abnormal dreams, 37% of somnolence and 35% of insomnia (Fumaz 2002). Although these symptoms seem to resolve during the course of treatment, they may persist in about one fifth of patients (Lochet 2003). In such cases, efavirenz should be replaced if possible. One study showed that CNS side effects can be reduced by a two-week lead-in dosing, but this approach has not yet been validated (Gutiérrez-Valencia 2009). However, lipids are not as favorably affected as with nevirapine (Parienti 2007). Gynecomastia is seen on efavirenz, which is not only a psychological burden, but can be physically painful as well (Rahim 2004). In such cases, efavirenz should be replaced with nevirapine if possible. Efavirenz is teratogenic and contraindicated in pregnancy. Although, according to a newer meta-analysis, the teratogenic risk is relatively low (Ford 2011), efavirenz should be avoided in women of child-bearing age. In cases of pregnancy or trying to get pregnant, nevirapine should be favored. Since 2007 efavirenz is available in the fixed-dose combination with tenofovir and FTC called Atripla®.

Etravirine (ETV, Intelicence®) is a diarylpyrimidine (DAPY) analog developed by Janssen-Cilag. This new second-generation NNRTI was approved in 2008 for antiretroviral treatment-experienced adult patients. Etravirine works well against wild-type viruses, as well as resistant mutants, among them the classical NNRTI mutations such as K103N (Andries 2004). The genetic resistance barrier is higher than that of other NNRTIs. This appears to be because by changing its confirmation etravirine can bind very flexibly to the HIV-1 reverse transcriptase (Vingerhoets 2005). Mutations at the enzyme binding site therefore hardly affect the binding and therefore the potency of this NNRTI (Das 2004). The reduction of etravirine activity by resistance mutations appears to occur slower in patients on a nevirapine-failing regimen compared to efavirenz (Cozzi-Lepri 2012).

In Phase I/II studies, etravirine lowered viral load by an average of 1.99 logs in treatment-naive patients after only one week (Gruzdev 2003) and by 0.89 logs in the presence of NNRTI mutations (Gazzard 2003). In C233, a large Phase II trial on 199 patients with NNRTI and PI mutations, who had previously been intensively treated, the viral load was significantly lower than the placebo arm after 48 weeks (TMC125 Writing Group 2007). Another Phase II study (C227) brought a setback: etravirine was compared with an investigator-selected PI in NNRTI-resistant, PI-naive patients. In an unplanned interim analysis, patients receiving etravirine demonstrated suboptimal virological responses relative to the control PI and trial enrolment was stopped prematurely (Ruxrungtham 2008). The sponsor argued that in this study baseline resistance was higher than expected. The formulation of etravirine used then also showed poor bioavailability, which has since been improved (Kakuda 2008). Up to now there is no evidence of a correlation between pharmacokinetic data and virological success (Kakuda 2010).
Two large studies, DUET-1 and -2, led to the approval of etravirine. In these double-blind, placebo-controlled, Phase III trials, patients on failing antiretroviral therapy with resistance to currently available NNRTIs and at least three primary PI mutations were randomly assigned to receive either etravirine or placebo, each given twice daily with darunavir/ritonavir, investigator-selected NRTIs, and optional T-20 (Lazzarin 2007, Madruga 2007). After 96 weeks, 57% of patients on etravirine achieved a viral load of less than 50 copies/ml compared to 36% on the placebo arm (Katlama 2010). However, the overall effect of etravirine decreased with an increasing number of NNRTI resistance mutations. As with all ARVs, etravirine needs active partner agents to develop full efficacy (Tambuyzer 2010, Trottier 2010).

In most cases, etravirine is well-tolerated (Cohen 2009). In the DUET trials, tolerability was comparable to placebo. Only the typical NNRTI rash was observed more frequently (19% versus 11%) although they were mostly mild (Katlama 2009). In October 2009, FDA issued a warning on a limited number of cases of severe allergies (toxic epidermal necrolysis, Lyell’s syndrome, DRESS syndrome). A switch from efavirenz to etravirine can help reduce CNS side effects and improve lipid profiles (Faetkenheuer 2011, Gazzard 2011, Waters 2011). However, patients who are tolerating efavirenz will see no advantage in the switch (Nguyen 2011).

There does not appear to be any relevant interaction with methadone or with other antiretroviral agents, with one exception: the level of etravirine is lowered significantly when combined with tipranavir (Kakuda 2006). Etravirine, at a dose of 400 mg (2 x 200 mg tablets BID), should be taken with a meal as this increases absorption. Tablets can be dissolved in water.

Etravirine is an important option for patients with NNRTI resistance. Current data suggest that etravirine should always be combined with a boosted PI, preferably darunavir.

**Rilpivirine (RPV, Edurant®, also in Complera® or Eviplera®)** was approved in 2011. Like etravirine, it is also a DAPY NNRTI (Janssen 2005). It has a very long half-life of 40 hours. A Phase IIa study on therapy-naive patients receiving monotherapy for 7 days decreased viral load by an average of 1.2 logs but no dose-dependent effect between 25 and 150 mg was seen (Goebel 2005).

The 25 mg doses were studied vs efavirenz in 1368 ART-naive patients in two Phase III trials (ECHO and THRIVE). At 48–96 weeks a comparable effect with better tolerability was observed (Cohen 2011, Molina 2011). However, resistance as well as virological failure were observed more frequently with rilpivirine (9% vs 5%) (Cohen 2012). Resistance mutations were mainly seen in the NNRTI loci (E138K or K101E) but also in the NNRTI region (Rimsky 2012). Compared to efavirenz, the risk of resistance-associated virologic failure was significantly elevated in highly viremic patients. Thus, the approval of rilpivirine is restricted to treatment naïve patients with a baseline viral load of less than 100,000 copies/ml.

The QT prolongation seen while on rilpivirine observed earlier (at a higher dose), seems to occur less frequently at 25mg (Vanveggel 2009) and the teratogenic risk is small (Desmidt 2009). A parenteral nano-suspension is being investigated, in which ripilvirine levels are achieved via monthly injections, corresponding to a daily dose of 25 mg (Verloes 2008).

Rilpivirine has still not been approved for treatment-experienced patients, despite its effect against most NNRTI-resistant viruses (Anta 2012), so its broader use as the fixed-dose triple combination with TDF+FTC (Complera®) is still impeded. Efforts are being made to apply for an extension of the indication. There is an ongoing GS-106 (SPIRIT) trial investigating a switch from PI-containing regimens to Complera®. Gilead has been instructed by the FDA to run an interactions trial between efavirenz
and rilpivirine (GS-111), as metabolism of rilpivirine is escalated by activating the cytochrome P450 CYP3A system. A certain disadvantage in everyday practice is the requirement that the substance must be taken with food (a meal of at least 500 kcal is necessary) to guarantee sufficient resorption. This can be a problem if patients have irregular daily habits.

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6.2. Overview of Antiretroviral Agents


Protease Inhibitors (PIs)

Mechanism of action and efficacy

The HIV protease cuts the viral gag-pol polyprotein into functional subunits. If the protease is inhibited and proteolytic splicing prevented, non-infectious virus particles will result. With the knowledge of the molecular structure of the protease encoded by the virus, the first protease inhibitors were designed in the early nineties; these agents were modified in such a way that they fit exactly into the active site of the HIV protease (Youle 2007).

Since 1995, protease inhibitors have revolutionized the treatment of HIV infection. At least three large studies with clinical endpoints demonstrated the efficacy of indinavir, ritonavir and saquinavir (Hammer 1997, Cameron 1998, Stellbrink 2000). Although PIs were at first criticized for their high pill burden and side effects (see below), they remain an essential component of antiretroviral therapies. With growing knowledge of the mitochondrial toxicity of nucleoside analogs and through the introduction of easier-to-take PIs, this class of drugs is currently experiencing a renaissance – today, even PI-only regimens are being investigated.

At first, there was competition to establish which PI had superior efficacy. Current data suggest that the differences are not significant enough to completely rule out any members of this class. Exceptions that have since been taken off the market are: the hard gel capsule saquinavir (Fortovase®) and ritonavir on its own as a PI. Boosted PI combinations are more effective than unboosted (see below).

Besides gastrointestinal side effects and pill burden, all PIs used in long-term therapy show tolerability problems – to a greater or lesser extent, all are associated with lipodystrophy and dyslipidemia (Nolan 2003). Other problems include drug interactions, which can sometimes be substantial. Cardiac arrhythmias (Anson 2005) and sexual dysfunction have also been attributed to PIs (Schrooten 2001), although the data does not remain unchallenged (Lallemand 2002).

All PIs are inhibitors of the CYP3A4 system and interact with many other drugs (see chapter on Drug Interactions). Ritonavir is the strongest inhibitor, saquinavir probably the weakest. There is a high degree of cross-resistance between protease inhibitors, which was described even before PIs were put on the market (Condra 1995). With darunavir and tipranavir we have two second-generation PIs effective even in the presence of several resistance mutations (see below).

Why boost PIs?

Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome P450 hepatic enzyme system. Inhibition of these gastrointestinal and hepatic enzymes allows the most important pharmacokinetic parameters of almost all PIs to be significantly increased or “boosted” (Kempf 1997): maximum concentration (Cmax), trough levels (Ctrough or Cmin) and half-life. The interaction between ritonavir and the other PIs simplifies daily regimens by reducing the frequency and number of pills to be taken every day, in many cases independent of food intake. Some PIs can now be used in once-daily regimens.

Boosting with ritonavir is usually indicated by addition of an “/r” after the drug name. Resistance is only rarely observed on boosted PIs, at least in therapy–naïve patients, as the genetic barrier is high. This has been shown not only for lopinavir/r (Hammer 2006), but also for fosamprenavir/r (Eron 2006), atazanavir/r (Mallan 2008), saquinavir/r (Ananworanich 2006) and darunavir/r (Ortiz 2008). Patients with an elevated viral load should therefore receive boosted PIs at the start of therapy. Nelfinavir is the only PI for which boosting with ritonavir is not recommended as plasma levels do not rise significantly.
Boosting can be effective against resistant viral strains due to the elevated drug plasma levels (Condra 2000). However, at least one large randomized study evaluating TDM-guided dose escalation of boosted PIs in almost 200 patients with extensive resistance mutations failed to show a significant benefit with this strategy (Albrecht 2011). Ritonavir boosting is also associated with risks. There is a high degree of variability in plasma levels among individuals. As well as trough levels, peak levels are also elevated, which may lead to more side effects. If in doubt (reduced efficacy, more side effects), plasma levels should be measured in cases of boosting, especially in patients with severe hepatic disease, because the extent of interaction cannot be predetermined for individual cases. Dose adjustment is often necessary.

Table 2.4: Current doses of protease inhibitors with ritonavir boosting.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Pills*/day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>1 x 300/100</td>
<td>1 x 2</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>2 x 600/100</td>
<td>2 x 2</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>1 x 800/100</td>
<td>1 x 3</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>2 x 700/100</td>
<td>2 x 2</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>1 x 1400/200</td>
<td>1 x 4</td>
</tr>
<tr>
<td>Indinavir/r</td>
<td>2 x 800/100</td>
<td>2 x 3</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>2 x 400/100</td>
<td>2 x 2</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>1 x 800/200</td>
<td>1 x 4</td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td>2 x 1000/100</td>
<td>2 x 3</td>
</tr>
<tr>
<td>Tipranavir/r</td>
<td>2 x 500/200</td>
<td>2 x 4</td>
</tr>
</tbody>
</table>

*Number of pills including the ritonavir dose

**Individual agents: Special features and problems**

**Amprenavir** (APV, Agenerase®) was the fifth PI to enter the European market in June 2000. It was replaced by fosamprenavir in 2004 (Telzir® or Lexiva®, see below) and subsequently withdrawn from market.

**Atazanavir** (ATV, Reyataz®) was licensed in March 2004 as the first PI on the market for once daily administration. In treatment-naïve patients, atazanavir was compared to many other agents. Both boosted and unboosted atazanavir proved as effective as efavirenz (Squires 2004, Daar 2011) or nevirapine (Soriano 2011). The CASTLE study, which compared atazanavir/r once-daily with lopinavir/r twice-daily in 883 treatment-naïve patients, proved that virologically atazanavir/r was at least as good or even better with more favorable lipid profiles and better gastrointestinal tolerability (Molina 2008+2010). In 2008 the results of the CASTLE study led to complete approval of atazanavir. Although several studies have shown no difference between boosted and unboosted atazanavir (Malan 2008, Squires 2009), boosting with ritonavir is recommended. Atazanavir is slightly less effective than lopinavir in treatment-experienced patients when it is not boosted (Cohen 2005). However, when boosted atazanavir is comparable to lopinavir, at least when PI resistance is limited (Johnson 2006).

In comparison to first-generation PIs such as lopinavir, atazanavir does not have a negative effect on lipid levels (Review: Carey 2010). Lipids improve when nelfinavir or other PIs are replaced by atazanavir (Gatell 2007, Soriano 2008, Mallolas 2009). However, it is not yet clear, whether improved lipids on atazanavir actually lead to less myocardial infarctions. Contrasting with earlier reports, recent data suggest that boosting atazanavir with ritonavir seems to have some negative effects on lipid levels (Review: Carey 2010). Moreover, current data suggest that there are no differences
compared to newer PIs such as darunavir/r (Aberg 2012) and that lipid levels on atazanavir/r are even worse compared to nevirapine (Podzamczer 2011). Endothelial function that poses a risk for cardiovascular incidence caused by an increase in lipids is not improved by atazanavir (Murphy 2010). This also true for lipodystrophy. There is at least one randomized study showing no beneficial effect on body changes after a switch from other boosted PIs to atazanavir/r (Moyle 2012). In a randomized trial on treatment-naïve patients, compared to the efavirenz group, subjects assigned to atazanavir/r had a trend towards higher mean percentage increase in visceral fat (McComsey 2011).

More than half of patients on atazanavir experience elevated bilirubin levels, which can reach grade 3–4 in approximately one third of all cases (Squires 2004, Soriano 2008). Some patients even develop jaundice. The mechanism for this resembles that of Gilbert’s Syndrome; there is reduced conjugation in the liver. A genetic predisposition has been identified (Rotger 2005). Although the hyperbilirubinemia is understood to be harmless and only few cases of serious hepatic disorders have been published to date (Eholie 2004), liver function should be monitored while on atazanavir. Treatment should be discontinued in cases of significantly elevated bilirubin (> 5–6 times the upper limit of normal).

Unfavorable interactions occur particularly in combination with proton pump inhibitors (see chapter on Drug Interactions). Boosting is generally recommended, particularly for combinations that include NNRTIs, tenofovir or raltegravir, which significantly lower atazanavir levels (Le Tiec 2005).

The primary resistance mutation for this drug is I50L, which does not impair sensitivity to other PIs (Colonno 2003). On the other hand, there are a number of cross-resistant mutations and susceptibility to many viral isolates with moderate PI resistance is reduced (Schnell 2003).

Darunavir (DRV, Prezista®) is a nonpeptidic PI, developed by Janssen-Cilag. Due to its impressive potency in the presence of PI-resistant mutants (Koh 2003), darunavir was initially an important drug for therapy-experienced patients with limited options. In 2008 the license was extended to all HIV-infected patients.

Two Phase II studies, POWER-I (US) and -2 (Europe), brought darunavir to the forefront of attention and sped up the licensing for darunavir in the US in June 2006 and in Europe in February 2007 for therapy-experienced patients. The POWER studies included nearly 600 patients with extensive pretreatment (three classes and an average of 11 drugs) and high resistance (Clotet 2007). Several ritonavir-boosted darunavir doses were tested against a boosted comparison PI. Despite considerable resistance at baseline, in 46% of patients in the 600/100 mg BID group, the viral load fell to less than 50 copies/ml after 48 weeks – a significantly improved result in comparison to the control PI (10%), and a success that had thus far not been seen in this patient group with such limited options. Encouraging results in salvage treatment were also reported from the DUET trials, in which darunavir was combined with etravirine (see above).

In patients with moderate pre-treatment (naïve to lopinavir), darunavir/r was superior to lopinavir/r. In the TITAN study with 595 (lopinavir-naïve) patients, mainly pretreated with PIs, 71% showed a viral load of below 50 copies/ml at 48 weeks compared to 60% on lopinavir (Madruga 2007). Superiority was observed in all patient groups. Virologic failure and resistance against associated agents were significantly less on darunavir. Of note, efficacy was not compromised by the occurrence of PI resistant mutations (De Meyer 2008+2009).

In 2008, the license for darunavir was extended to treatment-naïve patients. The ARTEMIS trial demonstrated comparable efficacy of once-daily darunavir/r compared
to lopinavir/r in this patient population (Ortiz 2008, Mills 2009). Once-daily darunavir/r also showed potential in treatment-experienced patients with no darunavir resistance mutations (De Meyer 2008, Cahn 2011).

Darunavir is well-tolerated. Gastrointestinal side effects are moderate and less severe than with other PIs (Clotet 2007, Madruga 2007). Dyslipidemia and raised liver enzymes do not appear to be significant. Rash, which may occur in up to 5–15% of patients, is usually mild. Relevant interactions occur with lopinavir causing a decrease of plasma levels of darunavir. This combination must be avoided. The same applies for sildenafil and estrogen.

The potency of darunavir is, of course, not unlimited. 11 mutations associated with darunavir resistance were identified in the POWER studies. These mutations are usually located at codons 32, 47, 50 and 87 (De Meyer 2006). With accumulation of at least three mutations, susceptibility to darunavir is reduced (Pozniak 2008). Darunavir and fosamprenavir in vitro susceptibility patterns are very similar. However, predicted incidence of clinically meaningful cross-resistance is low, due to differences in clinical cut-offs, which are higher for darunavir (Parkin 2008). Thus, pre-treatment with amprenavir or fosamprenavir does not appear to compromise efficacy of darunavir. In view of the high resistance barrier, there are several trials currently testing darunavir as monotherapy (see below).

Fosamprenavir (Telzir®, USA: Lexiva®) as a calcium phosphate ester, has better solubility and absorption than its original version, amprenavir. Fosamprenavir was licensed for treatment-naïve and -experienced patients in 2004. The recommended doses are either 1400 mg BID, 700 mg plus 100 mg ritonavir BID or 1400 mg plus 200 mg ritonavir once daily. Once-daily dosing is not recommended for treatment-experienced patients, and, like the unboosted dose, is not licensed in Europe. A recent trial suggested that for once-daily dosing, 100 mg ritonavir is sufficient (Hicks 2009). Several large studies have compared fosamprenavir to other PIs. In treatment-naïve patients, fosamprenavir boosted once-daily was as effective as atazanavir/r in the relatively small ALERT study (Smith 2006). No resistance was found with boosted fosamprenavir even after 48 weeks (MacManus 2004). In the KLEAN study (Eron 2006), fosamprenavir/r twice daily in treatment-naïve patients provides similar antiviral efficacy and control of emergence of resistance as lopinavir/r, each in combination with ABC+3TC. Of note, severe diarrhea and cholesterol elevations were observed at the same frequency in both groups. In treatment-experienced patients in the CONTEXT study, fosamprenavir was not quite as effective as lopinavir/r although the difference was not significant (Elston 2004).

Fosamprenavir currently does not play an important role in HIV medicine. There is no convincing argument for its use. One advantage of the drug is that there are no restrictions with respect to food intake. It is important to note that efavirenz can significantly (probably with clinical relevance) lower plasma levels, as can nevirapine, although this does not occur when fosamprenavir is boosted (Elston 2004).

Indinavir (IDV, Crixivan®) is one of the first PIs, initially very successful in large studies (Gulick 1997, Hammer 1997). Later, in the 006 Study, it was clearly weaker than efavirenz (Staszewski 1999). Its main problem is tolerability. Firstly, it causes nephrolithiasis in 5–25% of patients (Meraviglia 2002) and thus requires good hydration (at least 1.5 liters daily). Unboosted indinavir must be taken three times daily on an empty stomach (Haas 2000). When boosted at 2 x 800/100 mg, indinavir/r side effects increase (Voigt 2002). Specific side effects associated with indinavir include mucocutaneous side effects reminiscent of retinoid therapy: alopecia, dry skin and lips, and ingrown nails. Many patients may also develop asymptomatic hyperbilirubinemia. Although it seems that the dose and toxicity can be reduced in
most patients by boosting and monitoring plasma levels (Wasmuth 2007), indinavir is no longer among the regular choices for therapy.

**Lopinavir/r (LPV, Kaletra®)** was licensed in April 2001 and is so far the only PI with a fixed boosting dose of ritonavir. This increases concentrations of lopinavir by more than 100-fold (Sham 1998). In 2006, the old Kaletra® capsules were replaced by tablets, allowing a pill reduction (Gathe 2008). Lopinavir is still the most frequently prescribed PI worldwide and has also been licensed as once-daily since October 2009 after several studies showed efficacy and tolerability (Molina 2007, Gathe 2009, Gonzalez-Garcia 2010). However, others have suggested a slightly reduced potency of once-daily dosing (Ortiz 2008, Flexner 2010). Lopinavir once-daily is only recommended if the number of PI resistance mutations is low.

In treatment-naïve patients, lopinavir/r was significantly superior to an unboosted regimen with nelfinavir (Walmsley 2002). It was regarded as the preferred PI for years. However, more recently, large randomized trials such as KLEAN, GEMINI, ARTEMIS and CASTLE have shown that there are no significant differences compared to boosted PIs such as fosamprenavir/r (Eron 2006), saquinavir/r (Walmsley 2009), or atazanavir/r (Molina 2008). In ACTG 5142, lopinavir/r was inferior to efavirenz (Riddler 2008), possibly due to lower tolerability.

In treatment-experienced patients, lopinavir/r showed slightly better results than boosted saquinavir (the old Fortovase® formulation) in an open-label randomized trial (MaxCmin2) on a heterogeneous population of treatment-experienced patients. This was particularly true for tolerability, but also with respect to treatment failure (Dragstedt 2005). On the other hand, in two large studies in PI-experienced patients, virologic efficacy of lopinavir/r was not significantly higher than that of boosted atazanavir (Johnson 2006) or fosamprenavir (Elston 2004) – although patient numbers in these studies were rather small. In comparison to darunavir, efficacy was even lower (Madruga 2007, De Meyer 2009).

Development of resistance with lopinavir/r first-line is rare, but is theoretically possible (Kagan 2003, Conradie 2004, Friend 2004). Lopinavir/r has a high genetic barrier to resistance, and it is likely that at least 6–8 cumulative PI resistance mutations are necessary for treatment failure (Kempf 2002). That is why lopinavir is also considered for monotherapies (see below).

A significant concern with lopinavir are the gastrointestinal side effects (diarrhea, bloating) which are probably more frequent on a once-daily dosage (Johnson 2006). In addition, lipodystrophy and often considerable dyslipidemia, have been observed, probably more marked than with atazanavir (Molina 2008, Mallolas 2009), darunavir (Mills 2009) and saquinavir (Walmsley 2009), but not more so than with fosamprenavir (Eron 2006). A number of interactions should also be considered. The dose must be increased in combination with efavirenz and nevirapine, probably also with concurrent administration of fosamprenavir.

**Nelfinavir (NFV, Viracept®)** was the fourth PI on the market. The dose of five capsules BID is just as effective as three capsules TID. Boosting with ritonavir does not improve plasma levels. The most important side effect of nelfinavir is diarrhea, which may be considerable. In comparison to NNRTIs or other PIs, nelfinavir is probably slightly less potent. This was demonstrated with efavirenz (Albrecht 2001, Robbins 2003) and lopinavir/r (Walmsley 2002). A newer formulation (625 mg) that enables a reduction to two capsules BID is produced by ViiV Healthcare and is available in the US. In Europe, Roche has the marketing rights, but nelfinavir no longer plays much of a role in HIV treatment. Consequently, Roche is planning to discontinue the production of Viracept® globally when the marketing authorisation in the EU expires in January 2013.
Ritonavir (RTV, Norvir®) was the first PI for which efficacy was proven on the basis of clinical endpoints (Cameron 1998). However, ritonavir is now obsolete as a single PI, since tolerability is poor (Katzenstein 2000). As gastrointestinal complaints and perioral paresthesias can be very disturbing, ritonavir is now only given to boost other PIs. The “baby dose” used for this purpose (100 mg QD) is better-tolerated. Ritonavir inhibits its own metabolism via the cytochrome P450 pathway. The potent enzyme induction results in a high potential for interactions. Many drugs are contraindicated for concomitant administration with ritonavir. Metabolic disorders probably occur more frequently than with other PIs. Caution should be exercised in the presence of impaired liver function. It is no longer necessary to store ritonavir at cool temperatures thanks to the new Meltrex formulation that came onto the market in early 2010.

Saquinavir (Invirase 500®), previously Invirase®, Fortovase®, was the first PI to be licensed for HIV therapy in December 1995, and is still today one of the few agents with efficacy based on clinical endpoints (Stellbrink 2000). Boosting with ritonavir raises the plasma level sufficiently, as does simultaneous food intake, so saquinavir should be taken with meals. Saquinavir is well-tolerated – there are hardly any serious side effects. The earlier hard gel (Invirase®) and soft gel (Fortovase®) capsules were replaced in 2005 by Invirase 500® tablets, which significantly reduced the number of pills to four a day (Bittner 2005). It is probable that much data from the Fortovase® capsules cannot be easily transferable to the tablets. Newer data from the GEMINI trial compared ritonavir-boosted Invirase 500® tablets to lopinavir/r in 330 ART-naive patients who all received TDF+FTC. There were no significant differences with respect to efficacy at 48 weeks (Walmsley 2009). Some adverse effects such as lipid elevations, particularly triglycerides, were less pronounced with saquinavir, as was diarrhea. However, discontinuation rates due to adverse events were comparable between arms. Thus, it is difficult to clearly mark an advantage over other PIs such as atazanavir, darunavir or lopinavir.

Tipranavir (TPV, Aptivus®) is the first non-peptidic PI licensed in Europe in July 2005 for treatment-experienced patients. As oral bioavailability is only moderate, double the standard ritonavir boosting (McCallister 2004) is necessary, so 2 x 200 mg (BID) has to be used. The plasma levels can also be increased by a high fat meal. Tipranavir shows good efficacy against PI-resistant viruses (Larder 2000). It even has a considerable effect in the presence of resistance mutations such as L33I/V/F, V82A/F/L/T and I84V. However, efficacy is not limitless – with a combination of the above mutations, sensitivity declines significantly (Baxter 2006). RESIST-1 (USA) and RESIST-2 (Europe) were two Phase III studies on 1483 intensively pretreated patients with a viral load of at least 1000 copies/ml and at least one primary PI mutation. All patients received either tipranavir/r or a comparison PI/r, each combined with an optimized therapy according to resistance testing. After 48 weeks, virologic and immunologic response to tipranavir was better than with the comparison PI (Hicks 2006).

A significant problem with tipranavir, apart from dyslipidemia (grade 3–4 increase in triglycerides: 22% vs 13% for the comparison PI), is an increase in transaminases. This is sometimes substantial (grade 3–4: 7% versus 1%) and requires careful monitoring of all patients on tipranavir, especially those coinfected with hepatitis B or C. In treatment-naïve patients, tipranavir/r was less effective than lopinavir/r, mainly due to more adverse events leading to discontinuation (Cooper 2006). In addition, some unfavorable interactions also occur. Plasma levels of lopinavir, saquinavir, atazanavir and amprenavir fall significantly, so that double PI therapy with tipranavir is not recommended. As the levels of AZT, abacavir and etravirine also drop, these
combinations are not recommendable either. Use with delavirdine is contraindicated and ddI has to be taken with a two-hour time delay.

Tipranavir remains an important option in extensively treated patients harboring PI-resistant viruses. Unfortunately, a study that directly compared tipranavir/r to darunavir/r was halted due to slow accrual. Cross-trial comparisons between these drugs should be discouraged as patient populations in the RESIST (tipranavir/r) studies differed considerably from those of the POWER (darunavir/r) trials.

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Entry inhibitors

Mode of action

There are three crucial steps for entry of HIV into the CD4 T cell:
- Binding or attachment of HIV to the CD4 receptor (target of attachment inhibitors),
- Binding to co-receptors (target of co-receptor antagonists),
- Fusion of virus and cell (target of fusion inhibitors).

Every step of HIV entry can theoretically be inhibited. All three drug classes, namely attachment inhibitors, co-receptor antagonists and fusion inhibitors are currently called entry inhibitors. One important difference to other drug classes is that entry inhibitors do not inhibit HIV intracellularly. They interfere early in the replication cycle of HIV. It is speculated that this will lead to a better tolerability of this class.

In May 2003 T-20 was licensed as the first entry inhibitor in Europe and the US. Maraviroc was the first CCR5 co-receptor antagonist and the first oral entry inhibitor in 2007. Numerous other drugs are in the pipeline, but most will not be available soon. T-20 and maraviroc will be discussed in this section, for other entry inhibitors refer to the next chapter, ART 2012/2013.

Co-receptor antagonists

Preface

In addition to CD4 receptors, HIV requires so-called co-receptors to enter the target cell. The two most important ones, CXCR4 and CCR5, were discovered in the mid-1990s (Alkhatib 1996, Deng 1996, Doranz 1996). These receptors, of which there are probably more than 200 in total, are named after the natural chemokines that usually bind to them. Their nomenclature is derived from the amino acid sequence. For CCR5 receptors these are the CC chemokine MIP and RANTES, for CXCR4 receptors it is the CXC chemokine SDF-1.

HIV variants use either the CCR5 or the CXCR4 receptors for entry into the target cell. HIV variants are termed R5-tropic if they use CCR5 as a co-receptor, whereas viruses with a preference for CXCR4 are termed X4-tropic viruses. R5 viruses predominantly infect macrophages (formerly, M-tropic). X4 viruses mainly infect T cells (formerly, T-tropic). Dual-tropic viruses are able to use both receptors. There also exist mixed populations of R5 and X4 viruses.
In most patients, R5 viruses are found in the early stages of infection. X4 viruses, which are probably able to infect a wider spectrum of cell types, usually occur in the later stages of disease. In addition, X4 viruses almost always occur in X4/R5-mixed populations and an exclusive X4 virus population is very rare. The change in tropism is frequently associated with disease progression (Connor 1997, Scarlatti 1997). It is still not completely clear why this happens after several years of infection, although the tropism shift only needs a few small mutations. However, it is possible that X4 viruses are significantly more virulent, but because of their low glycosylation, more immunogenic. X4 viruses are neutralized better by the immune system and it is therefore likely that they only become apparent in the presence of a significant immune deficiency.

In some individuals expression of CCR5 co-receptors on the cell surface is reduced. These individuals are usually healthy. The reduced expression of the receptor is usually due to a defective CCR5 allele that contains an internal 32-base pair deletion (Δ 32 deletion). This deletion appears to protect homozygous individuals from sexual transmission of HIV-1. Heterozygous individuals are quite common (approximately 20%) in some populations. These individuals have a slower decrease in their CD4 T cell count and a longer AIDS-free survival than individuals with the wild type gene (Dean 1996, Liu 1996, Samson 1996). Thus, targeting the interaction between HIV-1 and the CCR-5 receptor appears to be an attractive therapeutic goal to prevent or slow disease progression.

In 2008 the case of a person (the “Berlin” patient) with acute myeloid leukemia and HIV-1 infection was published. This patient underwent stem cell transplantation from a donor who was homozygous for the CCR5 Δ 32 deletion. The patient has remained without viral rebound for more than four years after transplantation and discontinuation of ART. This outcome demonstrates the critical role CCR5 plays in maintaining HIV-1 infection (Hütter 2009, Allers 2011).

In treatment-naive patients, R5 strains are found in 80–90%, compared to only 50–55% in patients with antiretroviral exposure (Hoffmann 2007). The most important predictor of R5 tropism seems to be a higher CD4 T cell count in both naive and antiretrovirally-pretreated patients. A low HIV plasma viremia seems to be associated with R5 tropism only in untreated patients (Moyle 2005, Brumme 2005). In contrast, X4 viruses are almost exclusively found in advanced stages of the disease. When the CD4 T cell count is > 500/µl, they are only found in 6%; at < 25 CD4 T cells/µl, in more than 50% of patients (Brumme 2005).

CCR5 antagonists probably need be given earlier in the course of disease. In the salvage situation, patients often harbor X4 viruses. The role of CCR5 antagonists might lie rather in the substitution of other antiretroviral agents in case of toxicity.

**Testing for co-receptor usage (Tropism testing)**

Since CCR5 blockers are effective only when a predominant R5 virus is present in the patient and co-receptor switch is not systematic, a baseline determination of the co-receptor usage of the virus is mandatory. Tropism testing prior to treatment avoids unnecessary costs and additional risks for the patient. Non-effectivity of CCR5 antagonists may cause regimen frailty and lead to resistance. This is why the development of CCR5 antagonists has brought along a completely new laboratory branch which focuses on predicting the co-receptors mainly or exclusively used by viral population (see the chapter on Resistance).
Several commercial assays have been developed to determine HIV tropism phenotypically, such as Trofile® (Monogram Biosciences), Phenoscript® (VIRalliance) or XtrackC/PhenX-R® (inPheno). These assays amplify the HIV-1 envelope glycoprotein gene sequence from patient plasma samples to produce either replication-competent or replication-defective recombinant viruses. There are now several improved assays on the market. For example, the originally licensed Trofile® assay has been replaced by Trofile-ES®. This assay can detect smaller numbers of X4 virus (ES, enhanced sensitivity), resistant to CCR5 inhibitors, when they constitute a minor subpopulation of virus within a swarm of CCR5-using virus. Several studies have illustrated the potential benefit of the use of the newer, more sensitive tests (Saag 2008, Su 2008).

Consequently, there is a need for the development of tests which are easy and less time-consuming. One technically more simple and economic genotype tropism testing has been validated (Sierra 2007). Presently the focus of research is on the V3 loop of the envelope protein gp120, as this is the region where HIV binds to the co-receptor (Jensen 2003, Briz 2006). However, tropism does not only seem to be defined by the V3 loop sequence – viral isolates with identical V3 loops can differ in tropism (Huang 2006, Low 2007). Nevertheless, at present, genotypic tropism testing seems to be able to substitute the more complex and expensive phenotypic assay (Poveda 2009, Swenson 2011).

With genotypic testing, CCR5 antagonists may be suitable for many patients who have side effects on other agents, as long as the viral load is well suppressed. As mentioned above, phenotypic testing requires a viral load of at least 1000 copies/ml, whereas genotypic testing probably require less virus. At present, great efforts are being made in determining tropism from proviral DNA in patients with a low (even undetectable) viral load. This method investigates the genotype of HIV that is integrated into the genomes of infected cells. First runs show that this is possible and effective (Soulie 2009, Bellecave 2012).
Tropism shift and other consequences
During treatment failure of antiretroviral regimens containing CCR5 antagonists, many patients often show a selection shift to X4 viruses. This shift is mainly due to selections from preexisting pools (Westba 2006). In a pilot study in which patients with X4/R5 mixed populations received maraviroc, CD4 T cells were higher in comparison to placebo (Saag 2009). An X4 shift (induced HIV progression) while on CCR5 antagonists therefore seems very unlikely.

What other consequences could a CCR5 blockade have? Although individuals with a ∆32 gene defect for the CCR5 receptor are usually healthy, there are worries about negative effects of blocking these receptors, i.e., this chemokine receptor must exist for some reason.

Individuals with the ∆32 deletion have been examined in numerous studies to see if they suffer more frequently from illnesses compared to patients without this gene defect. An increased appearance of West Nile viral infection (Glass 2006) or FSME (Kindberg 2008) was greatly discussed, whereas the ∆32 deletion seems to be protective for rheumatism (review: Prahalad 2006). However, a recently published randomized trial did not show a beneficial effect of maraviroc in rheumatoid arthritis (Fleishaker 2012).

Presently the data is so heterogeneous that it is difficult to speak of a distinct association of the gene defect with certain illnesses. However, it is advisable to monitor carefully, as experience with CCR5 antagonists has so far been limited.

Moreover, in theory, docking onto the receptor could cause an autoimmune reaction. However, this has not occurred in testing with monkeys (Peters 2005). Negative effects towards vaccinations have also been discussed (Roukens 2009). An analysis of the complete Phase I/II studies with maraviroc has shown no negative effects on immune function (Ayoub 2007). The initially disquieting report of malignancies in a study with vicriviroc (Gulick 2007) has not been confirmed in any following studies.

Immune modulation with CCR5 antagonists?
Early observations led to the supposition that CCR5 antagonists may be able to serve as immune modulators. Effects of an additional dosage in patients with poor immune constitution have not shown the results hoped for in studies so far (Lanzafame 2009, Stepanyuk 2009, Hunt 2011). A recent meta-analysis found no evidence for a beneficial effect of maraviroc on immune reconstitution (Pichenot 2012). However, there are indications of positive effects on immune activation (Funderberg 2009, Sauzullo 2010, Wilkin 2010+2011) and latent viral reservoir (Gutiérrez 2010). There is little experience outside experimental studies and the results are not yet confirmed.

Individual agents (for unlicensed agents, see chapter 3, ART)
Maraviroc (MVC, Celsentri® or Selzentry®) from Pfizer (now ViiV Healthcare) was the first drug in its class to be licensed for the treatment of HIV infection in September 2007. Maraviroc allosterically binds to CCR5. This means that it does not bind directly to the receptor but induces conformational changes within CCR5 that result in the inhibition of its binding to viral gp120. During maraviroc monotherapy, viral load declines by 1.6 logs after 10–15 days (Fätkenheuer 2005).

Two almost identical Phase III studies led to approval of the drug, MOTIVATE-1 (US, Canada) and -2 (Europe, Australia, US). A total of 1049 treatment-experienced patients with R5-only virus were enrolled (Gulick 2008, Fätkenheuer 2008). Patients had been treated with or had resistance to three antiretroviral drug classes and had a baseline viral load of more than 5000 copies/ml. Patients were randomly assigned to one of three antiretroviral regimens consisting of maraviroc once-daily, maraviroc BiD or placebo, each of which included OBT – agents such as darunavir, etravirine
or raltegravir were not allowed. At 48 weeks in both studies more patients in the maravirocin arms were below 50 copies/ml (46% and 43% versus 17% with placebo). A treatment benefit of maravirocin over placebo was also shown in patients with a high viral load and multiple resistance mutations (Fätkenheuer 2008). Results remained the same after 96 weeks (Hardy 2010). Tolerability of maravirocin was excellent and did not differ from that of placebo. In addition, the shift to X4 viruses in those with no virological success had no negative effects.

Maravirocin has also been tested in treatment-naïve patients (Cooper 2010, Sierra-Madero 2010). In the MERIT study, a total of 721 patients randomly received AZT+3TC plus either efavirenz or maravirocin BID (the arm with maravirocin QD was prematurely closed in 2006 due to lower efficacy). After 48 weeks, 65.3% of patients in the maravirocin arm reached a viral load below 50 copies/ml, compared with 69.3% in the efavirenz arm. Virological failure was more frequent on maravirocin (11.9% versus 4.2%). Although the CD4 T cell increases were significantly more pronounced on maravirocin, the study failed to show non-inferiority of maravirocin compared to efavirenz. Of note, there were significant differences seen between study populations in the northern versus southern hemisphere in this worldwide trial. Response rates proved almost equal in northern hemisphere countries, but not as good south of the equator. In addition, a retrospective analysis revealed that at least 4% of the patients in the maravirocin arm had experienced a tropism shift from R5 to dual tropic virus between screening and baseline. In these patients with dual tropic virus, response rates were very poor. Would a better and more sensitive test have been able to demonstrate a more relevant difference between maravirocin and efavirenz? A retrospective analysis using the enhanced Trofile assay, in which no differences were observed, seems to back this argument (Cooper 2010, Swenson 2011). On the basis of this data the FDA extended the license for maravirocin to therapy-naïve patients in November 2009. However, the available data was not sufficient for EMA to permit such an extension in indication.

As in the MOTIVATE studies, maravirocin’s tolerability was excellent in the MERIT study. The discontinuation rates due to adverse events were significantly lower than with efavirenz (4.2% vs 13.6%) and lipid profiles were better (MacInnes 2011). There seems to be no liver toxicity as seen with aplavirocin, a CCR5 antagonist whose development was halted in 2005, not even in those with existing liver damage (Abel 2009). What about the efficacy of maravirocin in the presence of non-R5 viruses? In a double-blind randomized Phase II study on 113 patients the effect was, as expected, moderate. There was no antiviral effect compared to placebo. However, CD4 T cells improved significantly in those on maravirocin despite the lack of virologic efficacy (Saag 2009). With regard to resistance, only limited data exist to date. Mutations in the gene regions coding for the V3 loop of the envelope protein gp120 may lead to complete resistance to maravirocin. This may occur by de novo acquisition of mutations allowing the virus to use the CXCR4 receptor or via “true” resistance. The latter may occur in viral isolates that remain R5 tropic. A shift to X4 tropism is not necessary as resistance may happen via an increased affinity of the viral envelope for unbound CCR5 molecules or through an ability of the viral envelope to use compound-occupied receptors for entry (Westby 2007, Lewis 2008). It seems that the resistance barrier for true maravirocin resistance in R5 viruses is high (Jubb 2009).

In practice it is important that the recommended dosage of maravirocin is adjusted depending on the concomitant therapy (Abel 2005). With boosted PIs (except for tipranavir) the usual dosage of 2x300 mg is halved, while with efavirenz (or other enzyme inducers such as rifampicin or carbamazepin) it is doubled. No adjustment is required with integrase inhibitors such as raltegravir and elvitegravir (Andrews 2010, Ramanathan 2010).
Despite excellent tolerance, application of maraviroc still remains relatively limited, as obstacles such as requirement for tropism testing, restricted indication (in Europe) and slightly complicated dosage still stands in the way. Reluctance may change if the nuke-sparing strategies with maraviroc prove successful (see Nuke-Sparing).

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Fusion inhibitors

Fusion inhibitors prevent the final step of entry of HIV into the target cell. The fusion of virus and cell is complex and not completely understood. Simplified, it seems that binding to the CD4 and to the co-receptor induces conformational changes in the gp41, the transmembrane subunit of the viral envelope protein. In the course of these rearrangements, the N-terminal fusion peptide of gp41 translocates and inserts into the target cell membrane. A proposed extended conformation of the gp41 ectodomain, with its fusion peptide thus inserted and the transmembrane anchor still in the viral membrane, has been called the “pre-hairpin intermediate”. This is the target of fusion inhibitors, including T-20 (Root 2001).

Individual agents

T-20 (Enfuvirtide, Fuzeon®) is the prototype of the fusion inhibitors. T-20 was licensed in Europe and the US in May 2003 for the treatment of HIV-1 infection in antiretroviral-experienced adults and children over 6 years of age. It is a relatively large peptide comprised of 36 amino acids, and therefore needs to be administered by subcutaneous injection. It binds to an intermediate structure of the HIV gp41 protein, which appears during fusion of HIV with the target cell.

Initially, HIV-infected patients were given T-20 monotherapy intravenously. Antiviral activity was dose-dependent, and at the higher dose of 100 mg BID, the viral load was reduced by almost 2 logs (Kilby 1998+2002). In early studies of the subcutaneous application, an effect on viral load was still evident in one third of patients after 48 weeks.

Two Phase III studies led to the licensing of T-20. TORO 1 (T-20 versus Optimized Regimen Only) enrolled 491 extensively pretreated patients in North America and Brazil, most with multiresistant viruses. In TORO 2, 504 patients in Europe and Australia were enrolled. Patients in both studies on an optimized ART regimen either received 90 mg T-20 BID subcutaneously or none at all (Lalezari 2003, Lazzarin 2003). In TORO-1, the reduction in viral load was 0.94 logs better with T-20 than optimized therapy without T-20. In TORO-2 this difference was 0.78 logs (Nelson 2005). A strong impact on viral load was also seen with tipranavir, darunavir, maraviroc or raltegravir. In all large studies evaluating these agents (RESIST, POWER, MOTIVATE, BENCHMRK), the additional use of T-20 was of significant benefit. If at least two active substances are not available, the option of T-20 should be discussed with the patient. Small pilot studies such as INTENSE or INDEED suggest that T-20, given as “induction”, i.e., in the first weeks of a new salvage therapy, lowers the viral load more rapidly (Reynes 2007, Clotet 2008).

The success of T-20 therapy should be monitored early on, particularly in view of the cost. Patients without a decrease in viral load of at least one log after 8–12 weeks will not benefit and can be spared the required twice-daily injections. It is also not recommended to inject the full daily dose of T-20 once a day: although 180 mg QD has the same bioequivalence (as measured by AUC) to the standard 90 mg BID, at least one study has shown a trend towards a smaller decrease in viral load with the QD dose that was clearly associated with lower trough levels (Thompson 2006).

One observation in the TORO studies was the increased frequency of lymphadenopathy and bacterial pneumonia in those on T-20 (6.7/100 versus 0.6/100 patient years) (Trottier 2005). Septicemia also occurred more often on T-20, but the difference was not significant. The reason for the increased rate of infections remains unclear, but binding of T-20 to granulocytes has been suspected. Substantial side effects remain constant (98% in the TORO studies), and over the course of therapy, severe local skin reactions occur at the injection site. These can be particularly painful and can result in interruption of therapy: 4.4% of cases in the TORO studies. In our
experience of everyday clinical treatment, therapy is interrupted frequently due to these skin problems (see section on Side Effects). Unfortunately the development of a bio-injection system in which T-20 is pressed into the skin was halted. Resistance mutations develop relatively rapidly on T-20, but seem to reduce viral fitness (Lu 2002, Menzo 2004). Receptor tropism of the virus seems to be not significantly affected. There are some changes to a short sequence on the gp41 gene, causing reduced susceptibility to T-20, which is due to simple point mutations (Mink 2005). In contrast, viruses resistant to NRTIs, NNRTIs and PIs are susceptible to T-20 (Greenberg 2003). As it is a relatively large peptide, it induces antibody production. This does not seem to impair efficacy (Walmsley 2003). More disturbing is the fact that in a large TDM study there was a very large interpatient variability and extremely low plasma levels were often found (Stocker 2006).

In summary, patients with a well-controlled viral load or who still have options with classical ART do not require T-20. For salvage therapy the drug seems to be very valuable in individual cases. However, T-20 probably has only a minor role to play in the future of HIV treatment. Many patients have already successfully replaced T-20 with newer oral antiretrovirals like raltegravir (DeCastro 2009, Grant 2009, Santos 2009, Talbot 2009, Gallien 2011).

Increasing efficacy of ART and/or emptying latent reservoirs with T-20, as first reports suggested (Lehrmann 2005, Molto 2006), seem unlikely now (Gandhi 2010, Joy 2010). The price also remains significant — ART costs can skyrocket with the addition of T-20, the sponsor maintaining that it is one of the most complicated drugs it has ever manufactured.

References


**Integrase inhibitors**

**Mode of action**

Integrase, along with reverse transcriptase and protease, is one of the three key enzymes in the HIV replication cycle. It is involved in the integration of the viral DNA into the host genome and is essential for the replication of HIV (Nair 2002). It is of note that there is no integrase in human cells so selective inhibition of this enzyme that does not induce side effects seems possible. There are at least four steps leading to the integration of viral DNA (Review: Lataillade 2006). All these steps may be theoretically inhibited by different integrase inhibitors.

Briefly, these steps are:

1. **Binding** of the integrase enzyme to viral DNA within the cytoplasm. This results in a stable viral DNA-integrase binding complex (pre-integration complex, PIC). This step can be inhibited by binding inhibitors such as pyrano-dipyrimides.

2. **3' Processing**. The integrase removes a dinucleotide at each end of the viral DNA producing new 3' hydroxyl ends within the PIC. This step can be inhibited by 3' processing inhibitors such as diketo acids.

3. **Strand transfer**. After the transport of the PIC from the cytoplasm through a nuclear pore into the cell’s nucleus, integrase binds to the host chromosomal DNA. By doing this, integrase mediates irreversible binding of viral and cellular DNA. This step can be inhibited by strand transfer inhibitors (STIs) such as raltegravir or elvitegravir.

4. **Gap repair**. The combination of viral and cellular DNA is a gapped intermediate product. The gap repair is done by host cell DNA repair enzymes. Integrase seems not to be necessary in this last step, which can be inhibited by gap repair inhibitors such as methylxanthines.

For almost a decade, the development of integrase inhibitors was slow. This was largely because of a lack of good lead compounds and reliable in vitro screening assays that incorporate each of the integration steps (Lataillade 2006). Only after 2000 did development progress and the principle of strand transfer was elucidated (Hazuda 2000). Since 2005, numerous clinical studies have evaluated integrase inhibitors (mainly strand transfer inhibitors). In December 2007, raltegravir was licensed as the first integrase inhibitor for the treatment of HIV-infected patients.

As with other antiretroviral drug classes, some questions remain unanswered. In August 2012, the FDA also approved elvitegravir, in combination with TDF+FTC and the pharmacoenhancer cobicistat (applications for marketing approval are pending in Australia, Canada and Europe) in treatment-naïve adults.

Although very well-tolerated during the first years of therapy, little is known about long-term toxicity of integrase inhibitors. Genetic resistance barriers, relatively low with Raltegravir and elvitegravir, may also be an important issue. Increased viral suppression was observed with treatment-experienced patients on boosted PIs (viral load below the limit of detection) when switching to raltegravir, especially in those with existing resistance (Eron 2009). There is also evidence for within-class cross-resistance. Future integrase inhibitors need to bind differently to enzymes. There is probably no need for “me-too” integrase inhibitors (Serrao 2009). Dolutegravir may meet these requirements (see next chapter). Problems also exist with the measurement of plasma levels (Cattaneo 2012). As soon as integrase inhibitor resistance develops, the agent should be stopped. This way, further resistance mutations (Wirden 2009) can be avoided, as well as unnecessary costs.
6.2. Overview of Antiretroviral Agents

Individual agents

**Raltegravir (RAL, Isentress®)** is a naphthyridine carboxamide derivative that inhibits the strand transfer step of integrase (Hazuda 2000). Raltegravir has a wide range of efficacy for R5 and X4 tropic viruses, and inhibits HIV-2 replication. During a 10-day monotherapy, viral load declined by 1.7–2.2 log (Markowitz 2006).

The encouraging results of an early Phase II study in extensively pre-treated patients (Grinsztejn 2007) were confirmed by two large Phase III studies which led to approval of raltegravir. In BENCHMRK-1 and -2, a total of 699 pretreated patients with triple-class resistance were randomized to raltegravir 400 mg BID or placebo, each combined with an optimized background therapy (Cooper 2008, Steigbigl 2008). After 16 weeks, 79% (versus 43%) of patients showed a viral load below 400 copies/ml. Even in patients initially without an active substance in their background therapy in genotypic assays, the success rate reached 57% (versus 10%). The effects were sustained beyond 144 weeks (Eron 2010).

Raltegravir has also been effective in treatment-naïve patients. The encouraging data from an early Phase II study (Markowitz 2009) were confirmed by a large Phase III study in which 563 patients received either raltegravir or efavirenz (Lennox 2009): at week 48, rates of patients achieving undetectable plasma viremia (<50 copies/ml) were 86% and 82%, respectively. Tolerability was better and the effects were maintained over 156 weeks (Rockstroh 2011). In September 2009, raltegravir was approved for first-line therapy.

Tolerability of raltegravir has so far been excellent. In BENCHMRK, raltegravir side effects were comparable to placebo. Apart from some anecdotal reports of rhabdomyolysis, hepatitis, rash and insomnia (Gray 2009, Santos 2009, Dori 2010, Tsukada 2010), frequently appearing side effects with raltegravir have not been seen. Raltegravir seems to be safe, including in those with liver disease (Rockstroh 2012). Expected autoimmune diseases observed in animal testing have so far not been clinically confirmed (Beck-Engeser 2010). In patients with renal impairment, no dosage adjustment is required. There are no data for pediatric or pregnant patients (Taylor 2011). Due to its excellent tolerability, raltegravir is currently being evaluated in the setting of nuke-sparing strategies (see below).

The fact that viral load decreased more rapidly in the first weeks in patients taking raltegravir compared to those taking efavirenz led to some speculations about higher potency (Murray 2007). Several experimental studies looked at strategies aimed at achieving viral eradication with raltegravir intensification (see chapter on Eradication). However, some experts believe that the faster response on raltegravir-based regimens is not a matter of potency, but rather due to its unique effect of blocking integration of the HIV genome (Siliciano 2009).

There are at least two common resistance pathways, via mutations Q148K/R/H or N155H. Both mutations are localized within the catalytic core of the integrase (Grinsztejn 2007, Malet 2008). A third pathway seems to be Y143 (Delelis 2010). Resistance may occur quickly on a failing regimen. In an early Phase II study virological failure occurred in 38/133 (29%) patients on raltegravir. In 34/38 patients, either the N155H or the Q148K/R/H mutation occurred after only 24 weeks (Grinsztejn 2007). In a study of a combination with darunavir/r in treatment-naïve patients, 5 out of 112 patients developed resistance mutations against raltegravir (Taiwo 2011). Thus, the resistance barrier of raltegravir seems not very high although it is higher than that for NNRTIs. A few days of monotherapy are not enough to select resistance mutations as is the case with nevirapine (Miller 2010). There is evidence for cross-resistance with elvitegravir (DeJesus 2007, Garrido 2012). Transmission of raltegravir-associated resistance mutations has been reported (Boyd 2011, Young 2011).
The randomized SWITCHMRK studies (Eron 2010) with more than 700 patients on a lopinavir/r-based ART with a viral load below 50 copies/ml for at least three months, showed that switching may not always be safe. Switching to raltegravir showed a better lipid profile, but did not demonstrate non-inferiority with respect to HIV RNA <50 copies/ml at week 24 vs remaining on lopinavir/r. Again, these results provide evidence for a possibly lower resistance barrier of integrase inhibitors compared to boosted PIs. Even if the smaller Spanish SPIRAL study did not confirm these results (Martinez 2010), switching from boosted PIs to other agents should be considered with care. Switching from T-20 to raltegravir, however, is probably safe (De Castro 2009, Grant 2009, Gallien 2011).

The recommended dosage of raltegravir is 400 mg BID. Once daily dosing is not possible, as the QDMRK study has shown (Eron 2011). Only limited data exist regarding interactions. Raltegravir is not an inducer or an inhibitor of the cytochrome P450 enzyme system. Clinically relevant interactions are not expected (Iwamoto 2008, Anderson 2008). During co-medication with rifampicin, levels of raltegravir may be reduced. In contrast, raltegravir plasma concentration increases with omeprazole coadministration in healthy subjects; this is likely secondary to an increase in bioavailability attributable to increased gastric pH (Iwamoto 2009). Taken together, there is no doubt that raltegravir has become an important option for patients harboring resistant viruses. Given its excellent efficacy and tolerability, application of raltegravir is also indicated for treatment-naive patients. A disadvantage is that raltegravir must be taken twice daily. More data is required for a wider application of raltegravir regarding long-term treatment, resistance and TDM.

**Elvitegravir** (ELV, part of Stribild®) is the second integrase inhibitor which was approved by the FDA in August 2012. Stribild®, referred to as “Quad” prior to FDA approval, combines four Gilead compounds in one daily tablet: elvitegravir, the pharmacoenhancer cobicistat and TDF+FTC. Since applications for marketing approval of Stribild® are still pending in Australia, Canada and Europe, the drug will be discussed in the next chapter.

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6.3. ART 2013/2014: The Horizon and Beyond
CHRISTIAN HOFFMANN

Over the past few years, several important new drugs have been licensed, namely the PI darunavir, the NNRTIs etravirine and rilpivirine, the integrase inhibitor raltegravir and the CCR5 antagonist maraviroc. Almost all HIV-infected patients can now be treated with a virologically successful regimen, even those with multiple resistance mutations. There are very few “untreatable” patients. However, despite this considerable progress, there is an urgent need for new drugs. This is not just true for patients with multiresistant viruses awaiting new treatment options. Significant problems related to long-term toxicity and adherence are anticipated for all therapies that will presumably need to span decades, as eradication of HIV is still out of reach. As a result, new drugs are needed that are easier to take, with high genetic barriers to development of resistance, and above all less toxic. To reach the goal of eradication, new drugs need to be more potent and even less toxic than those available today. The following overview of agents that could make it to the clinic based on current data (April 2012) does not claim to be complete.

New pharmacoenhancers (PKEs)

Many antiretroviral agents, among them almost all PIs, but also some new drugs such as elvitegravir, have to be boosted in order to enhance their pharmacokinetics. For more than a decade, ritonavir has been the only reliable option for boosting. At CROI in 2009, new PKEs were introduced for the first time that could challenge ritonavir’s booster monopoly. The advantages of these new agents inhibiting the CYP3A system is that they have no antiviral effect and thus would not cause resistance. Obviously, there are few reports yet about long-term side effects and the effects of such a total inhibition of enzyme systems.

Cobicistat (GS-9350) is a PKE developed by Gilead, which showed similar booster effects to ritonavir in first clinical PK studies (German 2009). In a randomized Phase II trial with 79 ART-naive patients who had received atazanavir plus TDF+FTC, effects were comparable to ritonavir (Elion 2011). Cobicistat has also been developed in a QUAD pill that contains the four Gilead agents tenofovir, FTC, the integrase inhibitor elvitegravir and cobicistat. In a first Phase II double-blind trial the QUAD was tested in 71 therapy-naive patients with Atripla®. The results showed similar effects after 24 weeks (Cohen 2011). The preliminary results of two large Phase III trials are very encouraging (DeJesus 2012, Sax 2012, see elvitegravir) and in August 2012, the FDA has approved the QUAD pill (Stribild®, see below).

Cobicistat seems to be well-tolerated, although a slight increase of creatinine was noted. This may only be explained by a lessened tubular creatinine secretion and may not indicate an impairment of renal function. However, problems regarding management of the creatinine levels with QUAD may still occur, as it also contains the potentially nephrotoxic agent tenofovir.

SPI-452 is a PKE developed by Sequoia that does not have any anti-HIV effect (Gulik 2009). In a first clinical study, different doses plus various PIs were given to 58 healthy volunteers. Tolerance was good. The levels of darunavir (37-fold) and atazanavir (13-fold) significantly increased. The booster effect lasted for a long time. Sequoia may continue research with SPI-452 as an individual agent and in fixed combinations. Their website recently closed down. Further development is questionable.
PF-03716539 is a PKE from Pfizer. Studies with healthy volunteers regarding its effects on midazolam, maraviroc and darunavir were concluded in 2009 according to clinicaltrials.gov. The results have not yet been officially released. The product is not listed in either the Pfizer or the ViiV websites.

TMC-558445 manufactured by Tibotec pharmaceuticals was tested in a recently finished Phase I dose escalation study. Results are not available yet. Janssen, the current official name of the company, does not have PKEs on their short-list of priorities for the future.

**New formulations**

Currently available drugs continue to be developed, the most important goals being a reduction in pill burden, easier dosing and fewer side effects. Agents that have entered the market already include Invirase 500®, Truvada®, Kivexa®, Atripla® and Complera® as well as the Viramune® Extended-Release or the new Norvir® tablets.

**Nelfinavir 625 mg** – this formulation was approved in the US in April 2003. It reduces the nelfinavir dose to 2 tablets BID. One study has shown that this formulation is better tolerated, particularly with respect to gastrointestinal side effects – despite the fact that plasma levels are around 30% higher (Johnson 2003). In Europe, where nelfinavir has been produced and sold by Roche, the 625 mg tablet has never been made available.

**Zerit PRC®** (PRC = “prolonged release capsule” or XR = “extended release”) is a cap-sulated once-daily d4T (Baril 2002). d4T XR was approved in Europe in 2002, but never made it to market – d4T is “gone”. There are attempts underway to improve d4T through minor modifications to its molecular structure. **OBP-601 (4’-Ed4T)** is a novel nucleoside analog with potent anti-HIV-1 activity and limited cellular toxicity with a unique *in vitro* resistance profile. BMS is apparently working on this substance under the name festinavir (Weber 2008).

**Generics** have been produced by companies from Africa, India, Brazil or Thailand. In most cases, bioequivalence has been demonstrated (Laurent 2004, Marier 2007). All generics approved by FDA and WHO are bioequivalent. Legally, a drug is not a generic if it is not bioequivalent to the original drug. In developing countries many new and previously unknown fixed drug combinations (FDC) are used. The most frequently used FDC is d4T+3TC+nevirapine that exists as Triomune (Cipla), GPO-vir (GPO), Triviro LNS (Ranbaxy) or Nevilast (Genixpharma). FDCs also exist for AZT+3TC+nevirapine, called Duovir N (Cipla) or Zidovex-LN (Ranbaxy). Patent rights for generics have often been ignored, making these insignificant in industrial countries (see Chapter on Access).

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New nucleoside analogs

Since the development of dexelvucitabine came to a halt, hopes are now limited that there will be new nucleoside analogs on the market in the near future. Developing NRTIs with strong potency against NRTI-resistant viruses that at the same time show less mitochondrial toxicity appears to be difficult. It is unlikely that any of the following agents will make it to the market. Many of them have already disappeared.

Amdoxovir (DAPD) is a novel dioxolane guanosine NRTI that is converted in vivo to the highly efficient DXG. DAPD has good efficacy against viruses resistant to AZT/3TC and against hepatitis B virus (Corbett 2001). When patients showed changes of the ocular lenses during early clinical trials (Thompson 2003), development was halted in 2004 and Gilead withdrew its licensing agreement with two US universities. However, there is still hope for DAPD. Supported by RFS Pharma from Georgia (US), development is ongoing. In this program, DAPD is combined with AZT to use the distinct resistance profiles of both compounds. In the first double-blind, randomized study in 24 patients, the viral load declined by an impressive 1.97 logs after 10 days on 500 mg DAPD + 200 mg AZT BID. There are obviously synergistic effects (Murphy 2010) that cannot be explained by interactions alone (Hurwitz 2010). The question is how to avoid the toxicity of DAPD.

Apricitabine (ATC, AVX-754, formerly SPD-754) is a heterocyclic cytidine analog that was sold by Shire Biochem to Avexa in 2005. ATC chemically resembles 3TC but has in vitro activity against a broad spectrum of TAMs. Up to 5 nucleoside mutations do not significantly impair its activity (Gu 2006). However, susceptibility to ATC is reduced when the K65R is present (Frankel 2007). A first placebo-controlled study in 63 HIV-infected patients treated with ATC monotherapy showed decreases in viral load of 1.2–1.4 logs depending on the dose – good potency for an NRTI (Cahn 2006). In 50 patients harboring the M184V mutation there was a reduction of 0.7–0.9 logs after three weeks on ATC (Cahn 2010). ATC-specific resistance mutations were not observed after 48 weeks and could not be selected in in vitro experiments (Oliveira 2009). Cephalgia and rhinitis are most frequent, otherwise tolerability of ATC seems to be good (Gaffney 2009). What about long-term toxicity? In monkeys, there were minor skin problems, usually hyperpigmentation, after 52 weeks of exposure. ATC was thus significantly less toxic than BCH-10652, which caused severe degenerative dermatopathy in all exposed monkeys (Locas 2004). 3TC and FTC significantly and competitively lower intracellular levels of ATC. Combination with other cytidine analogs is a problem. After negotiations with large pharmaceutical companies failed in May 2010, further development was discontinued and it is questionable if it will be resumed.
Dioxolanthymidine (DOT) is a newer thymidine analog. Dioxolane appeared to be relatively good in preclinical trials (Chung 2005, Liang 2006). Presently, prodrugs are being tested, however, clinical studies have yet to be conducted (Liang 2009).

EFda or 4-ethynol-2-fluor-deoxyadenosine seems to be a very effective NRTI according to the results of monkey testing. The SIV viral load decreased after 7 days by 2–3 logs (Parniak 2009). It is also being evaluated as a potential microbicide. Nothing listed on clinicaltrials.gov.

Elvucitabine (ACH-126,443) is a cytidine analog developed by Achillion Pharmaceuticals. It is an enantiomer of dexelvucitabine and is also effective against HBV. *In vitro* studies show potency even in the presence of numerous resistance mutations (Fabrycki 2003). It is also of interest as it seems to have an extremely long half-life of up to 150 hours – this may allow once-weekly dosing (Colucci 2005). A small double-blind study showed a reduction in viral load of between 0.7 and 0.8 logs after 28 days in HIV+ patients with the M184V mutation. However, this study had to be prematurely terminated, as 6/56 patients developed leucopenia or rash on a dose of 100 mg (Dunkle 2003). It seems that mitochondrial toxicity is lower than that of doxelvucitabine. On the other hand, this lower toxicity may also lower the efficiency of incorporation by drug-resistant versions of HIV-1 RT (Murakami 2004). Less toxicity at the expense of efficacy? In a smaller Phase II study in 77 therapy-naïve patients (with efavirenz and tenofovir), elvucitabine was comparable to 3TC at 96 weeks (DeJesus 2010). There appear to be problems with interactions with ritonavir, which may be due to ritonavir inhibiting an efflux gut transporter with activity present at various levels in subjects (Colucci 2009). Further development remains questionable as the only non-terminated trial on clinicaltrials.gov is some unsubstantiated expanded access that has not been updated for more than two years.

Fosalvudine is an NRTI from Heidelberg Pharma, a prodrug of the fluorothymidine alovudine. The active part is released only after enzymatic cleavage in the tissue. It is hoped that the toxicity commonly seen with fluorothymidines can thus be reduced. In a Phase II trial with 43 ART-naïve HIV+ patients, fosalvudine was well-tolerated and after 2 weeks of monotherapy with 5–40 mg, viral load decreased by up to 1 log (Cahn 2007). Trials with pretreated patients are being conducted in Russia as well as in Argentina, although nothing is listed on clinicaltrials.gov under “fosalvudine”. Animal testing on rats, however, indicate high mitochondrial toxicity (Vennhoff 2009). Further development is questionable.

Fozivudine is another NRTI developed by Heidelberg Pharma according to the “enhanced pro-drug-principle”. In Phase I/II trials (Bogner 1997, Girard 2000), fozivudine was well-tolerated, but only moderately effective – after 4 weeks, a decrease in viral load at the highest doses of approximately 0.7 logs was reached (Girard 2000). According to the company’s website, they are looking for partners to be able to conduct further trials. It has been silent for a while – no one seems to be very interested in a new AZT.

GS-7340 is a prodrug of tenofovir that enables higher tenofovir concentrations in peripheral blood mononuclear cells. GS-7340 was looked at in different doses vs tenofovir in 30 HIV+ patients. After 2 weeks viral load decreased to 1.71 logs vs 0.94 logs. In more recent trials even lower doses were looked at (Ruane 2012). After 10 days of 10 mg and 40 mg, respectively, viral load decreased by 1.46 and 1.73 logs. Viral load even decreased in the 8 mg arm vs tenofovir (1.08 vs 0.97 logs). Tolerance was good. A highly promising tenofovir backup seems to be emerging here with improved efficacy and lower systemic exposure (Markowitz 2011). With the success of tenofovir and due to the fact that its patent will last another few years, the company will be in no hurry to develop a competition, but it is probably preparing the pathway.
Phosphazide (Nicavir) is a nucleoside analog that was developed (and is marketed) in Russia, which is very similar to AZT (Skoblov 2003). After 12 weeks of phosphazide monotherapy (400 mg), viral load in a small group of patients dropped by median 0.7 logs. Since phosphazide is a prodrug of AZT, it requires an additional activation step. The D67N mutation seems to reduce efficacy (Machado 1999). A small study has shown potency in combination with ddI and nevirapine (Kravtchenko 2000), another with ddI and saquinavir (Sitdykova 2003). It is still hard to see the advantage over AZT – although better tolerability was presumed, this has not been shown.

Racivir is a cytidine analog produced by Pharmasset. It is a mixture of FTC and its enantiomer, 3TC. Possibly, both enantiomers have different resistance profiles so that, theoretically, the development of resistance is impeded (Hurwitz 2005). It has shown good antiviral activity in combination with d4T and efavirenz after two weeks (Herzmann 2005). In a double-blind randomized study in 42 patients harbouring the M184V mutation, viral load declined by 0.4 logs after 28 days (Cahn 2007). Pharmasset has been looking to out-license this compound, without success, since 2008.

Stampidine is a nucleoside analog developed by the Parker Hughes Institute. It resembles d4T and is apparently 100 times more potent than AZT in vitro (Uckun 2002). It also has activity against HIV mutants with up to 5 TAMs (Uckun 2006). It has been discussed also as a potential microbicide (D'Cruz 2004).

Out of sight, out of mind: the following NRTIs are no longer being pursued:

- Adefovir dipivoxil (bis-POM PMEA) from Gilead, low activity against HIV, nephrotoxicity, has an indication in hepatitis B
- Dexelvucitabine (DFC or Reverset) from Incyte, stopped in 2006 due to several cases of pancreatitis
- dOTC from Biochem Pharma, stopped due to toxicity in monkeys
- FddA (Lodenosine) from US Bioscience, stopped in 1999 due to severe liver/kidney damage
- KP-1461 from Koronis, stopped in June 2008 due to lack of efficacy
- Lobucavir from BMS, stopped due to carcinogenicity
- MIV-210 from Medivir/Tibotec, currently being developed for HBV
- MIV-310 (alovudine, FLT) from Boehringer Ingelheim, stopped in March 2005 due to a disappointing Phase II study
- SPD-756 (BCH-13520) and SPD-761

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New NNRTIs

In 2008 and 2011, etravirine and rilpivirine were the first second-generation NNRTIs. Encouraged by this, some pharmaceutical companies have NNRTIs in their pipeline again.

Lersivirine (UK 453,061) is a new NNRTI by ViiV Healthcare with good efficacy against classic NNRTI resistance (Corbeau 2010). In HIV+ patients, a decrease of viral load up to 2.0 logs was observed at doses of 10–750 mg after 7 days of monotherapy (Fätkenheuer 2009). In a larger double-blind randomized Phase IIb trial (A5271015), 193 patients on a TDF+FTC regimen received either lersivirine or efavirenz (Vernazza 2011). The number of patients reaching undetectable was 70% with either dose of lersivirine, 500 or 750 mg, slightly less than with efavirenz at 86%. Tolerance was good with fewer cases of rash and CNS disturbances. However, more patients suffered from nausea than with efavirenz. In light of these data and due to the fact that with dolutegravir, ViiV has another promising drug in the pipeline, it is difficult to predict if a further expensive phase III trial will follow. The recently published trials on pharmacokinetics and a positive (ie, negligible) effect on QT intervals give reason for optimism (Vourvahis 2012).

RDEA806 is an NNRTI by Ardea Biosciences. The resistance barrier is very high and the potential for interactions low (Hamatake 2007). Monotherapy trials with HIV-infected patients showed a reduction of over 1.8 logs at 7 days with excellent tolerability (Moyle 2010). The data seem promising enough to start Phase IIb trials. However, the company’s website is strangely blank on the topic.

Out of sight, out of mind: the following NNRTIs are no longer being developed:
- Atevirdine – Upjohn focused their research on delavirdine (a good idea?)
- BIRL355BS from Boehringer Ingelheim, in 2007 due to toxicity/metabolites
- Calanolide A from Sarawak, poor efficacy
- Capravirine (AG1549) from Pfizer, limited activity
- DPC 083 (BMS-561390), poor PK/secure data
- DPC 961 due to suicidal thoughts in healthy volunteers; DPC 963
- Emivirine (EMV, MKC-442, coactinone) from Triangle, due to limited activity
- GSK 761 (previously IDX-899) from ViiV Healthcare, seizures
- GW420867X from ViiV, too much of a me-too drug
- GW8248 and GW5624 from GSK, due to poor bioavailability
- HBY-097 from Hoechst-Bayer, due to unfavorable side effects
- Loviride, Janssen pharmaceuticals, due to limited activity in the CAESAR study
- MIV-150 from Medivir/Chiron, poor bioavailability, now being developed as a microbicide
- PNU 142721, Pharmacia & Upjohn, too similar to efavirenz (Me-too)
- TMC120 (dapivirine) from Tibotec, poor oral bioavailability, now being studied as a microbicide
References


New protease inhibitors (PIs)

Even among PIs, many agents have been lost along the way. Following the licensing of darunavir, not much can be expected from PIs in the near- to mid-term. This may also be due to the high bar on any new PI (Review: Pokorná 2009).

DG17 is a prodrug of DG35 and has been under clinical testing for some time. One study showed a clear boosting effect with ritonavir and significant pharmacoenhancement warranting further clinical development (Cherry 2008).

SM-309515 is a PI from Sumitomo Pharmaceuticals and has apparently entered Phase I studies. Earlier versions failed due to the short half-life, and attempts have been made to improve this (Mimoto 2008). The drug showed activity in the presence of some PI mutations. Ritonavir boosting is purportedly being tested in humans. No mention on their website or clinicaltrials.gov.

SPI-256 from Sequioa Pharmaceuticals is effective in vitro against PI-resistant isolates (Gulnik 2006). Healthy individuals have tolerated it well. There is no mention on clinicaltrials.gov and they do not seem to have a website.

TMC-310911 is a new PI from Tibotec, currently being examined with the booster-drug TMC-558445 in a Phase I study. In vitro data are encouraging (Dierynck 2012). Clinical data are not yet available.

Out of sight, out of mind, the following PIs are no longer being developed:

- AG-001859 from Pfizer
- Brecanavir from GSK, stopped in 2006 due to poor PK data
- DPC 684/681, narrow therapeutic range due to cardiotoxicity
- GS 9005, previously GS 4338 from Gilead
- JE-2147, AKA AG1776, KNI-764 from Pfizer, no news since 1999
- KNI-272, Kynostatin – due to poor PK data
- Mozenavir, DMP-450 from Gilead, a me-too drug, nothing new to offer
- PL-110 (MK8122) from Merck, allowed the out-license to expire
- RO033-4649 from Roche, probably too similar to saquinavir
- SC-52151 and SC-55389A, poor bioavailability
- TMC-126 from Tibotec, they concentrated on darunavir

References

Two entry inhibitors have already been licensed (T-20 and maraviroc, see Chapter 2). Even if the antiviral effects of the drugs are not overwhelming, the concept is intriguing and entry inhibitors could open up new possibilities for the treatment of HIV infection in the coming years. On the other hand, a lot of the data below does not go beyond basic science at this stage and many of the drugs discussed may eventually disappear. Most significantly, co-receptor antagonists have had to bear several setbacks.

**New attachment inhibitors**

Attachment of the viral glycoprotein gp120 to the CD4 receptor is the first step in the entry of HIV into the target cell. In theory, this step can be inhibited by at least two different mechanisms, namely blocking either gp120 or CD4. Both modes of action are currently under investigation. Consequently, attachment inhibitors are very heterogeneous and it is not possible to speak of a single drug class.

Since the beginning of the nineties, there have been a number of investigations into soluble CD4 molecules that prevent the attachment of HIV to the CD4 cell (Daar 1990, Schooley 1990). But, after disappointing results (probably due to the very short half-life of soluble CD4), this approach was abandoned for a time. With the growing knowledge of the mechanism of HIV entry, as well as following the success of T-20, the development of attachment inhibitors has been reinvigorated. However, most drugs are not yet very advanced, often have problematic PK data, and are therefore still in the proof-of-concept stage. There is some evidence for some polymorphisms in the gp120 gene associated with *in vitro* resistance to attachment inhibitors (Charpenier 2012).

**BMS-663068** is an attachment inhibitor from BMS. As a small molecule it binds very specifically and reversibly to HIV gp120 and thereby prevents attachment of HIV to the CD4 cell. Thus, it does not bind to CD4 like ibalizumab (see below). This agent drew a lot of attention at CROI in 2011 (Nettles 2011). 50 treatment-naïve patients received different doses once or twice daily over 8 days. Viral load decreased by 1.2 and 1.8 logs – the maximum reduction in both arms was achieved a few days after treatment had concluded. Unfortunately, no dose-related dependence was observed and inter-individual bioavailability was high. Headaches (44%) and rash (16%, mostly mild) were most frequent. Nevertheless, it is considered promising. BMS-663068 is a prodrug of **BMS-626529**, with a broad range of efficacy against several HIV isolates (Nowicka-Sans 2011). It is the replacement for **BMS-488043**, stopped in 2004 after first clinical data were released (Hanna 2004). Resistance occurs quickly as the binding site of gp120 is one of the most variable gene regions of all (Madani...
Fortunately, no resistance to BMS-626529 was selected on monotherapy with BMS-663068 (Ray 2012). However, another study showed that some patients without previous treatment with attachment inhibitors developed resistance to BMS-626529 due to subtype-related polymorphisms in the gp120 region (Charpentier 2012).

Ibalizumab (formerly TNX-355 or HUSA8) is a monoclonal antibody that binds to the CD4 receptor preventing entry of HIV. The mechanism of action has not been clearly described. In contrast to other attachment inhibitors, ibalizumab does not seem to prevent binding of gp120 to CD4, but rather through conformational changes and thereby the binding of gp120 to CXCR4. Some experts describe it as a co-receptor antagonist. It is administered intravenously. Following the initial early studies (Jacobsen 2004+2009, Kuritzkes 2004), data from a placebo-controlled Phase II trial were very encouraging (Norris 2006). In this study, extensively pretreated patients received ibalizumab as an infusion every two weeks for a year in two different doses (10 mg/kg or 15 mg/kg) or placebo in addition to an optimized ART regimen showed a long-lasting decrease in viral load of approximately one log after 48 weeks in both arms.

Following this, ibalizumab appears to be one of the more promising agents in HIV medicine. There seems to be an inverse correlation between the sensitivity for ibalizumab and soluble CD4, which does not work on its own, as shown above (Duensing 2006). Resistance causes a higher sensitivity towards soluble CD4 and the gp120 antibody VCO1, which is why attempts were made to administer ibalizumab in a cocktail of CD4 and VCO1 (Pace 2011). First data on resistance have been published (Toma 2011). However, one issue will be whether binding to CD4 will affect the functionality of the CD4 T cells. There have been no negative effects reported so far and it seems that the binding site for ibalizumab to CD4 receptors is localized differently from the molecules. The CD4 T cells may be able to function normally, even if ibalizumab occupies the HIV binding site.

Originally ibalizumab was being developed by Tanox Biosystems (Houston, USA) and later taken over by the biotechnology company Genentech in 2007. ACTG passed on sponsoring the Phase III trials. In mid-2007 Genentech sold the license for ibalizumab to TaiMed Biologics, a Taiwanese biotech company – they are presently planning Phase Ib trials in Europe and the USA. According to www.clinicaltrials.gov, however, the only study currently running is a trial on subcutaneous injections in the setting of pre-exposure prophylaxis.

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**New co-receptor antagonists**

In addition to CD4 receptors, HIV also requires so-called co-receptors to enter the target cell. The two most important ones, CXCR4 and CCR5, were discovered in the mid-90s (see Chapter 2). Both receptors can be blocked. In 2007, maraviroc was licensed as the first CCR5 antagonist. These small molecules are given orally and bind allosterically to the receptor. Besides these allosteric inhibitors there are monoclonal antibodies binding directly to the receptor. Below we will discuss those agents with published data.

**CCR5 antagonists (small molecules)**

**Vicriviroc (SCH-D)** was a CCR5 antagonist from Schering-Plough. Clinical development of this promising substance was halted in July 2010 after a pooled analysis of two Phase III trials, VICTOR E3 and E4 (Gathe 2010). A total of 721 pretreated patients received 30 mg vicriviroc or placebo in an optimized therapy containing mainly darunavir/r and/or raltegravir. No difference was observed after 48 weeks (64% versus 62% below 50 copies/ml). Despite obvious differences in patients who only had two active drugs (70% versus 55%), Merck decided to stop development of vicriviroc. We mention this because it clearly shows the problems new agents will face in the future. With the improvement of therapies over time, it is becoming more and more difficult to show positive effects – background therapies have become “too” good.

**Cenicriviroc** (TBR-652 or formerly TAK-652) is an orally-available CCR5 antagonist by the Japanese company Takeda that has now been bought by Tobira. Laboratory data demonstrated that several mutations in the V3 region (and in the env gene) must exist for complete resistance towards TAK-652. Tropism does not seem to change when resistance occurs (Baba 2007). Oral bioavailability is good and with a half-life of 35–40 hours a once-daily dosage is possible (Martin 2012). The oral availability is improved with food intake. TBR-652 also seems to be effective against CCR2, a receptor on monocytes, dendritic and memory T cells that may have anti-inflammatory properties as well. There are no concerns regarding its safety and the substance has shown good tolerability in healthy volunteers (Palleja 2009). In a first double-blind dose-ranging study of 10 days monotherapy in 54 patients, the viral load decreased by a maximum of 1.5–1.8 logs (Lalezari 2011, Marier 2011). Another Phase II study on 150 patients, in which different doses of cenicriviroc are compared with efavirenz, is ongoing.

**PF-232798** is an orally available CCR5 antagonist by ViiV Healthcare. It has a long half-life and can probably be administered once daily. *In vitro* it reacts well to mar-
aviroc resistance (Stupple 2011). In healthy volunteers, it was well tolerated (Dorr 2008).

SCH-532706 is a new CCR5 antagonist from Schering (now Merck). At first, there seems to be no advantage of this agent over vicriviroc. A total of 12 patients receiving 60 mg of SCH-532706 (with 100 mg ritonavir) showed a reduction of viral load of up to 1.6 logs at 15 days (Pett 2009). A once-daily administration seems possible. There may be a positive effect on immune activation (Pett 2010) – however, facing the experiences with vicriviroc, it seems unlikely that this agent will be further developed.

Other innovative CCR5 blockers

HGS004 (CCR5mAb004) developed by Human Genome Sciences is a monoclonal antibody showing a high resistance barrier in vitro (Giguel 2006). The half-life is approximately 5–8 days, and 80% of the receptors are occupied over a period of up to 4 weeks after a single dose. In an initial trial, 54 ART-naïve patients received a single infusion between 0.4 and 40 mg/kg HGS004 or placebo (Lalezari 2008). More than half the patients in the higher dose arms showed a reduction of at least one log at 14 days. There are reports of synergistic effects with maraviroc (Latinovic 2011a). Possibly, the company has now turned their attention to HGS101, which is even more effective in vitro and in addition effective against maraviroc-resistant virus (Latinovic 2011b).

PRO 140 is a monoclonal antibody by the company Progenics, directed against human CCR5 receptors (Trkola 2001). It is not a chemokine derivative like maraviroc or vicriviroc and even seems to have a synergistic effect (Murga 2006). The resistance barrier is probably high (Jacobsen 2010). PRO 140 is administered intravenously. The normal function of CCR5 receptors should not be interfered with, at least not in the required dosages for inhibition of HIV replication (Gardner 2003). Healthy patients showed excellent tolerability to intravenous single administration of the drug and dose-dependent concentrations were measured (Olson 2005). What was particularly surprising was the extended effect – CCR5 receptors were occupied for up to 60 days and more (Olson 2006). In a trial with 39 HIV patients treated with intravenous single doses of between 0.5 and 5.0 mg/kg, viral load decreased with the highest doses by 1.83 logs with a nadir at day 10 (Jacobson 2008). A higher dosage does not seem to achieve more (Jacobsen 2010). Comparable effects are reached with weekly subcutaneous administration (Jacobson 2010). PRO 140’s tolerability seems excellent, and it has the possibility of being a weekly therapy (Tenorio 2011).

ESN-196 is a pilot agent developed by Euroscreen, which does not block the coreceptor, but is agonistic, like the chemokine RANTES, causing internalization of the receptor (Ferain 2011). This CCR5 agonist reduces the receptor density on the cell surface. Therefore, it is as effective as maraviroc in vitro. As an agent with an extended effect, it could become an alternative, even with CCR5A-resistant viruses, if proven safe in clinical trials.

Aprepitant (Emend®) is approved as a neurokinin-1 receptor antagonist and as an antiemetic in patients receiving highly emetogenous chemotherapy. It apparently has an effect on R5-tropic viruses caused by a down-regulation of the CCR5 receptors. Lab data showed dose-dependent effects on HIV replication (Wang 2007, Manak 2010). In a first clinical trial in HIV patients, however, no effects on plasma viremia were found (Tebas 2011).
CXCR4 antagonists

In the early stages of infection, the R5 virus is found in most patients; X4 virus appears at later stages. X4 viruses are found in approximately 50% of cases in intensely pre-treated patients (Hoffmann 2007). This is why theoretically the blocking of CXCR4 receptors seems so attractive – those patients with limited options would benefit most. The combination with CCR5 antagonists seems to be an interesting option. However, the development of CXCR4 antagonists is less advanced than that of the CCR5 antagonists (Peled 2011). This is mainly because theoretically, less clinical consequences are feared with the CCR5 blockade – individuals with a CCR5 genetic defect are healthy; although, an inherent and mostly harmless defect with CXCR4 in humans, has not been seen. CXCR4 blockade had severe consequences in animal testing, for example in angiogenetic hematopoiesis or brain development (Tachibana 1998, Nagasawa 1998, Zou 1998). Years of basic research will certainly be necessary until large clinical studies can be attempted. Nevertheless, several chemically different substances are in preclinical testing (Jenkinson 2010, Miller 2010, Skerl 2010, Steen 2010, Thakkar 2010). Despite the hurdles, CXCR4 antagonists seem to be a promising class. Research has shown an interesting side effect: some agents are able to mobilize stem cells. This is why one of the pilot drugs, AMD 3100, presently under the name plexifor, is being further developed as a growth factor for leukocytes as well as a G-CSF alternative (Kean 2011, Ratajczak 2011). Such an effect, however, is obviously not desired in permanent HIV therapy. CXCR4 antagonists are also being discussed with regard to lupus erythematodes (Chong 2009).

AMD 11070 is a CXCR4 antagonist developed by AnorMED. Healthy volunteers showed excellent tolerability with AMD 070, but often developed leukocytosis (Stone 2004). The efficacy in HIV-infected patients with dual-tropic viruses was validated in two pilot studies (Moyle 2007, Saag 2007). Viral load was lowered by at least one log in 7/15 patients on 10 days of monotherapy. However, in 2007, development was preliminarily stopped because of liver toxicity. Binding to the X4 receptor is localized differently than the precursor agent AMD 3100, so there may be some scope for development of new, more potent and less toxic CXCR4 antagonists (Wong 2007) – at least a start was made with AMD 11070 and evidence of efficacy was found. Presently AMD 3465 seems to be another possibility (Bodart 2009).

KRH-3955 and KRH-3140 are two CXCR4 antagonists that have proven effective in mouse models (Tanaka 2006). According to preclinical data, KRH-3955 seems especially promising (Murakami 2009) and bioavailability is good (in dogs). Likewise, POL3026 is still preclinical and may help inhibit selected X4 shifts while on CCR5 antagonists (Moncunill 2008).

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New fusion inhibitors

Since the first fusion inhibitor (FI) T-20, there has been little development in the field (Review: Berghout 2012). Subcutaneous injection required for many FIs is unappealing for patients and clinicians. It still needs to be demonstrated, whether small molecule FIs, i.e., that are orally bioavailable, are effective (Jiang 2004). Addition of a cholesterol group to an HIV-1 peptide fusion inhibitor may dramatically increase its antiviral potency (Ingallinella 2009).

Sifuvirtide is an FI developed in China. In animal testing with monkeys a longer half-life (39 hours) and a higher affinity towards gp41 rather than towards T-20 was observed (Dai 2005). Sifuvirtide was well-tolerated in healthy patients (He 2008) and interesting synergetic effects were reported with T-20 (Pan 2009). However, there seem to be some cross-resistances (Liu 2010, Yao 2012). This may not be the case for the newer FI albuvirtide, from China as well (Chong 2012).

SP01A from Samaritan Pharmaceuticals is especially interesting because its effects are different from other entry inhibitors. As a procaine hydrochloride, SP01A reduces the expression of the key enzyme HMG-CoA reductase, removes cholesterol from the cell membrane and seems to inhibit, not only in vitro, the fusion of virus and cell. The efficacy of this agent, which has been repeatedly tested in HIV+ patients for years, was shown in three Phase II trials. Results were moderate, showing that only 50% of patients have a reduction of viral load at the highest doses of 800 mg. After 10 days of monotherapy, viral load fell by 0.4 logs and after 28 days by 0.5 logs. These results were published in July 2007 on the company’s website (www.samaritanpharma.com). No news since then.

TR-999 and TR-1144 are two 2nd generation fusion inhibitors, developed by Trimeris in cooperation with Roche (Delmedico 2006). According to studies in monkeys, the potency, duration of action and pharmacokinetics of these peptides are much improved in comparison to T-20. Although administration is still by injection, it
may be possible to limit this to once a week. They have only been involved in one clinical trial since 2007, with data due in 2008. They have stopped developing both compounds and were looking for buyers/investors.

**Virip** blocks entry of HIV-1 into the cell by interacting with the gp41 fusion peptides. It is also called an anchor inhibitor. Researchers from Ulm, Germany, discovered the peptide in hemofiltrate, the liquid that is filtered out of the blood of dialysis patients, when replacing it with electrolytic solution. Thus virip is a “natural” entry inhibitor whose antiretroviral activities can significantly be increased by slight modifications or replacement of certain amino acids (Munch 2007). Several modified agents are currently under investigations, such as Virip-576 and -353. In a first study with HIV-infected patients, continuous infusion with the highest dosage of Virip-576 led to a reduction of approximately 1 log at 10 days (Forssmann 2010). Tolerability was good and a subcutaneous application is presently being evaluated. However, potential resistance mutations have been shown (Gonzalez 2011).

Out of sight, out of mind – entry inhibitors not moving forward:
- AMD 3100 (CXCR4) from AnorMed, due to cardiotoxicity
- Aplaviroc (CCR5) from GSK, due to hepatotoxicity
- BMS 806, BMS-488043 two attachment inhibitors, due to poor PK data
- FP-21399 (FI) from Lexigen/Merck, due to low potency
- INC9471 from Incyte
- PRO-542 from Progenics, to focus on PRO-140
- SCH-5 (CCR5) from Schering-Plough, due to cardiac arrhythmia
- T-1249 and T-649 (FIs) from Roche/Trimeris, due to little prospect of success
- TAK-779, TAK-220 (CCR5) from Takeda, replaced by TAK-652

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New integrase inhibitors

The integration of viral DNA, enabled by the HIV enzyme integrase into the host DNA, is a major step in the replication cycle of HIV. In 2007, raltegravir, the first integrase inhibitor for treatment of HIV infection, was licensed (see Chapter 2). On account of its great success, it can be expected that clinical research will focus on this class for the next few years. Elvitegravir and dolutegravir are already in Phase III trials. One major problem seems to be cross-resistance, which makes it necessary to find integrase inhibitors that interact differently with the enzyme from how raltegravir does – me-too integrase inhibitors marginally different in their efficacy and pharmacokinetics are not needed (Serrao 2009).

Dolutegravir (GSK-1349572 or DTG) is an integrase inhibitor that initially emerged via Shionogi cooperating with GSK and is now being developed by ViiV Healthcare. As a second-generation integrase inhibitor it shows improvements, especially with regard to pharmacokinetics (once daily unboosted administration, independent from food intake) and resistance profile. In a Phase IIa study with 35 patients, a reduction of 2.5 logs was observed and 7/10 achieved a viral load below 50 copies/ml during 10 days monotherapy (Min 2011).

In SPRING-1, a Phase IIb study, 205 treatment-naïve patients received different doses of either dolutegravir (10, 25 or 50 mg) or efavirenz plus 2 NRTIs. After 96 weeks 79–88% achieved a viral load of less than 50 copies/ml compared to 72% on efavirenz (Stellbrink 2012). Tolerance was excellent and better than with efavirenz, showing only a slight increase in creatine levels, which seems not to be significant and is caused by inhibition of a renal transporter system. No resistance mutations were observed in cases of therapy failure (van Lunzen 2012). The resistance barrier is possibly higher than with other integrase inhibitors, probably due to prolonged binding with integrase complexes (Hightower 2011).

Cross-resistance with other integrase inhibitors does not seem to be a problem (Kobayashi 2011). An important resistance mutation appears at T124A, as well as mutations typical for raltegravir at codon 148. Efficacy seems to decline with additional mutations (Canducci 2011, Garrido 2011). Preliminary data from the VIKING study show that a higher dosage may help overcome raltegravir resistance. In VIKING II, 13 out of 24 patients with raltegravir resistance reached a viral load of 400 copies/ml after 10 days monotherapy with 100 mg dolutegravir. The results were better than in VIKING I with 50 mg dolutegravir (Eron 2011). There are no interactions with boosted Pls. However, etravirine reduces the levels of dolutegravir significantly (Song 2011). This also applies for antacids and it is recommended not to administer them simultaneously (Patel 2011). When rifampicin is given, a higher dose of dolutegravir seems necessary (Dooley 2012). Fortunately, there is no effect of food intake on resorption (Song 2012).

Dolutegravir is currently being tested at 50 mg with ABC+3TC. Phase III studies are ongoing. Dolutegravir seems to be one of the agents that will make it to the market.

Elvitegravir (GS-9137, formerly JTK-303) is an integrase inhibitor developed by Gilead, with a biochemical similarity to chinolone antibiotics (Sato 2006). Like raltegravir, elvitegravir inhibits strand transfer. Individual doses were orally bioavailable, safe and well-tolerated (Kawaguchi 2006). In a study with 40 patients (ART-naïve and pre-treated), viral load decreased by 2 logs at 10 days of monotherapy (DeJesus 2006). In pre-treated patients there was a good effect when compared to a boosted PI (Zolopa 2010). A disadvantage is that elvitegravir must be boosted (Kearney 2006), but on the other hand a single administration per day seems possible.
To avoid dependency on ritonavir as a booster agent, Gilead has investigated combinations of elvitegravir with cobicistat (GS-9350), a new pharmacoenhancer (PKE). The so-called QUAD tablet, a combination of the four Gilead substances tenofovir, FTC, cobicistat and elvitegravir in a single tablet, showed good efficacy in a phase II trial on therapy-naïve patients. Several larger phase III trials investigating QUAD on therapy-naïve patients are ongoing. Results so far have been good: In 236-0102, 700 patients received either QUAD or TDF+FTC+efavirenz (Sax 2012) and in 236-0103, 708 patients were treated with either QUAD or TDF+FTC+atazanavir/r (DeJesus 2012). After 48 weeks, 88% under QUAD (versus 84%) and 90% (versus 87%), respectively, achieved a viral load below 50 copies/ml. Both trials showed no difference in subgroups (sex, age, CD4 cell count, amount of viral load). Tolerance was good, except for more cases of nausea (21 versus 14%) under elvitegravir. However, rarer cases of dizziness (7 versus 24%) and dyslipidemia were observed. Based on these results, the QUAD pill (Stribild®) has received approval by the FDA for treatment naïve adults. However, applications for marketing approval of Stribild® are still pending in Australia, Canada and Europe.

Another large randomized double-blind Phase III trial with over 700 pre-treated patients with documented resistance showed similar effects with elvitegravir or raltegravir (Molina 2012).

In vitro resistance mutations can be selected with elvitegravir, too, and there seems to be at least two resistance pathways, at T661 or E92Q (Shimura 2008). Especially E92Q requires a high resistance (36-fold). In the case of Y143, a raltegravir resistance, efficacy seems to persist (Métifiot 2011). Resistance of elvitegravir and raltegravir overlap to a great extent, thus cross-resistance seems possible (Garrido 2012). No virologic response was observed in a small clinical study with patients who switched from elvitegravir to raltegravir (DeJesus 2007). Major interactions with elvitegravir are not expected, at least not with NRTIs, darunavir, tipranavir, fosamprenavir or etravirine. Dose adjustments with lopinavir/r and atazanavir/r may be necessary. The dose of maraviroc must be halved (Ramanathan 2011).

GSK-774 is probably a backup for dolutegravir, but not less effective. In a first double-blind randomized study with 48 volunteers the agent showed good tolerability over 14 days. In the 13 HIV+ patients viral load was reduced by 2.6 logs (Mín 2009).

MK-2048 is a second-generation integrase inhibitor by MSD with presumably limited cross-resistance to raltegravir (Goethals 2010, Bar-Magen 2011, Van Weesenbeeck 2011). It also is being looked at for PrEP.

Out of sight, out of mind: integrase inhibitors no longer being studied:
- BMS-707035, probably no advantage over raltegravir
- GSK-364735, liver toxicity in monkeys, stopped in Phase I in 2007
- L-870810 (Merck), liver toxicity in dogs
- S-1360 (Shionogi/GSK), stopped in 2005 due to toxicity

References


### New maturation inhibitors

The so-called maturation inhibitors stop HIV replication in a very late phase of the HIV reproduction cycle, i.e., at the budding or maturation of new virions. As is the case for integrase inhibitors, 2005 can be called the introductory year: this was the first time an agent was shown to have an antiviral effect on HIV-infected patients. Maturation inhibitors are, without a doubt, an interesting class of new drugs. Whether any of the agents will make it out of the clinic remains uncertain, as several problems have surfaced during the development of the prototype, bevirimat.

**Bevirimat (MPC-4326, formerly PA-457)** is a derivative of betulinic acid, which is isolated as triterpene carbonic acid from birch bark. It was produced by Panacos, which was sold to Myriad Pharmaceuticals. Bevirimat inhibits budding or maturation of new virions (Li 2003) by inhibiting the transition of the capsid precursor (p25) into the mature capsid protein (p24). This prevents the production of infectious viruses. Its long half-life allows once daily dosing (Martin 2007, Smith 2007). Tolerability of bevirimat in more than 650 patients has been good, including in the presence of atazanavir (Martin 2008). However, interactions seem to exist with darunavir (reduces bevirimat levels) and raltegravir (raltegravir levels increase) (Beelen 2010).

Data from a placebo-controlled Phase IIa trial was published in autumn 2005, in which patients received an oral once-daily monotherapy of bevirimat for 10 days (Beatty 2005). In the highest dose group (200 mg) viral load decreased by 1.03 logs (median); in the 100 mg group it was just 0.48 logs. However, some patients showed no effect on the viral load, which can be ascribed to “natural” polymorphisms in the gag gene (van Baelen 2009, Lu 2011). Patients harbouring viruses with no gag polymorphisms (mutations) on the positions Q369, V370 or T371 before therapy responded better to bevirimat. In a more recent monotherapy study with 32 patients receiving higher dosing, a reduction of viral load of 0.54 and 0.7 logs respectively, was observed with 200 or 300 mg after 14 days. Without the polymorphisms, effects were greater than the one log level, those with the polymorphisms had a drop of only 0.2 logs (Bloch 2009). Only about 50–70% of all individuals tested, seemed not to have these gag polymorphisms. There appears to be no difference between treatment-naive and pre-treated patients, nor is there any influence due to the degree of the underlying immunodeficiency (Margot 2009, Knapp 2009, Seclén 2010). However, there seems to be a strong correlation with PI resistance (Verheyen 2010, Fun 2011).

This shows clearly the need for tests on these gag polymorphisms before starting therapy with bevirimat and possibly with other maturation inhibitors – not unlike the tropism test with CCR5 antagonists. In June 2010, Myriad announced that they will not continue to develop bevirimat.

**PA1050040** works in the same way as bevirimat, but seems to be effective against bevirimat-resistant viruses (with L363M). PK data appear to be better, while the potential for interactions is less. According to Panacos, a Phase I study was initialized (Kilgore 2007). However, Panacos does not exist anymore and the agent is not listed anywhere else since 2007.

**UK-201844** is a maturation inhibitor developed by Pfizer. It was detected after screening over a million agents (Blair 2007). The method of efficacy seems to lie in the interaction with gp160 processing resulting in the production of non-infectious viruses.

**BIT-225** from the Australian company Biotron is a specific HIV replication inhibitor in macrophages, but not in T cells (Khoury 2007). It works with a different mecha-
nism than the Vpu ion channel inhibitor and inhibits the release of viral particles from macrophages. BIT-225 could play a role in eradication from latent cell reservoirs. According to Biotron, a successful Phase I study ended in September 2007, showing no relevant toxicity with 40 healthy volunteers receiving doses of 35–400 mg and providing acceptable PK data.

MPC–9055 is, like bevirimat, a maturation inhibitor by Myriad Pharmaceuticals in Salt Lake City, US. The agent demonstrated good tolerance and acceptable pharmacokinetics with 55 healthy volunteers (Beelen 2009). After the end of bevirimat, development of MPC-9055 seems unlikely.

References


Immunotherapy

In recent years, in addition to ART, immunomodulatory treatment strategies have been investigated. Although repeatedly discussed as an alternative or supplement, these therapies lack proof of clinical benefit. An important example is the failure of the two large IL-2 studies (see below). Some approaches are nevertheless addressed here briefly (in alphabetic order).

Cyclosporin A (Sandimmune®) – Immune activation may lead to increased HIV replication, and a treatment hypothesis has been to suppress the immune system in an attempt to slow down viral replication. This is the rationale behind studies investigating the use of cyclosporin A, a drug normally used for prophylaxis of transplant rejection after allogenic organ transplantation. However, results of clinical trials have been disappointing. Cyclosporin A had no effect on CD4 or CD8 count, nor on expression of activation markers (Calabrese 2002, Lederman 2006). This was not only the case in chronically but also in acutely infected patients (Miro 2009, Markowitz 2010). Cyclosporin A therefore probably has a limited future in HIV therapy.

G-CSF (granulocyte colony-stimulating factor) is available as filgastrim (Neupogen®), lenogastrim (Granocyte®) and most recently as less expensive biosimilars (in Europe). It is also licensed for permanent neutropenia in advanced HIV infection to avoid bacterial infection. In a randomized study with 258 HIV-infected patients with CD4 T cells under 200/µl, the rate of severe neutropenia was 2% versus 22% in the control group after 24 weeks (Kuritzkes 1998). Incidence of bacterial infection was reduced by 31% and the number of inpatient days dropped by 45%. No effects on viral load were seen. Patients with CMV retinitis showed a large survival benefit on G-CSF (Davidson 2002). Although severe neutropenia has become rare on ART, G-CSF can be useful, especially in chemotherapy, with interferon or other myelo-suppressive drugs such as valgancyclovir.

GM-CSF (granulocyte macrophage colony-stimulating factor) is available as molgramostim (Leucomax®) or sargramostim (Prokine®). Three double-blind, randomized studies showed a slight effect on viral load (Angel 2000, Skowron 1999, Brites 2000). However, in one study in patients with uncontrolled infection, there was a slight increase of viremia (Jacobsen 2003). GM-CSF seems to prevent significant loss of CD4 T cells during treatment interruptions (Fagard 2003). Given the side effects and significant cost of GM-CSF, it cannot be recommended outside clinical studies. GM-CSF is not licensed in Europe.

Hydroxyurea (HU, Litalir®) is an old chemotherapeutic agent with relatively low toxicity still being used today in hematology (mostly in chronic myelogenous leukemia). It inhibits DNA synthesis via the ribonucleotide reductase, and leads to an intracellular shortage of deoxynucleotide triphosphates. A synergistic effect on HIV replication in combination with ddl was demonstrated in 1994 (Lori 1994). A Swiss study, in which 144 patients were treated with hydroxyurea (HU) or placebo plus d4T+ddl, attracted attention in 1998 (Rutschmann 1998). After 12 weeks, 54% (versus 28% in the placebo group) demonstrated a viral load below 200 copies/ml. Was this the discovery of a new cheaper option for HIV treatment? Hydroxyurea became even more fashionable after publication of the first “Berlin Patient”, a patient who had been treated with hydroxyurea in addition to indinavir and ddl during acute infection, had stopped all therapy after a few months and subsequently showed no detectable plasma viremia (Lisziewicz 1999). Was this unexpected outcome due to hydroxyurea? Several small studies from the US and Argentina seemed to confirm these positive results. Many treating physicians added the drug to ART and many started to dream of a cheap combination of ddI+HU for Africa. These initial hopes
subsided rapidly. In particular, the combination of HU with ddI and d4T turned out to be particularly toxic: severe polyneuropathy (Moore 2000) and fatal pancreatitis were reported (Havlir 2001). Three randomized studies failed to show any effect, except for high rates of toxicity (Blanckenberg 2004, Stebbing 2004, Swindels 2005). Even in patients with acute HIV infection there was no effect. Thus, more Berlin patients could not be “reproduced” (Zala 2002). Hydroxyurea should not be used in antiretroviral therapy.

**Interferons** have an antiretroviral effect that has been known for years (Mildvan 1996). The antiviral effect of 3 million IU daily or with pegylated interferon weekly is about 0.5–1 log (Haas 2000, Hatzakis 2001, Asmuth 2010). Higher dosing may increase this effect (Hatzakis 2001). We have seen patients coinfected with HIV/HCV, who achieved an undetectable HIV RNA during hepatitis C therapy with interferon and ribavirin only. However, an in-depth investigation of the antiviral activity of interferon was not conducted, because of the subcutaneous delivery route and its not insignificant side effects. Recently, interferons seem to be experiencing a comeback, as they may acheive importance as an immune modulator and play a role in eradication (Papasavvas 2012, Mexas 2012). In one trial, 9 out of 20 patients who received pegylated interferon and interrupted ART, showed viral load below 400 copies/ml after 12 weeks of IFN monotherapy (Azzoni 2012).

**Interleukin-2 (IL-2, aldesleukin, Proleukin®)** is a cytokine produced by activated T cells that induces proliferation and cytokine production in T cells, B cells and NK cells. It has been employed in oncology for years and is now usually administered subcutaneously. The most important effect of IL-2 in HIV medicine is the increase in CD4 and CD8 T cells, which may be quite impressive in individual cases. CD45RO memory cells initially increase, followed by naïve CD45RA T cells (Chun 1999, Cercalein 2003). This effect is mainly due to a reduced T cell turnover (Kovacz 2005, Sereti 2005, Vento 2006).

The question of whether the CD4 T cells generated by IL-2 would lead to clinical benefit, was answered by two large randomized studies, ESPRIT and SILCAAT, in 2009 (Abrams 2009). In the ESPRIT study, 4131 patients with at least 300 CD4 T cells/µl were treated with and without IL-2 in addition to ART. SILCAAT had a similar concept, but enrolled 1695 patients with 50–299 CD4 T cells/µl. The results were very disappointing. Although supplementation of ART with IL-2 resulted in a statistically significant increase in CD4 T cell count (ESPRIT: +160, SILCAAT: +59 CD4 T cells/µl), it did not lead to a clinical benefit. Despite improved CD4 T cells with IL-2, patients did not develop less opportunistic infections and mortality was not reduced. Moreover, serious adverse events (including fever, malaise, injection site reactions and deep-vein thrombosis) were more likely to occur among patients receiving IL-2 in the ESPRIT study. Another randomized study (STALWART) provided similar results (Tavel 2011). Conclusion: IL-2 as a supplementary therapy in HIV-infected patients is no longer viable.

**Interleukin-7** may be more promising. This cytokine plays a fundamental role in T cell homeostasis and is implicated in thymopoiesis and in peripheral expansion and survival of T lymphocytes (Review: Chahroudi 2010). Two small randomized placebo-controlled pilot trials with 6 and 16 HIV patients, respectively, demonstrated a good increase of CD4 T cells with different subcutaneous doses. The tolerability was good and side effects typical for interleukin-2 were not observed (Levy 2009, Sereti 2009). If these results are confirmed, interleukin-7 may become a good option for patients whose immune constitution remains poor despite good viral load suppression on ART. However, a study published at the end of 2010 showed that the viremia isolated before and after IL-7 was from the same source. Therefore IL-7 may simply be amplifying the existing virus rather than “purging” the reservoirs (Imamichi 2011).
Interleukin-12 stimulates T lymphocytes and NK cells to generate a Th1-type immune response. In a randomized Phase I study with rhIL-12 100 ng/kg 2 x week, the drug was well tolerated but had no effect on lymphocyte subpopulations, antigen-specific immune response or viral load (Jacobson 2002). Further development has not happened. The same would appear to be true for interleukin-10 (Angel 2000) or interleukin-15 (Ahmad 2005). In the age of highly effective antiretroviral therapies, such experimental therapies have to meet ever-increasing standards.

Corticosteroids do not stand the test of controlled studies. In a placebo-controlled study with 0.5 mg prednisone/kg over 8 weeks, there were no effects on CD4 T cells or viral load (McComsey 2001). In ACTG 349, 24 patients were treated with 40 mg prednisone daily or not in a double-blind randomized design (Wallis 2003). After 8 weeks, there was a trend towards higher levels of CD4 T cells in the prednisone arm, but there were no effects on activation markers or apoptosis. Two patients on prednisone developed necrosis of the femoral head. This study should caution anyone before considering steroids for immunological reasons.

Murabutide is a synthetic muramylpeptide with a variety of effects on the immune system. It can raise unspecific resistance to infection, induce anti-inflammatory cytokines and growth factors, and strengthen the antiviral effects of cytokines such as IL-2 or interferon. In HIV-infected patients, a team in France has used it mainly as an immune modulator, although only in small studies, and at best, with moderate results (Bahr 2003).

Mycophenol (Cellcept®) has a theoretical concept similar to that of hydroxyurea and cyclosporin A. Mycophenol inhibits inosine monophosphate (IMP) dehydrogenase and is normally used for prophylaxis of acute transplant rejection in patients with allogenic kidney, heart or liver transplants, as well as for some autoimmune diseases. Inhibition of lymphocyte proliferation and the subsequent reduction of target cells should theoretically inhibit replication of HIV. Initial reports seem to demonstrate an effect on viral load, at least in some patients (Margolis 2002, Press 2002). Whether this will be confirmed by randomized trials seems uncertain. More current data suggest that this is unlikely (Sankatsing 2004, Margolis 2006).

Remune®, the prototype of therapeutic vaccination, has gone from disaster to disaster. Developed by a team headed by the since-deceased Jonas Salk, Remune® was a therapeutic vaccine comprised of an envelope-depleted (gp120) virus which, although indeed immunogenic, does not seem to provide any clinical benefit (i.e., prolongation of life or delay of disease progression). A large trial was interrupted prematurely in May 1999. More than 2500 patients had taken part for a mean of 89 weeks in this study, which was designed to evaluate the addition of Remune® to ART. As well as the lack of clinical benefit, advantages with respect to CD4 T cell counts or viral loads could not be shown (Kahn 2000).

THC, cannabinoids have no anti-HIV effect. A controlled, randomized study, in which patients could either smoke marijuana or receive THC (dronabinol, Marinol®) or placebo in addition to ART, showed no effects on lymphocyte subpopulations, lymphocyte function or viral load after three weeks (Bredt 2002). THC, which is metabolized via the cytochrome P450 system, had no detrimental effects on PI plasma levels (Abrams 2003). One randomized study showed that smoking cannabis was well-tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings were comparable to oral drugs used for chronic neuropathic pain (Abrams 2007).
References


6.4. Goals and Principles of Therapy

CHRISTIAN HOFFMANN

With current antiretroviral therapies, eradication of HIV is not possible. The ultimate goal in HIV medicine – a cure – is not a realistic scenario in the immediate future, although more and more effort and time is being spent in the cure arena (see section on The Cure). Patients and physicians most likely have to deal with lifelong treatment. Lifelong, meaning decades, as many epidemiological studies suggest a normal life expectancy for HIV-infected patients (Obel 2011, Hogg 2012, Nakagawa 2012). The goal of ART in 2012 is to prolong the patient’s life and maintain the best possible quality of health and life.

In the fine-tuning of regular evaluations – including CD4 T cell count, viral load, routine laboratory, genotypic and phenotypic resistance and/or tropism testing and drug plasma levels, it may be useful to reflect upon this goal. Patients and physicians should not lose sight of the big picture. Even if a high CD4 T cell count and a low viral load are useful therapeutic goals, the patient’s condition is as important as the laboratory results. Patients, too, can often lose focus. The response to the doctor’s query: “How are you?” is often accompanied by a glance toward the CD4 T count result on the chart: “That’s what I’d like you to tell me!” Treatment aimed only at improving laboratory values with little emphasis on the physical and mental well being of the patient cannot be successful in the long-term.

Success and failure of treatment

Both success and failure of treatment can be evaluated using the same criteria – virologic, immunologic or clinical. The first indicator, virologic, is the change in viral load. This is followed, often a little later, by immunologic markers (rise or fall in CD4 T cell count). Clinical outcome usually only becomes apparent much later – first the lab values deteriorate, then the patient; or vice-versa, as lab values get better, the patient generally follows. The clinical success of ART for asymptomatic patients is often not perceived, although the risk of opportunistic infections is reduced to half after only three months on ART (Ledergerber 1999) – the individual may not realize what was avoided by starting therapy.

Virological treatment success and failure

Virological treatment success is usually understood as being the reduction of viral load to below the level of detection (usually 50 copies/ml). This is based on the understanding that, the more rapid and greater the decrease in viral load, the longer the therapeutic effect (Kempf 1998, Powderly 1999). In the INCAS Trial, the relative risk of treatment failure (defined here as an increase to above 5000 copies/ml) in patients who had reached a viral load below 20 copies/ml was 20 times lower than in those who never reached 400 copies/ml (Raboud 1998). If this still matters in the era of newer antiretroviral therapies is not clear, but the concept of lower is better (less is more?) is very valid today.

On ART, viral load declines in at least two phases (see chapter on Monitoring). An initial, very rapid decrease in the first few weeks is followed by a slower phase, in which plasma viremia declines slowly. A reduction to below the level of detection should be reached after 3–4 months; in cases of very high baseline viral load it may take longer. However, a viral load above the level of detection after six months of treatment almost always needs to be evaluated. The same is true if a rebound in viral load is confirmed (usually 2 weeks later). Consideration needs to be given to factors that will improve therapy (drug levels, resistance, compliance, etc).
Virologic treatment failure can be recognized quite early – therefore, initial monitoring after four weeks is useful not only to the patient for reasons of well-being (“less virus, more CD4 cells”). But it is also an important indication for the continued success of treatment. If the viral load is not below 5000 copies after four weeks of ART, later treatment failure is likely (Maggiolo 2000). If the patient’s viral load is not below 500 copies/ml or at least one log below baseline, the likelihood of having a viral load of 500 copies/ml at week 24 is only 9% (Demeter 2001). According to one prospective study, virologic response can be anticipated after 48 weeks or even only 7 days (Haubrich 2007). However, such early controls of plasma viremia are not routine.

The cut-off point of 20 or 50 copies/ml is somewhat arbitrary. It is based on the currently available assays for measurement of viral load. Whether 60 copies/ml are indeed worse than 30 copies/ml and indicate a lower success of treatment has yet to be proven. In the case of a persistent low level viremia (LLV) between 20 and 50 copies/ml, the risk of virological failure seems not to be increased (Charpentier 2012). In the setting of LLV, immune activation and inflammatory parameters appear not to be increased (Eastburn 2011, Taiwo 2012). There are, however, other studies that have found an association between the level of viremia and virological failure, even at very low levels (Maggiolo 2012). Thus, the significance of LLV is still a matter of debate.

At such low levels, methodological inaccuracies must also be taken into account. A single viral load “blip” to low levels (~1000 copies/ml) is often irrelevant (see below). Blips need to be distinguished from low, repetitive, measurable plasma viremia (50–400 copies/ml), in which the risk of resistance has been shown to be much higher (Gunthard 1998, Nettles 2004, Taiwo 2012).

A viral load “below the level of detection” of 50 copies/ml means just that – no more, no less. 50 copies/ml indicate that 5 liters of blood contain 250,000 virions; in addition, even more actively replicating viruses are present in the lymphatic organs. Thus, theoretically, a measurable viremia, even at very low levels, may possibly translate to a higher risk of resistance in the long-term. Perhaps there is indeed a relevant difference between 50 and 10 copies/ml with regard to the risk of developing resistance. We just do not know yet.

Risk factors for virological failure are pre-treatment with antiretroviral agents (existing resistance mutations) and low adherence. Whether the level of the CD4 T cell counts or of the plasma viremia at the time of treatment initiation play a role in treatment-naïve patients has not been conclusively proven (see chapter on When to Start ART).

It seems that many other risk factors associated with virological failure or response are not known. A new area in this setting is pharmacogenetic research focusing on how genes influence an individual response to drugs. Investigators have begun to identify associations among human genetic variants, predisposition to HIV drug toxicities, and likelihood of virologic response. These include associations among abacavir hypersensitivity reactions, HLA type, and enzyme polymorphisms (Haas 2006). Pharmacogenomic testing will ultimately benefit persons living with HIV through better individualized treatment.

More good news is that morbidity and mortality may be lowered significantly even if the viral load is not decreased to below the level of detection (Mezzaroma 1999, Grabar 2000, Deeks 2002). Patients often remain immunologically stable for relatively long periods of time, even with insufficient viral suppression. A large cohort study has shown that CD4 T cells do not drop as long as the viral load remains below 10,000 copies/ml or at least 1.5 logs below the individual set point (Lederberger 2004).
However, with the introduction of new drug classes much more is possible now than in the 90s. In the era of darunavir, tipranavir, etravirine, maraviroc and raltegravir, virological success (achieving an undetectable viremia) is possible even in patients with excessive pre-treatment. Thus, plasma viremia should be reduced to below the limit of detection in every patient.

**How long does virological treatment success last?**

Little is known about how long treatments remain effective. The belief that treatment success is limited to only a few years is widespread. It originated during the early years of ART. Many patients at the time were inadequately treated or had been pretreated with mono- or dual-therapy, and had thus developed extensive resistance. In such patients, the effect of treatment was often limited, as even a single point mutation was often enough to topple a whole regimen. Today, especially in therapy-naïve patients without pre-existing mutations, the risk of treatment failure is much less. After fifteen years of using combination ART, a very high number of patients still have viral loads below the level of detection. This is particularly true for patients who were adequately treated from the start (starting with triple therapy and/or rapid switching of several drugs upon failure). One of the few trials with a longer follow-up period studied 336 antiretroviral-naïve patients who had reached a viral load below 50 copies/ml within 24 weeks (Phillips 2001). After 3.3 years, the risk of viral rebound seemed at first glance to be relatively high at 25.3%. More detailed analysis showed that a large proportion of the patients experiencing viral rebound had actually interrupted ART. True virological failure was only seen in 14 patients, which corresponds to a risk of 5.2% after 3.3 years. Most importantly, the risk of virological failure decreased significantly with time.

This is supported by cohort studies showing that the rates of virological failure due to resistance have markedly declined in recent years (Lohse 2005, Lampe 2006). Antiretroviral therapies and treating physicians are getting better and better. As demonstrated by a large cohort study in Europe in 1995–96, 58% achieved HIV-1 RNA of 500 copies/ml or less by 6 months, compared with 83% in 2002–03 (May 2006). Nowadays, most patients have a constant viral load below 50 copies/ml. In many centers today, at least 90% of patients on ART have an undetectable plasma viremia. The cohort in Bonn is a good example. In 2007, only 57 out of 560 (10%) patients on ART showed detectable viremia. In 32 of these patients, adherence problems were a major cause and only 9% had a multiresistant virus (Klein 2009).

These studies clearly show that, providing treatment is not interrupted, viral load can remain below the level of detection for many years, perhaps decades.

**Blips – do they mean virological failure?**

Blips are understood to be transient and relatively small increases in viral load, where the viral load before and after the blip was below 50 copies/ml. At least three measurements of viral load are therefore required to be able to identify a blip. Blips are a frequent phenomenon of patients on ART and are observed in 20–40% (Sungkanuparph 2005). Blips often worry both patients and clinicians: Is this the beginning of treatment failure?

Although a few studies indicate that this is not the case in the medium-term (Havlir 2001, Mira 2002, Sungkanuparph 2005), little is known about the causes of blips. For example, there has been no consistent data about association between compliance and blip frequency. While some studies did not find any association (Di Mascio 2003, Miller 2004), others did (Podsadecki 2007).

It is possible that blips are the result of immunological mechanisms. The earlier patients are treated in the course of infection, i.e., the higher the CD4 T cell count
at therapy initiation, the more seldom blips seem to occur (Di Mascio 2003+2004, Sungkanuparph 2005). There does not appear to be any association with particular antiretroviral combinations – in a large cohort study (Sungkanuparph 2005), the frequency of blips on an NNRTI regimen was 34% and 33% on a PI regimen, even the size of the blips were equivalent (median 140 and 144 copies/ml, respectively). In both groups, the risk of virological failure at 2 years was approximately 8%. One important observation of this trial was that blips did not increase the risk of treatment failure, not even on NNRTIs, anticipated due to the rapid development of resistance to NNRTIs. Another team has since confirmed these results (Martinez 2005).

But what do blips actually mean? At the beginning of 2005, a study team led by Bob Siliciano set out to investigate this. In a labor-intensive study (Nettles 2005), 10 stalwart patients who had had a viral load of less than 50 copies/ml for at least six months, had blood samples taken every 2–3 days over a period of 3–4 months. The obvious result: the more you look, the more you find. During the observation time, at least one transient increase in the viral load was measurable above 50 copies/ml in nine of the ten patients. Each blip was moderate, with a median value of 79 copies/ml, ranging from 51 to 201 copies/ml. The blips were not associated with either specific clinical data, low plasma levels, or resistance. This observation led the authors to believe that blips (with low, measurable values) mainly represent biological or statistical exceptions and are not involved in treatment failure. In an estimated steady state level of viral load at around 20 copies/ml, the values are distributed randomly. However, 96% of the randomly distributed measurements (“random noise”) were less than 200 copies/ml. In other words: Random noise above 200 copies/ml is unlikely.

It should be noted that other factors may be responsible for intermittent viremia. Sporadic immune activation during concomitant infections may elevate the level of chronically infected cells and replenish viral reservoirs, including the latent cell reservoir, providing a mechanism for recurrent viral blips and low levels of viremia while on ART (Jones 2007). In one large retrospective analysis, 26% of blips were caused by intercurrent infections (Easterbrook 2002). For example, syphilis can cause a significant increase in viral load and reduction of CD4 T cells (Buchacz 2004). Viral load can also increase temporarily after immunizations (Kolber 2002).

Based on available data, blips do not necessitate an immediate change of ART. However, caution should be applied for higher blips (>200–500 copies/ml). It should be stressed that blips need to be distinguished from low, repetitive, measurable plasma viremias, in which the risk of resistance has been shown to be much higher (Gunthard 1998, Nettlers 2004, Taiwo 2012). Blips should raise the opportunity to talk to the patient about compliance. It cannot be discussed often enough. Does the patient take his or her drugs regularly or are doses occasionally missed? Are the dosing directions (on an empty stomach or with a meal) followed correctly? All these points should be considered before changing therapy prematurely. Each new therapy can cause new problems. Therefore, any suspected increase in the viral load should be controlled within a short interval (two weeks), especially if it is relatively small, before the treatment is changed.

Immunological treatment failure and success

Immunological treatment success is generally defined as an increase in the CD4 T cell count. A more precise definition for immunological treatment success does not currently exist. Depending on the study, increases of 50, 100 or 200 CD4 T cells/µl or increases to above 200 or 500 CD4 T cells/µl are evaluated as a success. Failure is usually described as a lack of increase or reduction of CD4 T cell count in patients receiving ART.
It is difficult to individually predict the immunologic success of therapy for patients on ART, as it varies significantly from one person to another. As with the decrease in viral load, the increase in CD4 count also seems to have two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1000 patients, the CD4 count increased during the first three months by a median of 21.2 CD4 T cells/µl per month; in the following months the increase was only 5.5 cells/µl (Le Moing 2002). In EuroSIDA, the greatest mean yearly increase in CD4 count of 100 cells/µl was seen in the year after starting ART. Significant, but lower, yearly increases in CD4 count, around 50 cells/µl, were seen even at 5 years after starting ART in patients whose current CD4 count was less than 500 cells/µl (Mocroft 2007). Of course, this might also depend where you start. If you start relatively late in the disease, CD4 recovery will be more blighted than if you start closer to transmission. It is still under debate whether the immune system is restored continuously after a long period of viral load suppression or whether a plateau is reached after three to four years beyond which there is little or no expected improvement (Smith 2004, Mocroft 2007, Lok 2010). In our experience, both are possible. There are patients showing immunological improvement even 6–8 years after initiation and there are patients in which CD4 T cells remain stable at a low level. The lower the CD4 count at baseline, the less likely it is to normalize completely (Kaufmann 2005, Robbins 2009). The immune system often does not recover completely. In the Swiss Cohort, only 39% of 2235 patients who had begun ART in 1996–97 reached a CD4 T cell count above 500/µl (Kaufmann 2003). However, it appears that the increase within the first 3–6 months provides certain clues as to how well the immune system will be restored (Kaufmann 2005). Negative consequences of a low CD4 cell count at the time of ART initiation are often present for a long time. In one study, 25% of patients who started an ART at lower levels of CD4 T cell count did not reach normal levels of 500 CD4 T cells/µl, even after a decade of otherwise effective ART with good viral suppression (Kelley 2009, Lok 2010).

Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression can result in improved CD4 T cell count (Kaufmann 1998, Ledergerber 2004). The initial level of viral load is also not significant. What seems to be important is that the viral load remains lower than before treatment (Deeks 2002, Ledergerber 2004). In view of the numerous factors that occur independent of ART that are able to influence therapy success and individual immuno-regeneration (see below), it is generally not wise to look at the CD4 T cell count alone as the deciding criterion for the success of ART. Virological success is more appropriate for judging the efficacy of specific regimens. Once CD4 T cells have “normalized” and plasma viremia remains undetectable, it is unlikely that they will significantly change (Phillips 2002). In such cases, immunological treatment success does not require constant monitoring.

**Discordant response**

Failure to achieve therapeutic goals – in terms of immunologic and virologic success – is referred to as a discordant response. The frequencies of such discordant responses in adults are outlined in Table 4.1. Therapies can be virologically successful without immunological improvement; despite undetectable viral load, CD4 T cell counts remain low (Piketty 1998, Grabar 2000, Moore 2005, Tan 2007). Conversely, ART may be extremely effective immunologically and induce significant increases in the CD4 count, while viral load remains detectable. Although therapies have constantly improved, discordant responses appear in one fourth of all treatment-naïve patients. Especially in patient groups
showing virological success but little immunological improvement, it is often not clear how to continue therapy. Mortality seems to be slightly higher in this patient group, but has not been related to AIDS diseases (Gilson 2010). If there is any increase of AIDS incidence in the setting of discordant response, this is restricted to the first six months (Zoufaly 2011).

The risk factors for a lack of immunologic response can often not be influenced and are also heterogenic (Review: Aiuti 2006). Low CD4 counts at baseline, as well as a low viral load at treatment initiation are only two factors (Florence 2003, Kaufmann 2005, Moore 2005, Kelley 2009). Age may also play a role. In older patients, immunologic response is often only moderate in comparison to virologic response. This may be mainly due to thymic degeneration (Lederman 2000, Grabar 2004). Various studies have demonstrated that the probability of not achieving a rise in CD4 count increases with patient age and with progressive decrease in thymus size as detected by CT (Goetz 2001, Piketty 2001, Teixera 2001).

Other possible causes for a lack of immunological response, despite good viral suppression, may be immuno- or myelosuppressive concomitant therapies. We have seen patients with less than 50 CD4 T cells/µl for more than a decade, despite virological suppression. A significant immune reconstitution only set in after removing prophylaxis with ganciclovir or cotrimoxazole. Other causes may be autoimmune diseases (Crohn’s disease, lupus erythematosus) or liver cirrhosis.

However, there is some evidence that certain antiretroviral regimens have unfavorable effects on immune reconstitution. Significant drops in CD4 T cell count were observed in patients with a suppressed viremia who switched to a simplified regimen of TDF+ddI plus nevirapine (Negredo 2004). The reason for this is still not understood, but seems to be related to negative interactions between ddI and tenofovir. Where possible, this combination should be avoided, especially in primary therapy. In two other studies, the CD4 T cell increase with abacavir+3TC or TDF+FTC was significantly better than with AZT+3TC (all combined with efavirenz), despite comparable virological success. This may be related to the myelotoxicity of AZT (DeJesus 2004, Pozniak 2006). In the Swiss cohort, patients on an AZT-containing regimen had 60 CD4 T cells less than patients without AZT over a period of two years (Huttner 2007). Whether it makes sense for patients showing poor immunologic success to switch to AZT-free regimens is an open question. There is no difference between NNRTIs and PIs regarding immune reconstitution and a switch is ineffective (Torti 2011).

What about new substances? One meta-analysis showed that an increase of CD4 T cells on maraviroc was better than with other agents, and led to several other studies. In these studies patients with poor immune reconstitution received an additional dose of maraviroc. The results were disappointing (LanzaFame 2009, Stepanyuk 2009, Wilkin 2010). The same applies to raltegravir (Byakwaga 2011, Hatano 2011) and T-20 (Joly 2010), none of them showing any positive effects on immune reconstitution.

<table>
<thead>
<tr>
<th>Response to ART</th>
<th>Grabar 2000 n = 2236</th>
<th>Moore 2005 n = 1527</th>
<th>Tan 2008 n = 404</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological and immunological</td>
<td>48%</td>
<td>56%</td>
<td>71%</td>
</tr>
<tr>
<td>Discordant: only immunological</td>
<td>19%</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>Discordant: only virological</td>
<td>17%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>No treatment response</td>
<td>16%</td>
<td>17%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Immunological response was defined as a rise in CD4 T cells >50/µl after 6 months (Grabar 2000) or at least >100/µl during follow-up (Moore 2005, Tan 2007). Virological response: <1000 copies/ml (Grabar 2000) or <500 copies/ml (Moore 2005) or <50 copies (Tan 2008)
Some reports show that the thymic function and corresponding immune reconstitution can be stimulated by growth hormone (Tesselaar 2008, Napolitano 2008). Such approaches are still experimental and not recommended as routine. Whether higher CD4 T cell counts have clinical benefits or not remains unknown. However, the example with interleukin-2 (see section on immune therapy) may call for caution, as in this case higher CD4 T cell counts had no positive effect on the frequency of opportunistic infections.

### Practical considerations in dealing with viral load and CD4 count

- Viral load (VL) is the most important parameter in treatment monitoring.
- If possible use only one type of assay (in the same lab) – bear in mind that there is considerable methodological variability (up to half a log) and at the same time of day.
- Virological success should be monitored one month after initiation or modification of ART.
- VL should be below 50 copies/ml after 3–4 months (in those with high initial viral load, after 6 months at the latest) – if it has not responded, look for why.
- The greater the decrease in viral load, the more durable the response to ART.
- Transient, low-level increases in VL (blips) are usually insignificant – but VL should be monitored at short intervals (e.g., 4–6 weeks after such blips).
- The older the patient, the more likely a discordant response (low VL with no significant increase in CD4 count).
- In contrast to VL, increase in CD4 T cells, i.e., immunological success, is difficult to influence. A hectic switch of antiviral agents will not help!
- CD4 T cells are probably more predictive of the individual risk for AIDS.
- Once CD4 T cell count is good, it requires less frequent monitoring. With higher CD4 counts, values may vary considerably from one measurement to the next (which may mislead the patient to either a false sense of euphoria or unnecessary concern).
- To help avoid false euphoria or concern, look at the big picture – measurements over time, not one specific measurement alone, for CD4 cells and viral loads.

### Clinical treatment success and failure

Clinical treatment success is dependent on virologic and immunologic therapeutic success. In individual patients, clinical response is not always easy to assess. After all, there is no way to show what might have occurred if treatment had not been started. As an asymptomatic patient cannot feel much better, it may be difficult to find good arguments to continue treatment in the presence of side effects, which, at least temporarily, may affect quality of life.

Clinical success is almost always evaluated via clinical endpoints (AIDS-defining illnesses, death), although the improvement on ART in a patient with considerable constitutional symptoms should also be seen as clinical success. With regard to risk of disease progression, the immunologic response is at least as important as the virologic response. However, the extent of virologic success is of great significance. In the Swiss Cohort, of those with a constantly undetectable viral load, the proportion of patients who went on to develop AIDS or die was 6.6% after 30 months. In contrast, this proportion was 9.0% in patients with viral rebound and up to 20.1% if the viral load was never suppressed to undetectable levels (Ledergerber 1999). The importance of complete and sustained virological treatment success for clinical benefit has also been reported from other cohorts (Thiebaud 2000, Lohse 2006).
Table 4.2: Risk of progression, as defined by immunologic and virologic treatment response (See previous table caption for definitions). 95% confidence intervals in parentheses

<table>
<thead>
<tr>
<th>Response to ART</th>
<th>Grabar 2000</th>
<th>Piketty 2001</th>
<th>Moore 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 T cells (median)</td>
<td>150</td>
<td>73</td>
<td>180-250</td>
</tr>
<tr>
<td>Virologic and immunologic response only</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Immunologic response only</td>
<td>1.6 (1.0-2.5)</td>
<td>6.5 (1.2-35.8)</td>
<td>1.9 (1.1-3.0)</td>
</tr>
<tr>
<td>Virologic response only</td>
<td>2.0 (1.3-3.1)</td>
<td>9.7 (1.6-58.4)</td>
<td>2.5 (1.5-4.0)</td>
</tr>
<tr>
<td>No treatment response</td>
<td>3.4 (2.3-5.0)</td>
<td>51.0 (11.3-229.8)</td>
<td>3.5 (2.3-5.3)</td>
</tr>
</tbody>
</table>

Clinical endpoints: progression/death (Grabar 2000, Piketty 2001), death (Moore 2005).

Clinical failure is usually defined as the development of an AIDS-associated condition or death. However, illness is not always indicative of clinical treatment failure. This is particularly true for the immune reconstitution inflammatory syndrome (IRIS), where a pre-existing, subclinical infection becomes apparent during the first weeks after initiation of antiretroviral therapy (see chapter on AIDS). An OI with increased CD4 T cells does not necessarily mean that the ART has failed, but that the immune system is doing its job, to put it in simple terms. On the other hand, if a patient develops serious side effects or dies, this should clearly be evaluated as a clinical failure. Fortunately, this is rare. Other causes can also be considered. Many serious and life-threatening events that affect HIV-infected patients on ART today are not associated with ART nor AIDS, but related to hepatic or cardiovascular complications (Reisler 2003). The following table shows the diseases leading to death in patients in France in the years 2000, 2005 and 2010. According to this analysis, only every fourth patient actually dies of AIDS. Other diseases such as tumors or (mostly hepatic) liver diseases are becoming more important.

Table 4.3: Causes of death in HIV-infected patients in France (Lewden 2008, Morlat 2012)

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>2000 (n=964)</th>
<th>2005 (n=1042)</th>
<th>2010 (n=728)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining events</td>
<td>47%</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>Non-AIDS-defining cancers</td>
<td>11%</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>13%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Suicide</td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**What can be achieved today?**

Every HIV clinician sees the remarkable strides made possible by ART reflected in his or her own patients (see example below). In many areas, the incidence of AIDS has been reduced to less than a tenth of what it was at its height (Mocroft 2000). Some illnesses that occur only with severe immunodeficiency are rarely seen today. CMV retinitis or MAC disease have become unusual. AIDS cases in Western countries occur mainly in patients who are not being treated with antiretroviral therapy – usually because they are unaware of their infection or have not acknowledged it. These so-called late presenters now make up a large proportion of the cases of AIDS (see below). In patients who are continuously followed in specialized centers, AIDS has become a rare occurrence.
Table 4.4: Patient (female, 41 yrs old) showing advances due to ART*

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>CD4 T cells</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 95</td>
<td>AZT+ddC</td>
<td>23 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Nov 96</td>
<td>AIDS: Toxoplasmosis, MAC, Candida esophagitis</td>
<td>12 (1%)</td>
<td>815,000</td>
</tr>
<tr>
<td>Feb 97</td>
<td>d4T+3TC+SQV</td>
<td>35 (8%)</td>
<td>500</td>
</tr>
<tr>
<td>Jun 97</td>
<td>Stopped HAART due to polyneuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jul 97</td>
<td>AZT+3TC+IDV</td>
<td>17 (4%)</td>
<td>141,000</td>
</tr>
<tr>
<td>Mar 98</td>
<td>AZT+3TC+IDV/r+NVP</td>
<td>147 (22%)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Mar 99</td>
<td>AZT+3TC+IDV/r+NVP</td>
<td>558 (24%)</td>
<td>100</td>
</tr>
<tr>
<td>Mar 00</td>
<td>AZT+3TC+IDV/r+NVP</td>
<td>942 (31%)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Apr 05</td>
<td>AZT+3TC+LPV/r+NVP</td>
<td>744 (30%)</td>
<td>130</td>
</tr>
<tr>
<td>Jan 12</td>
<td>AZT+3TC+LPV/r+NVP</td>
<td>817 (29%)</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

*Excellent immune reconstitution despite initial severe immunodeficiency and several AIDS-defining illnesses. All prophylaxes (MAC, toxoplasmosis, PCP) have now been discontinued

In ART-CC, a collaboration of several large cohorts, life expectancy of a 20 year-old HIV-infected patient increased from 36.1 to 49.4 years between 1996–1999 and 2003–2005 (ART-CC 2008). Life expectancy of HIV-infected patients in many industrialized countries is approaching that of the general population (Porter 2008, Lodwick 2010, van Sighe 2010, Nakagawa 2012, Hogg 2012). However, all analyses show that a gap still exists between certain patient groups compared to the general population. This applies not only to patients with hepatitis coinfection or active drug or alcohol consumption, but also to black patients or patients with low CD4 T cell count when starting ART (Lohse 2007, ART-CC 2008, Harrison 2010).

Data from prospective controlled studies on this dramatic change is still limited, as there have not been many randomized trials with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). The results seen in these studies, due to their design, led to the licensing of the PIs. In ABT-247, a multi-center trial, 1090 clinically advanced patients received ritonavir liquid formulation or placebo in addition to their ongoing treatment. The probability of AIDS and death at follow-up of 29 weeks was 21.9% in the ritonavir arm and nearly double (37.5%) in the placebo arm (Cameron 1998).

Studies of mono- or dual therapy are no longer considered ethically justifiable and the number of clinical endpoints that occur is fortunately now extremely low. As a result, the duration of any contemporary study to prove clinical benefit of one combination over another would have to be extended over a long period of time. Unrealistically large study populations are now required given the extremely low probability of progression – only rarely will such investigations be undertaken in the future (Raffi 2001). One of the few trials that could confirm the benefits of ART on clinical endpoints was the SMART trial (see section on Treatment Interruption below). This is why data from large cohorts such as EuroSIDA, the Swiss Cohort and the US HOPS Cohort is usually used to demonstrate the benefit of ART (Table 4.5). The Swiss Cohort showed that the effect of ART increases over time – after more than two years on ART, the risk of disease progression was only 4% of the risk without ART (Sterne 2005). Numerous cohort studies (with more than 20,000 patients) have shown that during recent years there has been no further decline in AIDS and mortality rates. Like in 1997, the risk of AIDS remained relatively stable at 6% in 2003. It seems that, in many patients, ART is simply begun too late. Even in 2006, almost half of the patients initiating therapy have a CD4 T cell count of less than 200 cells/µl (May 2006).
The effect on AIDS-defining diseases appears to be different. The most obvious is the decline in the incidence of viral OIs, although this is not as pronounced for fungal infections (D’Arminio 2005).

Table 4.5: Decline in morbidity and mortality in large cohorts

<table>
<thead>
<tr>
<th>Where (n)</th>
<th>Patients (Period)</th>
<th>Mortality (/100 PY)</th>
<th>Morbidity (/100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palella 1998 USA (1255)</td>
<td>&lt;100 CD4+ T cells/μl (1/1994-6/1997)</td>
<td>29.4 → 8.8</td>
<td>21.9 → 3.7*</td>
</tr>
<tr>
<td>Ledergerber 1999 Switzerland (2410)</td>
<td>6 months before versus 3 months after HAART (9/1995-12/1997)</td>
<td>NA</td>
<td>15.1 → 7.7</td>
</tr>
<tr>
<td>Mocroft 2002 Europe (8556)</td>
<td>All (1994–2001)</td>
<td>15.6 → 2.7</td>
<td>NA</td>
</tr>
<tr>
<td>D’Arminio 2005 Worldwide (12,574)</td>
<td>The first 3 months after versus 3 years after HAART</td>
<td>NA</td>
<td>12.9 → 1.3</td>
</tr>
<tr>
<td>D:A:D 2010 Worldwide (33,308)</td>
<td>All (1999–2007)</td>
<td>1.7 → 1.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

* MAC, PCP, CMV. Mortality/Morbidity each per 100 PY = patient years

With regard to opportunistic infections and malignancies, the effect of ART is equally apparent on their clinical course as it is on their incidence. Illnesses such as cryptosporidiosis or PML can be cured, while Kaposi sarcoma can resolve completely without specific therapy. Prophylaxis of pneumocystis pneumonia, toxoplasmic encephalitis, CMV, or MAC infection can usually be safely withdrawn at the adequate CD4 counts. These effects are discussed in more detail in the corresponding chapters.

**Treatment goal – eradication**

In a chapter on the goals of therapy, we must discuss the cure. Only by addressing it will we finally achieve it. After the success of the last twenty years that has enabled many patients to control their infection for decades, many clinicians share the opinion that a cure has to be the major goal for the future.

The case of the new Berlin patient, published in 2008, shows that a cure is at least theoretically possible. This patient had suffered from acute myeloid leukemia and underwent allogeneic stem cell transplantation. The healthy stem cell donor was homozygous for the Δ32 mutation – after the transplant the viral load of this patient (which was very high before ART initiation) has disappeared for at least four years (Hütter 2009, Allers 2011). The virus was undetectable in the blood, in the lymph nodes and in the intestinal mucosa. The media hysteria following this publication made patients believe in a cure and physicians were put in the undesirable position of having to put these freshly raised hopes into context. An allogeneic stem cell transplant is not only complicated and expensive, but also highly risky (mortality up to 30%), making this approach not very practical, although it stirred hope for future academic purposes. One cannot say for sure that this patient is permanently cured and in no need of further treatment with ART but the case does raise hopes for the future.
What is the cure?
An important question is whether eradication is necessary for a cure. Must all virus be removed from the body? A cure could also mean that the body is able to control HIV without help of medication – i.e., in some viral infections, like herpes, low viral levels persist for a lifetime. This is why a difference is being made today between a sterilizing cure and functional cure (Reviews: Richman 2009, Lewin 2011). Currently at least four strategies are being pursued and partly combined. These are 1. Eradication of latently infected cells and 2. Eradication of residual replication, as well as 3. Improvement of the HIV-specific immune response and 4. Attempts to make cells more resistant against HIV infection.

Table 4.6: A case of an “elite controller”

<table>
<thead>
<tr>
<th>Date</th>
<th>ART</th>
<th>CD4 cells/μl</th>
<th>HIV RNA copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/03</td>
<td>Acute HIV infection (seroconversion)</td>
<td>203 (8%)</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td>04/03</td>
<td>Start with ART (AZT+3TC+IDV/r)</td>
<td>412 (12%)</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td>01/04</td>
<td>ART stopped after 8 months</td>
<td>838 (52%)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>06/04</td>
<td></td>
<td>467 (46%)</td>
<td>&lt;25</td>
</tr>
<tr>
<td>05/05</td>
<td></td>
<td>1288 (51%)</td>
<td>44</td>
</tr>
<tr>
<td>03/12</td>
<td>Eight years without ART</td>
<td>921 (38%)</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

Comment: Whether ART during acute infection had a positive effect remains unclear. Such a favorable course is also possible without intervention.

Some patients have already reached functional cure. These so-called elite controllers, some found in most large HIV centers, have normal CD4 T cells for many years and even more impressive, a viral load below the limit of detection without therapy (Table 4.6). Only when investigating with ultrasensitive methods or examining the lymph nodes can a relatively tiny amount of virus be found. Co-receptor defects explain only a few of the cases. But what is it that makes HIV-specific immune response in these patients so effective, what causes the virus to be so unfit, what are the underlying genetic modifications? These are some questions being pursued by many leading research teams.

The problem with latent reservoirs
At this point in time, eradication of HIV, the removal of all HIV from the body, is a theoretical goal. The main reason is that latently HIV-infected cells comprise a lifelong reservoir (Saksena 2003). Even after years of suppression, viral transcription can be detected (Finzi 1999, Furtado 1999, Zhang 1999, Sharkey 2000). This is particularly true in blood cells, but also in the lymph nodes and in sperm (Lafeuillade 2001, Nunnari 2002). Replication also takes place in cells of the gastrointestinal tract, even if no virus is detected in the blood. Even after myoablative chemotherapy and autologous stem cell transplantation, latent reservoirs persist (Cillo 2012). In addition, latently infected reservoirs consist of very heterogenic cell populations and their stability is probably independent of residual virus replication. Theoretically, how long does it take until the last latently infected cells are removed? A half-life of 44.2 months for the latently infected cell reservoir was measured in a study with 62 patients, whose viral load had been successfully suppressed on ART for a period of seven years (Siliciano 2003). The calculated time to eradication of these reservoirs was 73.4 years. Even in patients with no measurable blips during at least three years of stable ART and with a tendency for a more rapid decrease of viral load, the time to eradication was 51.2 years. Virus in resting CD4 memory cells with minimal evolution persists, even after close to 9 years on ART (Nottet 2009).
Intensification trials

Many studies have investigated whether viral decay rates can be improved or whether any change at all can be effected by intensifying therapy. Different strategies were tried, such as additional administration of integrase or entry inhibitors, but also of other compounds to try to to empty the latent reservoirs. These studies are discussed below:

Mega-HAART, entry inhibitors

In a trial with patients with good viral suppression and additional PIs or NNRTIs in their ART, an ultrasensitive single copy assay showed no further reduction of viral load by intensification (Dinoso 2009). The level of viral load depends not so much on the applied regime, but on on the pre-therapeutical setpoint (Maldarelli 2007). Additional administration of the entry inhibitor T-20 did not show any effects either (Ghandi 2010). Resting T cells are also not affected by T-20 nor by a combination with valproic acid (Archin 2010). Maraviroc, as a potential immune-modulating CCR5 antagonist, was also investigated as an intensification strategy. One study showed no relevant effects on the latent reservoirs (Gutiérrez 2012) and other studies showed effects on immune activation (Sauzullo 2010, Wilkin 2010). One study with acutely infected patients showed hardly any effects either on virologic or immunologic parameters (Evering 2010). Another carefully designed study with 40 patients with acute HIV infection compared a triple regime plus raltegravir plus maraviroc with a classic triple regimen. Results showed no advantages of the intensive therapy regarding residual viremia or regarding the degree of immune reconstitution or immune activation (Markowitz 2011). Obviously it is not a question of the number of ARVs.

Raltegravir

Hopes for additional effects of raltegravir were raised by a study in which treatment-naive patients on a raltegravir regimen achieved a viral load below detection significantly more rapidly than those on efavirenz (Murray 2007). At least two prospective studies in which raltegravir was added to an existing ART showed no additional antiviral effect by means of ultrasensitive viral load assays (Gandhi 2009, MacMahon 2010, Gandhi 2012). Immune activation was also not influenced by raltegravir (Luna 2009, Massanella 2011). Results are contradictory regarding the question of whether proviral DNA decreases more rapidly. While two small studies showed positive effects (Arponen 2008, Reigadas 2010), several larger studies did not confirm these results (Buzon 2010, Hatano 2011, Chege 2012).

Several studies showed an increase of episomal DNA while on raltegravir. This DNA, also referred to as 2-long terminal repeat (2-LTR) circular, develops when integrase inhibitors block the DNA integration process into the chromatin. Evidence of this episomal DNA (2-LTR circles) in approximately 30% of patients receiving raltegravir plus effective ART, shows that an active viral increase was stopped (Reigadas 2010, Buzon 2010, Llibre 2012). A recent study, however, found no increased 2-LTR circles during raltegravir intensification (Besson 2012). Another study demonstrated that resting CD4 T cells were not achieved with raltegravir or with a combination that included valproic acid (Archin 2010) (see below). Sites such as the CNS or gut are not influenced (Yukl 2010, Lee 2011, Yilmaz 2011).

“Kick and Kill” or reservoir eradicators

It is very doubtful that eradication is possible with currently available regimens (Shen 2008, Lewin 2011). Intensification or extension to a four- or five-drug therapy has not had meaningful results. Therefore, the old “Kick and Kill” strategy is being
revived, in which infected cells are first activated in hope of them being recognized by the immune system and killed more rapidly. Several attempts to empty viral reservoirs using different methods (IL-2, hydroxyurea or OKT) have not been successful (Kulkosky 2002, Pomerantz 2002). A pilot study on valproic acid, an epileptic drug, caused a stir in the summer of 2005. Implemented as an inhibitor of histone deacetylase 1 (HDAC), it suggested a clearance of HIV from resting T cells (Lehrmann 2005). In three out of four patients the number of infected resting CD4 T cells decreased significantly and half-life was reduced to 2–3 months compared to other studies showing a longer half-life of 44 months on ART (Siciliano 2003). Other smaller follow-up studies (Steel 2006, Siliciano 2007, Archin 2010) did not confirm these results. More recently, a randomized crossover study finally put an end to the discussion about valproic acid, showing no effect at all in 56 patients (Routy 2010).

With the end of valproate, several new and possibly more potent HDACi are being investigated (Wightman 2012). Among them are vorinostat, active in vivo (Archin 2012), panobinostat (Rasmussen 2012) and others (Edelstein 2009, Matalon 2010). Other chemical classes able to activate latent infected cells are quinolone derivatives (Xing 2012) or disulfiram (Spival 2012). It may be necessary to activate HIV-specific CTLs (Shan 2012) and even the old substance interferon is being discussed again as a possibly important immune modulator (Papasavvas 2012, Mexas 2012). In one study 9 out of 20 patients receiving pegylated interferon during a HAART interruption, demonstrated viral load levels below 400 copies/ml after 12 weeks of IFN monotherapy (Azzoni 2012).

Summary: Considering the complexity of the immune system, which is still not completely understood, a cure probably lies in the distant future. Latently infected cells differ minutely from non-infected cells, which cannot be easily discerned via those methods available in most clinics. They are also non-specific. Washing out the reservoirs or eliminating all the infected memory cells has either been unsuccessful or too toxic. Removing the HIV genome from infected cells with special recombinants has been successful in the laboratory; but there is still a long way to go before this can be used in the clinic (Sarkar 2007).

References


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6.5. When to Start ART?

CHRISTIAN HOFFMANN

“It’s the most important question in HIV therapy” (A. Fauci)

The indication for antiretroviral therapy is based on clinical assessment, CD4 T cell count and viral load. These three factors determine whether therapy should be started or if it should be deferred. At first glance, it appears straightforward, the lower the CD4 count and the higher the viral load, the higher the risk of AIDS (Mellors 1997, Lyles 2000), and the more urgent the indication for treatment. Nevertheless, the best time for initiation of therapy remains the subject of controversial debate. The risk of AIDS must be weighed against the risks of long-term toxicity and viral resistance. In Table 5.1, the current guidelines in the US, Europe, Britain and Germany on starting therapy are summarized. Significant differences can be seen especially in patients with high CD4 T cells.

Table 5.1: Recommendations from various guidelines on when to initiate therapy

<table>
<thead>
<tr>
<th>Clinical</th>
<th>CD4 T cells/µl</th>
<th>Initiation of HAART is …</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC B+C</td>
<td>All values</td>
<td>“Recommended” (DHHS, EACS)</td>
</tr>
<tr>
<td>CDC A</td>
<td>&lt;350</td>
<td>“Recommended” (DHHS, EACS)</td>
</tr>
<tr>
<td>CDC A</td>
<td>350–500</td>
<td>“Recommended” (DHSS) “Should be considered in asymptomatic patients, recommended in patients with hepatitis coinfection, malignant or renal diseases, high risk of cardiovascular/malignant diseases” (EACS)</td>
</tr>
<tr>
<td>CDC A</td>
<td>&gt;500</td>
<td>“Recommended (rating: moderate) in asymptomatic patients, recommended (rating: strong) in patients with hepatitis coinfection or renal diseases” (DHSS) “Should be deferred in asymptomatic patients, recommended if one of the points listed in 350–500 apply” (EACS)</td>
</tr>
</tbody>
</table>


The practice of treatment is ever-changing. In Europe, the median CD4 T cell count at initiation of ART was 200 CD4 T cells/µl in the first years of the last decade, after being 270/µl in 1998 (May 2006). But in more recent years, the pendulum is swinging back. With regard to new drugs that are more potent and better to tolerate, there is a strong trend towards earlier treatment initiation. Patients in resource-limited countries are still starting their ART at CD4 cells lower than 200/µl (Mugglin 2012). At least all international guidelines agree that all symptomatic patients as well as patients with less than 200 CD4 T cells/µl should be treated. Since 2007/2008, most guidelines have determined that a CD4 T cell count of <350 CD4/µl, instead of 200 CD4/µl, is the definitive threshold for initiation of ART. In the US, it has recently increased to 500 CD4/µl. Lack of randomized studies forces all guidelines to partially rely on cohort studies, meta-analyses and evaluation of larger databases. Such data is problematic, however, as important aspects such as compliance or prior treatment regimens are not captured, and very heterogeneous patient populations are included.
A Cochrane analysis concluded that evidence for initiating ART at CD4 levels higher than 200 or 250 cells/µl to reduce mortality rates in asymptomatic patients is of moderate quality. Guidelines merely provide points of reference and are not set in stone. Decisions must be made on a case-by-case basis, even if some health insurance providers tend to ignore this and use guidelines to their advantage. In some situations, therapy may be started earlier than recommended by the guidelines; in other cases, therapy might (or even should) be deferred. Last but not least, the patient should be ready to start. Experience as well as some intuition of the treating physician is mandatory.

### How high is the individual risk of progression?

The following table lists the (selected) risks of developing AIDS within six months, as identified in 3326 patients from the pre-HAART era (Phillips 2004). The range of the individual risk of progression, calculated by using CD4 T cells, viral load and age only, varies widely – from 0 to almost 50%. This may also demonstrate how helpful these surrogate markers can be.

<table>
<thead>
<tr>
<th>Age</th>
<th>Viral load 10,000 copies/ml</th>
<th>Viral load 100,000 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 years</td>
<td>5.3</td>
<td>10.6</td>
</tr>
<tr>
<td>55 years</td>
<td>10.7</td>
<td>20.5</td>
</tr>
</tbody>
</table>


But even after initiation of ART individual risk may vary considerably. Table 5.3 shows individual risks after initiation of ART for different age groups. These data were derived from 12 cohorts in Europe and North America, in which more than 20,000 patients started antiretroviral therapy between 1995 and 2003 (May 2007). It is of note that the data apply only to asymptomatic patients without intravenous drug use (IVDU). In patients with AIDS and in IVDUs, progression risks can be much higher. On the other hand, it seems possible that these data overestimate the individual risk as risk may be lower with the newer drug combinations. Moreover, treatment interruptions were not taken into account (every patient who started with ART was considered to be treated continuously). This fact may also have led to an overestimation of the risk of progression. Thus the values in Table 5.3 are only rough estimates and should be interpreted with caution. However, they could be helpful in any discussion with the patient, of course without browbeating or scaring them with statistics.

One important caveat of cohort studies is the fact that the individual treatment success of the patient is not taken into account. This was shown by an analysis of 13 cohort studies from Europe and North America including 9323 adult treatment-naïve patients who started ART with a combination of at least three drugs. At 6 months after starting ART, the current CD4 T cell count and viral load, but not values at baseline, were strongly associated with subsequent disease progression (Chene 2003).
Table 5.3: Probability (%) of experiencing a new AIDS-defining disease or death by the end of 1 year (5 years) after the patient starts ART. Only valid for patients without previous AIDS and non-IVDUs

<table>
<thead>
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<td>CD4</td>
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16–29 years

<table>
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<th>&lt;100.000</th>
<th>&gt;100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;100.000</td>
<td>10 (19)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>VL &gt;100.000</td>
<td>14 (26)</td>
<td>16 (29)</td>
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</table>

30–39 years

<table>
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<th>&gt;100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;100.000</td>
<td>13 (25)</td>
<td>16 (29)</td>
</tr>
<tr>
<td>VL &gt;100.000</td>
<td>16 (29)</td>
<td>19 (35)</td>
</tr>
</tbody>
</table>

40–49 years

<table>
<thead>
<tr>
<th>CD4</th>
<th>&lt;100.000</th>
<th>&gt;100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;100.000</td>
<td>12 (22)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>VL &gt;100.000</td>
<td>14 (26)</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

> 50 years

<table>
<thead>
<tr>
<th>CD4</th>
<th>&lt;100.000</th>
<th>&gt;100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;100.000</td>
<td>16 (29)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>VL &gt;100.000</td>
<td>19 (35)</td>
<td>22 (39)</td>
</tr>
</tbody>
</table>

From http://www.art-cohort-collaboration.org. VL is copies/mL, CD4 is cells/μl.

To evaluate the individual risk for a treatment-naïve patient, one can check www.art-cohort-collaboration.org (May 2007). Only a few parameters are needed. It is also possible to calculate the risk after 6 months on ART.

Practical experiences

Even if the indication for ART seems obvious, it should be clarified whether the patient is indeed prepared to start treatment (treatment readiness). The problem is not necessarily the initiation of ART, but the longer-term maintenance. The decision to initiate treatment is often made prematurely. It is usually unwise to prescribe antiretroviral medication to a patient in the very first consultation. One should first attain an overall picture of the patient, and try to get to know something about lifestyle and motives – why they have come to see a doctor and what they expect. In some cases, patients put themselves under pressure unnecessarily, or allow others to pressure them. A single low CD4 count, a prolonged case of flu seeming to indicate a weakened immune system (“I never had anything like this before”), springtime lethargy, new study results, a promising new drug in the newspaper (“I’ve heard a lot about the new integrase inhibitors”), a friend/partner who has started therapy – although all of these are good starting points for conversation, none are therapeutic indications. It is often particularly difficult to inform people that not every person with an HIV infection needs immediate therapy.

On the other hand, the patient’s wish to start therapy should be respected. If after a detailed discussion a well-informed patient wants to begin treatment, even though the results justify waiting, ART should not be withheld. For many patients, treatment can be a psychological support. Not everybody can sleep peacefully at night knowing that inside them a hundred million new viruses are being produced every day and a huge number of helper cells are being destroyed. However, if a vacation is planned, it is better to delay therapy, so that treatment response and side effects can be adequately monitored. On the other hand, patients may sometimes find one reason after another (stress at work, exams, change of job, etc) to delay initiation of treatment. Many patients are afraid of AIDS, but often just as afraid of ART (“the pills are the beginning of the end!”). They may have irrational...
or simply false expectations of ART and its consequences – starting therapy does not mean that one will be subjected to daily infusions and no longer able to work. Therapy should be explained to every patient from the outset. It is also useful to define individual threshold values for the commencement of therapy with patients early on, so that therapy is started only when these levels are reached. In our experience, patients are more motivated by this approach.

As a rule, as much time as is needed should be taken for the decision to start therapy. A well informed patient will adhere better. We recommend that patients come for several consultations to get prepared for treatment. There are two exceptions: acute HIV infection (see chapter on *Acute Infection*) and severe immunodeficiency. However, even in the presence of most AIDS-defining conditions, the acute disease should often be treated first before initiating ART, as the potential for complications with PCP, toxoplasmosis or CMV therapies unnecessarily jeopardize treatment options.

In asymptomatic patients with very low CD4 T cells, it makes sense to start first with a PCP prophylaxis. Over the next few days, one can perform an exam (X-ray, ultrasound, fundoscopy, etc) and check the patient’s readiness. Does the patient come back? Are they really motivated?

We also tend to start ART earlier in older patients (>50 years). The regenerative capacity of the immune system in older patients is significantly reduced (Ledermann 2002, Grabar 2004). More importantly, the risk of developing opportunistic infections also depends on age (Phillips 2004). Another example from the CASCADE Study (Table 5.2) exemplifies this: a 25 year-old patient with 100 CD4 T cells/µl and a viral load of 100,000 copies/ml, has a risk of approximately 10% for developing AIDS within six months – for a 55 year-old this level of risk is reached at 150 CD4 T cells/µl and a viral load of 30,000 copies/ml. In Table 5.3 there is a strong association between age and progression.

By now, several guidelines have taken age into account and state that therapy be offered to patients older than 50 years even if CD4 T cells are high. Guidelines also recommend initiation of therapy in cases of hepatitis coinfection, HIV-associated nephropathy, as well as cardiovascular risks and malignant diseases.

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**Practical tips for initiation of ART**

**Below 200 CD4 T cells/µl or an AIDS-defining event**
- Start immediately with ART. Do not wait until acute OI therapy is finished
- Get to know the patient (What took him/her so long to start treatment?), undergo diagnostic procedures, give proper counselling and start treatment with prophylaxes in advance

**Between 200 and 350 CD4 T cells/µl**
- More time can be spent getting to know each other and planning
- Address fears and anxieties before starting therapy
- Try not to start therapy before a holiday or other big event, but do not allow the patient put off therapy indefinitely

**Above 350 CD4 T cells/µl**
- Here again talk about ART at an early stage, so the patient knows what to expect
- Define thresholds below which ART can be initiated (follow current guidelines of 350)
- Do not only consider the absolute CD4 T cells, but observe other individual factors: Coinfection? Age? Malignancy? Pregnancy? If so, start earlier!
- Work with the patient’s wish for when to start
- Is the patient sexually active? Is there a negative partner? It may be also a good reason to start even at high CD4 cells to reduce rates of transmission
- Check to see if the patient is suitable for a clinical trial
It is also important to consider the percentage value along with the absolute value of the CD4 T cell count. In particular, when the CD4 T cell count is high and the immune status appears good, the CD4 percentage is the most important parameter for predicting the risk of developing AIDS. In one study, the risk of progression for patients with more than 350 CD4 T cells/µl was increased approximately four-fold if the percentage of CD4 T cells was below 17% (Hulgan 2005).

Finally, it should not be forgotten that the whole discussion is based on “minimum” figures, as CD4 T cells are actually surrogate markers. As a surrogate, they are a substitute for clinical endpoints. They are only a rough expression of the clinical reality. Although they usually do this very well, and even though the CD4 count is one of the best surrogate markers in medicine, it is not everything. The patient also has to be considered.

**Asymptomatic patients with more than 200 CD4 cells/µl**

**200–350 CD4 cells/µl:** Today, the guidelines all recommend an initiation of therapy for this patient group. Even if randomized studies are not available and the risk of infection is rather low, in the long run the risk of developing AIDS cannot be excluded (Emery 2008). There is no reason to think the patient 100% safe. We have seen patients in this range of CD4 cell counts develop Kaposi’s sarcoma, PML or lymphoma. A look at the calculation presented above (May 2007), gives a rough idea about the individual risk. After ART initiation, a 45 year-old asymptomatic patient with 200–350 CD4 T cells/µl, a viral load below 100,000 copies/ml and not a drug user has an AIDS mortality risk of 3.1% after one year, and 8.7% after five years. Starting ART above 350 CD4 T cells/µl, reduces the risk to 2.0% and 7.3% for the same patient. If the patient was 50 years old and the viral load over 100,000 copies/ml, the five-year risk would be lowered from 13.1% to 11.0%. Such a reduction of just 1 or 2% may seem insignificant at first. However, in times of well-tolerated antiretroviral therapies, the risk of developing AIDS or even dying from the infection is relevant. Is it worth exposing patients without urgent symptoms to the dangers of AIDS for the sake of a little more quality of life? How much long-term toxicity is really saved by one, two or maybe even three years without therapy over a period of twenty or thirty years? Talk with the patient. The lesser the probabilities of toxicity, the earlier ART will be initiated in the future.

A randomized study from Haiti published in the NEJM, showed that an immediate start also makes sense in developing countries: in 812 patients with 200–350 CD4 cell/µl, only 6 cases of mortality occurred in the group receiving ART immediately compared to 23 cases in the group who waited. The number of incident cases of tuberculosis was significantly reduced from 36 to 18 (Severe 2010).

New data were presented by HTPN-052, a trial with 1,763 HIV-discordant couples in the US, Africa and Asia. The requirements were that HIV-infected partners were treatment-naive with CD4 T cells between 350 and 550/µl. They were then randomized for ART, either immediately or in a rather late stage when CD4 T cells reached below 250/µl or even after manifestation of AIDS (Cohen 2011). Although the trial’s primary endpoint was HIV transmission, preliminary results showed that the numbers of severe HIV disease and death were significantly lower in the group starting ART immediately (45 versus 60, p=0.01). However, a major reason for this difference was caused by extrapulmonary tuberculosis (3 versus 17), which, at 55%, was most frequently observed in India.

**Above 350 CD4 cells/µl:** For this patient group according to the German-Austrian guidelines, therapy initiation is “acceptable” and, in the presence of additional criteria, “generally recommended” (i.e., hepatitis coinfection, patients above 50 years old). In the US, therapy initiation is recommended as of 500 CD4 cells/µl.
However, even beyond this level, there seems to be an associated risk with CD4 T cell counts and AIDS or mortality. In a large-scale British cohort (>30,000 patient years) with therapy-naïve patients the risk was 24.9 per 1000 PY at 350–499 CD4 T cell/µl, compared to 15.4 at 500–649 CD4 T cells/µl and 9.6 with more than 650 CD4 T cells/µl. The US HOPS cohort also suggests a survival benefit of patients who initiate ART above 350 CD4 T cells/µl (Palella 2003). This study also evaluated patients who had started with a mono- or dual-therapy. Possibly a difference would not have been visible with contemporary therapies. In addition, the mortality risk was low. According to more recent information from this cohort (Lichtenstein 2006), the risk was 15.9/1000 PY at 200–349 CD4 T cells/µl (350–500 CD4 T cells/µl: 11.5/1000; over 500: 7.5/1000).

In a new study from the US, 17,517 asymptomatic patients were evaluated who started ART between 1996 and 2005 (Kitahata 2009). In this very complex (incomprehensible for the layman) and expensive analysis an advantage was observed even above 500 CD4 T cells/µl. Other studies have not confirmed these results (Sterling 2003). This also applies to the ART cohort collaboration, in which 20,000 patients from 15 mostly European-based cohorts were evaluated, who started antiretroviral therapy after 1997. There was no benefit of starting above 450 CD4 T cells/µl (Sterne 2009).

To raise a heretical question, does early therapy initiation have benefits only in the US, not in Europe? Or are methodological problems of cohort analysis and statistical distortion the reason for this discrepancy? This debate will be interesting to follow. A worldwide randomized study to evaluate optimal therapy initiation with asymptomatic patients with good CD4 T cells is enrolling. Since 2009, worldwide 3000 patients with more than 500 CD4 T cells/µl are to be enrolled in the START study. One half will start with ART immediately, while the other half will wait until CD4 T cells are below 350 CD4 cells/µl or until symptoms appear. First results are expected in two to three years.

It is important that all asymptomatic patients with allegedly good values are still regularly followed. One should not only watch out for absolute CD4 T cell count, but other factors should also be observed, see box below.

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**Important factors to be considered even with good CD4 T cells**

- Is a drop of absolute CD4s visible: how fast is it? Always look at relative values (percentage), observe CD4/CD8 ratio, absolute values often vary greatly.
- Because variations exist, a CD4 T cell count should always be measured before starting therapy. One measurement is not enough.
- How high is the viral load, does the overall picture make sense? CD4 T cell count drops are rare at lower viral loads <10,000 copies/ml.
- What levels did the patient previously have? Someone whose CD4 T cells have always been at 1000 and suddenly falls to 350 probably has a higher immune defect than someone who goes from 450 CD4 T cells to 350.
- Is the patient ready for therapy? How well informed are they? How compliant will they be? If the patient is reluctant and anxious, more time must is needed for preparation before beginning therapy.
- How old is the patient? The immunologic regeneration capacity decreases with age. The older the patient, the earlier one should start.
- Are there symptoms that the patient has not noticed or considers not worth mentioning? Examine physically on a regular basis! OHL, thrush, mycoses, etc.
- A drop of 50–100 CD4 cells/µl per year is too much. Do not wait too long.
Late Presenters: AIDS and/or <200 CD4 T cells/µl

Although treatment possibilities have dramatically improved, many patients still present at a very late stage of infection. Questions about beginning an optimal therapy are superfluous as these patients are more or less classified as urgent. There is no consensus regarding the definition of “late presenter”. In most cases, a CD4-cell count below 200/µl and/or a manifest AIDS disease at the time of HIV diagnosis will do. “At the time of HIV diagnosis”, however, is broadly defined and ranges from three months to three years. Moreover, some authors also classify the groups “late testers”, “very late presenters” and even “long-term non-presenters”.

At the second “HIV in Europe” conference in November 2009, it was agreed that those patients with a CD4 cell count below 350/µl at initial presentation are to be referred to as late presenters (Antinori 2011). In the US and probably in other countries, they still constitute more than half of all patients (Althoff 2011). Even if this definition makes sense in terms of health policy (patients come “late”, because they have fallen below the recommended threshold value for therapy initiation), it is yet to be seen if this definition prevails. For clinical research, it already raises problems, as very heterogenic patient groups are being put together. Below, late presenters are restricted to patient groups showing symptoms or with less than 200 CD4 T cells/µl.

Incidence and risk factors of a late HIV diagnosis

How frequent are late presenters? Lacking an overall valid definition, rates between 10–44% are currently being reported in different European countries and the US with a recently slightly downward trend (Table 5.4).

### Table 5.4: Frequency of late diagnosis in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Period (n)</th>
<th>Definition of late diagnosis</th>
<th>% (ADE)</th>
<th>Trend over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy (Borghi 2008)</td>
<td>1992–2006 (884)</td>
<td>CD4 &lt;200 cells/μl or AIDS &lt;3 months</td>
<td>39 (24)</td>
<td>Decline from 43 to 35%</td>
</tr>
<tr>
<td>France (Delpierre 2008)</td>
<td>1996–2006 (6,805)</td>
<td>CD4 &lt;200 cells/μl or AIDS &lt;1 year</td>
<td>38 (17)</td>
<td>Decline from 43 to 32%</td>
</tr>
<tr>
<td>Spain (Carnicer 2009)</td>
<td>1987–2006 (6,186)</td>
<td>AIDS &lt;3 months</td>
<td>(44)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Great Britain (HPA 2009)</td>
<td>2008 (7,218)</td>
<td>CD4 &lt;200 cells/μl</td>
<td>32</td>
<td>Not stated</td>
</tr>
<tr>
<td>USA (CDC 2009)</td>
<td>1996–2005 (281,421)</td>
<td>CD4 &lt;200 cells/μl or AIDS &lt;1 year</td>
<td>38</td>
<td>Decline from 43 to 36%</td>
</tr>
<tr>
<td>Switzerland (Wolbers 2009)</td>
<td>1998–2007 (1,915)</td>
<td>CD4 &lt;200 cells/μl</td>
<td>31</td>
<td>No clear trend</td>
</tr>
</tbody>
</table>

ADE = AIDS-defining disease.

In the last few years several studies have looked at the risk factors of late diagnosis (Table 5.5). The characteristics of late presenter, observed in several countries (advanced age, migrant origin, heterosexual transmission, see above) indicate more complex reasons for a late diagnosis. They probably involve patients (less access to health system, lack of information, fear of stigmatization), as well as doctors and members of the health system (among others lack of HIV awareness with certain
6.5. When to Start ART?  161

patient groups). Several studies enforce the notion that, even with high-risk patients, many chances of diagnosing HIV at an earlier stage are missed (Duffus 2009, Jenness 2009). As much as 76% of 263 African patients living in London had visited a general doctor a year before HIV was diagnosed. Of note, 38% were in outpatient care and 15% had received inpatient treatment in the year before HIV diagnosis (Burns 2008).

Table 5.5: Risk factors for late diagnosis in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy (Borghi 2008)</td>
<td>Advanced age, male, foreign origin</td>
</tr>
<tr>
<td>France (Delpierre 2008)</td>
<td>Age over 30 years, non-MSM, hepatitis coinfection, HIV diagnosis before 2003</td>
</tr>
<tr>
<td>Spain (Carnicer 2009)</td>
<td>Male, age under 30 or over 40 years, MSM or heterosexual transmission. Protective: IVDU</td>
</tr>
<tr>
<td>USA (CDC 2009)</td>
<td>Advanced age, male, ethnic origin non-white</td>
</tr>
<tr>
<td>Great Britain (UK Chic 2010)</td>
<td>Heterosexual transmission</td>
</tr>
<tr>
<td>Switzerland (Wolbers 2009)</td>
<td>Advanced age, ethnic origin non-white. Protective: MSM, IVDU, living alone</td>
</tr>
<tr>
<td>Germany (Zoufaly 2011)</td>
<td>Higher age, heterosexual transmission, migration background</td>
</tr>
</tbody>
</table>

**Morbidity, mortality – consequences of a late HIV diagnosis**

Up to 90% of AIDS-defining diseases today, appear with viremic – mainly untreated – patients. This applies greatly to classical opportunistic infections such as PCP or CMV retinitis, but also to tuberculosis or Non-Hodgkin lymphoma (ART-CC 2009). In the German Lymphoma Cohort, two-thirds of patients with newly diagnosed NHL had not previously received ART. 40% of patients with AIDS, a group associated with the highest mortality rate even today, are diagnosed with NHL and HIV infection simultaneously (Hoffmann 2009). In a British analysis counting 387 deaths of HIV-infected patients in the years 2004/2005, as many as 24% of all deaths and 35% of HIV/AIDS-related deaths were ascribed to a late HIV diagnosis (Lucas 2008). An account analysis showed that, treating expenditures increased by 200% with less than 200 CD4 T cells at the time of HIV diagnosis (Krentz 2004). This may be attributed to the immune reconstitution syndrome (IRIS) frequently observed in late presenters (see chapter on AIDS).

There is no doubt that a late HIV diagnosis is associated with higher mortality and morbidity risk. The risk increases with lower CD4 T cells at therapy initiation (Egger 2002, Sterne 2009). An analysis of therapy-naïve patients in three major European cohort trials observed 8.3 new AIDS cases per 100 patient years in patients with less than 200 CD4 cells/µl at the beginning of therapy – and only 1.8/100 patient years in those with at least 350 CD4 T cells/µl. The mortality rate was slightly higher with 2.9 versus 0.7/100 (Phillips 2001). Several other cohort trials also found a clear association between CD4 T cells at therapy initiation and AIDS and mortality rates (Cozzi-Lepri 2001, Kaplan 2003, Palella 2003, Braitstein 2006). The lesser the CD4 T cell count, the higher the risk for the following time period, over many years (Lanoy 2007). Increased mortality remains with very low rates (less than 25 CD4 T cells/µl) even six years after starting ART and maybe longer (ART-CC 2007).

A complete reconstitution of the immune system is rarely the case if the patient's initial situation is poor – the worse the immune system, the more unlikely a complete recovery (Garcia 2004, Kaufmann 2005, Gras 2007). Viral suppression over
several years cannot change that. In a study with patients on ART showing a constant low viral load below 1000 copies/ml for at least 4 years, 44% of patients with less than 100 CD4 cells/µl at initiation of ART failed to reach 500 CD4 T cells/µl even after 7.5 years. Patients with 100–200 CD4 T cells/µl still showed a risk of immune non-recovery of 25% (Kelley 2009). Another risk factor, besides low CD4 T cells, is advanced age, which has been observed frequently with late presenters. The ability to regenerate the immune system decreases with age and is probably caused by degeneration of the thymus (Lederman 2000, Viard 2001, Grabar 2004). A consequence of a late start of ART can also mean that the antigen-specific immune reconstitution against HIV, as well as opportunistic viruses, remain poor. Many studies suggest that the qualitative immune reconstitution cannot keep up with the quantitative (Gorochov 1998, Lange 2002). Which seems obvious. But why does the risk of AIDS drop so dramatically with rising CD4 T cell count? How can patients with severe immunosuppression safely discontinue a prophylaxis, as soon as their CD4 T cell count is above 200/µl? Clinical observations seem to show differently, at least for the time being.

However, the relevance of a limited immune constitution in the long run is not yet clear. Recent data from the ClinSurv Cohort suggests that a discordant response (low CD4 T cells in spite of good viral suppression) is only associated with higher AIDS risk in the first few months. With virally well-suppressed patients, the CD4 T cells are no longer a good surrogate marker for risk of AIDS (Zoufaly 2009). In contrast to the immunologic response, virologic response in combination with poor starting conditions is generally not worse than with other patients. Nevertheless, 89% out of 760 patients with AIDS at HIV diagnosis showed a viral load below 500 copies/ml after initiating ART (Mussini 2008).

**When to start ART?**

Patients with a poor immunological state should begin ART quickly. This recommendation applies for CDC stage C (AIDS-defining diseases) and for all stage B diseases. However, it has not yet been agreed on how quickly one should start ART within the context of an acute opportunistic infection (OI). Up to now, many therapists preferred to tend to the acute disease first and to wait a few weeks before beginning ART. They hoped to avoid the unnecessary high complication potential of OI therapies. The first randomized trial addressing this idea has made this strategy questionable (Zolopa 2009). In ACTG A5164, 282 patients with acute OI (63% PCP, cases of tuberculosis were omitted) were randomized to start ART either immediately or at earliest time after completing OI therapy. On average, the “immediate” group started ART 12 days after initiation of OI therapy, whereas the “later” treated group after 45 days. Although the intervals were not so wide apart, distinct differences could be observed after 48 weeks: the group treated immediately showed significantly less fatalities and less new cases of AIDS. The risk to have to adjust ART was slightly higher, but not the number of severe undesired incidents, hospitalization or cases of IRIS. The authors concluded that patients with an acute OI (at least of PCP) should immediately start ART. In Germany, the IDEAL study with PCP and toxoplasmosis patients will check these results.

Regarding tuberculosis, at least five large randomized trials worldwide have discussed the optimal time to start ART (Abdool 2011, Blanc 2011, Havlir 2011, Török 2011, Wondwossen 2012). The general overview is as follows: Neither mortality nor AIDS-related mortality are significantly improved by immediate initiation of therapy. Patients showing below 50 CD4 T cells at diagnosis of tuberculosis seem to pose an exception. It must always be considered that immediate initiation always implies the risk of a paradoxical worsening of tuberculosis associated with IRIS, reaching up
to 30% in some trials. Negative effects on survival have been observed in the case of tuberculosis meningitis (Törok 2012). The same applies for cryptococcal meningitis (Makadzange 2009).

It is likely that differentiated recommendations depending on the OI must be given (Lawn 2011). There is also some controversial debate, as to whether patients with malignant lymphomas and newly diagnosed HIV infections should receive ART immediately or after chemotherapy (see chapter on Lymphoma).

**ART for late presenters – What to start with?**

An active OI is an obligatory exclusion criteria in almost every clinical trial. Thus, this patient group is always underrepresented in evaluation of clinical efficacy data. The question if late presenters should be treated with a special antiretroviral therapy is therefore not clear and depends more than with other patients on individual decision-making (Manzardo 2007) (see above on “What to Start?”). Regarding immunologic success, no relevant difference was measured between NNRTI- and PI-based regimens with late presenters (Landay 2003, Samri 2007). New ARV classes are also considered for late presenters. In favor of raltegravir are its low interaction potential, its overall tolerance and effectiveness in reducing viral load compared to efavirenz, especially in the first weeks (Murray 2007). However, as described in chapter 6.4, there is no evidence for a better immune reconstitution with drugs such as raltegravir or maraviroc (not yet indicated in Europe for first-line therapy).

**References**


Graz L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. J AIDS 2007, 45:183-92.


6.6. What to Start With?

CHRISTIAN HOFFMANN

Once the decision has been made to start, the next question is, what to start with? More than two dozen drugs are now available, and the number of theoretically possible combinations seems to be almost infinite. In many guidelines, more than ten different combinations are recommended as “preferred”, while numerous more are listed as “alternatives”.

It would be brilliant if every treatment-naïve patient participated in a clinical study. That would be the best way to continue improving the quality of antiretroviral therapy. However, in practice it is not always possible to sign everyone up for a clinical trial. For information regarding the treatment of naïve patients, the following summarizes the available data.

Recommended first-line regimens

Combinations that we currently recommend for first-line therapy (as of June 2012) are shown in Table 6.1. In the list, there is no order of preference. Moreover, many other combinations are possible. These other combinations may be acceptable in individual cases or in investigational studies, but general recommendations for their use are not given. Problematic drugs or combinations that are not advisable for use are listed at the end of this chapter.

Table 6.1: ART combinations suitable for initial therapy (in no order of preference)

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>3rd agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + FTC</td>
<td>Atazanavir/r (PI)</td>
</tr>
<tr>
<td>*ABC + 3TC</td>
<td>Darunavir/r (PI)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir/r (PI)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/r (PI)</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Efavirenz** (NNRTI)</td>
</tr>
<tr>
<td>AZT + 3TC</td>
<td>Nevirapine*** (NNRTI)</td>
</tr>
<tr>
<td>TDF + 3TC</td>
<td>Rilpivirine**** (NNRTI)</td>
</tr>
<tr>
<td></td>
<td>Raltegravir (INI)</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/c***** (INI)</td>
</tr>
</tbody>
</table>

* Only when HLA typing is possible; caution when risk for cardiovascular events is high.
** Caution in women of childbearing age (teratogenicity).
*** Beware of hepatotoxicity when CD4 T cells are high (women >250, men >400/μl).
**** Not in patients with high baseline viral load (>100,000 copies/ml).
***** Licensed in the US in mid-2012, in a fixed-dose with TDF+FTC.

Part 1: Practical approach to the first regimen – important rules

All current initial regimens consist of two nucleoside analogs combined with either a boosted PI, an NNRTI or the integrase inhibitor raltegravir. No single combination has clearly been shown to be superior to any other. There is no one gold standard. When choosing primary therapy, many factors are involved besides the antiviral potency and tolerability. Individual factors, such as compliance, concurrent illnesses and concomitant medications, as well as the needs of the individual, should be included in the decision. One should be aware that primary (first-line) therapy is of great significance and needs to be well prepared for. It is at this time that the chance of viral suppression followed by long-term maintenance of suppression is greatest. However, many patients are very nervous at this point. Knowledge is limited and expectations are often unrealistic (“do I need injections?”).
6.6. What to Start With?

**Practical tips for first-line therapy**

- The first regimen offers the best chance of suppression followed by long-term maintenance. The viral load should decrease to below detection levels within 3–6 months.
- Do not rush – the patient must be ready for ART. If in doubt, wait and continue to monitor levels.
- If possible, do not prescribe medication in the first consult with a new patient who brings their results. Do you know the patient well enough? Are they really motivated? Will they come back?
- For every patient, prescribe the ART they are able to take. Do not insist on theoretically superior combinations.
- The pros and cons (side effects) of different combinations should be discussed – make enough time for this.
- The initial regimen should be taken no more than twice daily. Once-daily treatment should be considered if it is important for the patient.
- The toxicity profiles should not overlap whenever possible – never use several allergenic drugs simultaneously.
- Ask about other medication (and drug use) – are relevant interactions to be expected?
- Concomitant illnesses should also be checked – what about the liver (hepatitis), kidneys?
- All drugs are started on the same day – no “lead-in” mono- or dual therapy.
- Be sure to check whether the patient would be eligible for a clinical study. All patients, especially if treatment-naïve, should be encouraged to participate in clinical trials, which may help the patient reach a better understanding of the importance of treatment and good adherence. Take your time.

**What should be clarified first**

**Dosing issues**

For many patients the numbers of pills or requirements for food intake are important. The range of licensed and recommended initial regimens varies from 2 to 7 pills per day. Some patients find it unacceptable to have to take pills at certain times during the day with fatty foods as required with rilpivirine. A patient who works in shifts should not take efavirenz. Patients today are more demanding than before – justifiably so. There are now alternatives. Even the size or consistency of tablets can be a problem. Such issues must be discussed before initiating therapy as ART needs to become one more part of normal daily life.

**Adherence**

Compliance is defined as a patient’s consent and acceptance of therapy. In the mid-90s a new term, “adherence”, from the English language, was adopted. Since then, the more politically correct term – “adherence” is frequently used. This term refers to both physician and patient working together to set up a treatment concept acceptable to both parties and emphasizes that responsibility for failure of the therapy is not automatically the patient’s fault.

Adherence includes all factors that influence staying on a regimen, in terms of acceptability, under these three headlines:

1. The success of a treatment is endangered if medication is taken irregularly
2. Clinicians tend to overestimate a patient’s adherence
3. Adherence diminishes with the complexity of the treatment
No doubt: adherence is the Achilles’ heel of every antiretroviral therapy and non-adherence the main, if not the major factor for developing resistance and treatment failure (Turner 2000). Partial viral suppression with insufficient drug levels is an ideal condition under which resistance grows. ART must be taken regularly, correctly or not at all. Taking either more than 90% or less than 69% of the treatment are both associated with a lower risk of resistance (Sethi 2003).

Not only drug users, those dependent on alcohol or patients with side effects are considered “risky patients” when it comes to adherence. In several studies, depressed patients, patients living alone and younger patients have been identified as problem groups (Murri 2001, Glass 2006). Positive factors are the physician’s experience, the patient’s confidence in the positive effects of ART, and social support. Race, sex or stage of disease does not seem to be relevant. The individual’s general view of illness and health, accepting modern medicine and fear of side effects are further considerations. However, all these factors vary greatly, and in the end, adherence is difficult to predict in individual cases (Lerner 1998). The physician must rely on experience and intuition.

The importance of taking drugs regularly has been demonstrated in numerous studies. In one study with 99 patients, in which compliance was evaluated via an electronic monitoring system, the rate of viral treatment failure was only 22% in patients with a compliance level of at least 95% (95% of doses taken). Failure rates of 61% and as much as 80% were measured with a patient’s adherence between 80–94% and <80% (Paterson 2000). However, it must be taken into consideration that this much-cited study is outdated. Newer drugs, such as darunavir, with longer half-lives, higher resistance barriers and better overall pharmacokinetics may forgive a clearly higher non-compliance (Nelson 2010). In the previously mentioned study, clinicians misjudged their patient’s compliance in 41% of the cases. Nurses did better – judging incorrectly in only 30% of the cases (Paterson 2000). Adherence tends to be overestimated in other studies as well (Miller 2002).

The importance of adherence was also demonstrated in patients with directly observed therapy (DOT) or directly administered ART (DAART), applied in some penal institutions in the US. In institutions in Florida, 100% of the patients in a DOT study achieved a viral load below 400 copies/ml after 48 weeks, compared to 81% in an unmonitored control group (Fischl 2001). According to one randomized study, response improved in drug-addicted patients receiving DAART (Maru 2009). However, more recent data indicate that effects of DAART with PI based regimens are marginal and disappear rapidly as soon as the patient is on his own (Gross 2009, Smith-Rohrberg 2009, Berg 2011). Only transient effects have also been seen in studies evaluating DOT in HIV-infected methadone patients or in African patients (Nachega 2010, Berg 2011, Nahvi 2012). The virologic benefit of these strategies wanes following transition to self-administered therapy.

Poor adherence not only leads to virologic failure. It also bears immunological consequences (Mannheimer 2002). Moreover, poor adherence has clinical effects beyond surrogate markers. In a Spanish study, patients who did not take more than 10% of their drugs showed a four-fold increase of mortality risk (Garcia 2002). This data has been confirmed in other studies (Maher 1999, Hogg 2000, Wood 2004). Hospital stays are also less frequent in patients with high adherence to ART (Paterson 2000). In addition, it should be considered that non-adherent patients increase the risk of transmission of primary resistant viruses.

The basic mechanisms for development of resistance should be explained to patients. Intensive early adherence counseling at ART initiation results in a sustained, significant impact on adherence and less virologic treatment failure (Chung 2011)! One must emphasize that, in contrast to other chronic illnesses, resistance mutations do
not disappear once they have developed. Diabetes and hypertension make effective examples. These diseases may “tolerate” forgetting some tablets occasionally, but HIV is different. Blood glucose and blood pressure levels can easily be lowered again the next day, but with HIV this strategy may not work. Even short-term lapses can have irreversible consequences. And every new occurrence of resistance complicates therapy. Patients have to be made aware of these dangers. Such conversations should be repeated from time to time and become a standard component of routine care. Cooperation with special treatment discussion groups offered by patient-centered support organizations can be useful. The 12-step table below provides additional suggestions.

In addition, a number of strategies on improving adherence have been investigated. They range from employment of additional nurses and patient community to telephoning patients regularly (Review: Kenya 2011). The effect of these strategies, however, depends on the individual setting of the patient (Collier 2005, Chung 2011, Pop-Eleches 2011).

**Twelve steps to improve compliance**

- Every patient should receive a written (understandable by the patient) treatment plan, which should be reviewed at the end of the visit. It should include a telephone number to call in case of problems or questions, accessible evenings and weekends would be even better.
- Patient and clinician should agree on the treatment plan. The patient’s concerns, questions and criticisms should be discussed.
- The patient should have the impression that the treatment regimen is not randomly chosen, but tailored to his/her individual needs.
- The explanation of a new or modified treatment plan takes time, and should not be rushed – all questions should be answered.
- The reasons why adherence is so important should be explained. It makes sense to repeat such conversations – they should not only take place when initiating or modifying treatment, but should be part of routine care.
- Possible side effects should be explained, as well as what can be done to alleviate them.
- Support groups and other types of assistance should be named and offered.
- It is important to tell the patient to come back if any problems are encountered with ART – it is better to try to solve them together rather than have the patient try to deal with them alone at home.
- The patient should know that the treatment regimen must be taken in its entirety (avoid, “Last month I left out the big tablets”).
- Prescriptions should be documented, in order to get a rough idea of adherence. Irregularities should be addressed openly. Pills counted, bottles checked?
- During all stages of therapy, the patient should be informed of treatment success as seen by reduction of viral load and rise in CD4 count.
- Ensure clinical vigilance to detect the early signs of depression and treat appropriately.

If adherence remains poor

Despite all efforts, some patients will not succeed in improving their adherence. Physicians and other healthcare providers should not take this personally or feel offended. Although it may be difficult to accept the patient’s views on life, disease and treatment, healthcare providers must keep tolerance and acceptance as key components in their interactions with patients. Some providers, especially those who treat selective patient populations in university settings, tend to forget the reality of
routine medical practice. Rigidly upholding the principles of modern medicine usually does not help here and putting patients under pressure achieves even less. It is important to clearly outline and explain, advise, help, question and listen. The question of whether noncompliant patients should continue to be treated with antiretroviral therapy is not always easy to address. On the one hand, there are patients who benefit even from suboptimal therapy; on the other hand, drugs are expensive and should not be prescribed too readily. Restraint should be applied until the reason for poor compliance is understood. Perhaps referral to counseling (peer support?) is needed.

**Duesbergians – a sect of HIV medicine**

Patients who refuse antiretroviral treatment on principle are a special case. These patients are frequently on treatment by (shockingly misdirected) doctors, who call themselves “Duesbergians” (after the US virologist and AIDS dissident Peter Duesberg, who denies any association between AIDS and illness). In such cases, it can be very difficult to leave patients to their fate. Informative consultations should be as detailed as possible and preferably documented in writing.

An example: An approximately 40-year-old patient with a long history of untreated HIV, 30 CD4 T cells/μl and cerebral toxoplasmosis (TE), which improved significantly after 4 weeks of acute treatment (the last MRI still showed scattered lesions) introduced his case to the HIV outpatient department. Clinically, he was relatively well and fully oriented and due for discharge that day. In a conversation, the patient categorically refused to start the urgently recommended antiretroviral therapy. His Duesbergian physician had advised him against HIV therapy (“You can die from AZT, and the other drugs are not much better, etc”). He refused antibiotics on principle as well. This was why the patient would not continue the TE maintenance therapy, which had made him suffer from diarrhea (NB, probably cryptosporidiosis), skin problems (seborrhoic dermatitis, thrush), and extreme loss of weight (MAC?) since his first day in hospital. It was very important for him to have a break from all medication. In such cases, we make sure the patients sign the information sheets. Every patient is allowed to and should decide for himself (if fully cognizant and capable) – they must know and be fully informed about what they are doing. It is important to give the patient control: if they change their mind, they may return! In our experience, arguing with medical Duesbergians leads to nothing at all. This sect has a very restricted view of the world and stick to their repetitive mantra-like arguments. Discussing with them is time-consuming and a waste of energy. Fortunately, these cases have become rarer. The initial widespread skepticism towards ART has decreased significantly, due to its overwhelming success in the last few years. Concerning Peter Duesberg, he is relatively quiet, as far as his HIV activities go. The sect is in decline.

**Concurrent illnesses**

Before starting treatment, possible concurrent illnesses should be identified (anamnesis, examination). This is fundamental in helping make the right choice (Table 6.2). For example, a patient with diarrhea should not be given fosamprenavir or lopinavir. Use tenofovir or indinavir with caution in patients with renal disease. Atazanavir may also be associated with renal diseases (Mocroft 2010). ddI and d4T are contraindicated in patients with a history of pancreatitis or polyneuropathy and are no longer recommended in first-line therapy. Non-insulin-dependent diabetes can become insulin-dependent with PI treatment. Patients with osteoporosis or osteopenia should avoid tenofovir. If caution is needed with abacavir in individuals with an increased risk of myocardial infarction, as recommend by some experts (Behrens 2010), is not clear (see abacavir).
Liver disease and chronic hepatitis must also be taken into account, because the risk of developing severe hepatotoxicity on nevirapine or ritonavir is high (Sulkowski 2000). Caution is also required with boosted PIs. However, one study conducted in over 1000 patients found no difference between lopinavir/r and an unboosted PI such as nelfinavir in patients coinfected with hepatitis C (Sulkowski 2004). In coinfections with HBV, 3TC, or even better, TDF+FTC should be utilized (Avihingsanon 2010). Long-term monitoring of HBV over a span of five years or longer is useful with tenofovir (de Vries-Sluijs 2010). However, in HBV-coinfected patients starting ART, two HBV drugs should be used in order to reduce the risk of HBV resistance. Avoid Combivir® or Kivexa® in cases of hepatitis B coinfection when no other HBV agent is on board – 3TC alone for HBV is not enough. Last but not least, a wish for parenthood should be considered. Women of childbearing age should avoid efavirenz.

**Interactions with medications and drugs**

Interactions are important in when choosing regimens. Whereas interactions between antiretroviral drugs are well known, those with other medications are often less well characterized (see section on interactions). The urgent need for more research was demonstrated in a study investigating the interactions between ART and lipid lowering agents. In healthy volunteers, the measurement of plasma levels showed that levels of simvastatin were elevated by 3059% after concurrent dosing with ritonavir or saquinavir (Fichtenbaum 2002). Several cases of fatal rhabdomyolysis on simvastatin, atorvastatin and PIs such as atazanavir, lopinavir and nelfinavir, have been described (Hare 2002, Mah 2004, Schmidt 2007). There are even case reports on pravastatin and rosuvastatin (Mikhail 2009, de Kanter 2011), so boosted PIs should be utilized with caution.

Many other drugs should be avoided in combination with particular antiretroviral drugs, as incalculable interactions may occur. These include certain contraceptives. Even drugs that seem unproblematic at first glance can have unfavorable effects. For example, the plasma levels of saquinavir can be reduced by half with administration of garlic capsules (Piscitelli 2002). Even a seemingly harmless agent such as vitamin C can influence plasma levels. A small study in healthy volunteers showed that vitamin C can significantly lower (14%) unboosted indinavir levels (Slain 2005).
Coumarin derivative anticoagulants, such as warfarin can also be a problem; ritonavir can significantly lower plasma levels (Llibre 2002). Further typical problem drugs include migraine remedies, prokinetic drugs and sedatives/hypnotics. One fatal case was described with ergotamine and ritonavir (Pardo 2003). The simultaneous administration of ART and PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) can also be problematic (see section on Sexual Dysfunction).

Drugs or alcohol can interact with ART (Neuman 2006, Mass 2006). For those in substitution programs, the methadone requirement may be significantly increased by certain antiretroviral drugs, such as nevirapine and efavirenz (Clarke 2001). To a lesser extent, this is also true for ritonavir and nelfinavir. There is inconsistent data on lopinavir but it may also require dose adjustments. Raltegravir, again, seems to have no effects (Anderson 2010).

Other interactions have even more dangerous consequences. Several deaths have been reported after simultaneous dosing with ritonavir and amphetamines or MDMA/ecstasy, the popular narcotic gamma hydroxybutyric acid (GHB) or “liquid ecstasy” (Henry 1998, Harrington 1999, Hales 2000). Ritonavir in particular inhibits the metabolism of amphetamines (speed or MDMA/ecstasy), ketamines or LSD (Antoniou 2002). Clinicians and patients are well advised to have an open conversation about drug use before starting therapy. Marijuana and THC appear to have a low potential for interactions (Kosel 2002). Amphetamines seem to be particularly dangerous and neurotoxic in HIV patients (Chana 2006).

Not every agent can be discussed here. Many are described in the respective drug chapters and in the Interactions chapter. It is always recommended to check the package insert. Initiation of ART provides a good opportunity to re-evaluate existing prescribed medications.

### Additive toxicities

Several potential additive toxicities should be considered in the choice of therapy. If other myelotoxic drugs (i.e., valgancyclovir, cotrimoxazole) are necessary, caution is required with AZT. When treating hepatitis C with interferon and ribavirin, ddl must be avoided. Ribavirin should not be combined with AZT or d4T. d4T should generally be avoided due to its potentially high toxicity. Tenofovir, indinavir, possibly also atazanavir should also be avoided with potentially nephrotoxic drugs. Lastly, it is not advisable during primary therapy to start with potential allergy-inducing agents if anti-infectious prophylaxis with cotrimoxazole or other sulphonamides is necessary. Included here are all NNRTIs and abacavir, but also fosamprenavir and darunavir. In these cases, it is better to avoid these ARVs. Otherwise, it can be difficult to clearly identify the causative agent for a drug-induced exanthema.

### References


Part 2: What drug classes should be used?

All combinations currently used as initial regimens consist of two NRTIs plus either a PI, an NNRTI or the integrase inhibitor raltegravir. In summer 2012, the FDA approved the integrase inhibitor elvitegravir (boosted with the new pharmacoenhancer cobicistat, see below). A third NRTI (triple nuke) is only used in exceptional cases and is only briefly mentioned here. All other combinations are currently (June 2012) not justified for use outside the framework of clinical studies. Advantages and problems of these three strategies are outlined in Table 6.3.

Table 6.3: Combining drug classes: Advantages (↑) and disadvantages (↓)

<table>
<thead>
<tr>
<th>2 Nukes + PI</th>
<th>2 Nukes + NNRTI</th>
<th>2 Nukes + INI</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ a lot of data, including clinical endpoints and severely immunocompromised pts.</td>
<td>↑ equivalent, perhaps even better suppression of viral load than with PIs</td>
<td>↑ very good efficacy, excellent tolerability</td>
</tr>
<tr>
<td>↑ long-term data available</td>
<td>↑ low pill burden, once-daily may be possible</td>
<td>↑ few interactions</td>
</tr>
<tr>
<td>↑ high genetic resistance barrier</td>
<td>↑ leaves PI options</td>
<td>↑ maintains options</td>
</tr>
<tr>
<td>↓ high pill burden (for the older PIs), some once-daily regimens not licensed</td>
<td>↓ clinical effect not proven (only surrogate marker studies)</td>
<td>↓ limited long-term data</td>
</tr>
<tr>
<td>↓ frequent drug interactions</td>
<td>↓ less data in severely immunocompromised patients</td>
<td>↓ once-daily with raltegravir not possible</td>
</tr>
<tr>
<td>↓ some PIs with cross-resistance, leaving limited options</td>
<td>↓ rapidly occurring complete cross-resistance, low resistance barrier</td>
<td>↓ No clinical endpoints</td>
</tr>
<tr>
<td>↓ long-term toxicity, lipodystrophy, dyslipidemia with most PIs</td>
<td>↓ strict monitoring required initially (esp. nevirapine), allergies frequent</td>
<td>↓ relatively low resistance barrier</td>
</tr>
</tbody>
</table>
Studies comparing these strategies are listed in Table 6.4. The validity of previous milestone trials such as Atlantic (van Leeuwen 2003) is considered limited today due to outdated combinations and are not mentioned here.

In most of the trials, the antiviral potency of the regimens was comparable, measured by the number of patients with viral load below the limit of detection. In ACTG 5142, an advantage of efavirenz over lopinavir/r was observed after 96 weeks (12% more patients got to below 50 copies/ml). However, if ART failed, resistance was less frequent and CD4 T cells increased more in the LPV/r arm. The ACTG 5142 trial showed that NNRTIs were possibly more effective than boosted PIs, because they were better tolerated. Resistance, however, occurs faster on NNRTIs than on PIs, which is probably due to the low resistance barrier. This phenomenon was observed in trials such as FIRST, ARTEN and ACTG 5202 (Gardner 2008, Daar 2011, Soriano 2011).

Table 6.4: Randomized studies on agents of different classes as initial regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>3rd agent</th>
<th>Major results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large well-powered studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTG 5142 (Riddler 2008)</td>
<td>EFV versus LPV/r (n=250+253)</td>
<td>Less VF on EFV, severe AEs same (but more lipoatrophy on EFV)</td>
</tr>
<tr>
<td>ACTG 5202 (Daar 2010)</td>
<td>EFV versus ATV/r (n=929+928)</td>
<td>VF same, more severe AEs on EFV (in combination with ABC+3TC), but better lipid profile</td>
</tr>
<tr>
<td>ARTEN 5202 (Soriano 2011)</td>
<td>NVP versus ATV/r (n=376+193)</td>
<td>VF same, slightly more severe AEs and resistances with NVP, better lipid profile with NVP</td>
</tr>
<tr>
<td>STARTMRK (Rockstroh 2011)</td>
<td>EFV versus RAL (n=282+281)</td>
<td>VF same, more AEs</td>
</tr>
<tr>
<td><strong>Smaller trials or trials in resource-limited countries or in subgroups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALTAIR (Puls 2010)</td>
<td>EFV versus ATV/r (n=114+105)</td>
<td>VF same, AEs same (slightly less increase of peripheral fats with EFV)</td>
</tr>
<tr>
<td>KISS (Maggiolo 2009)</td>
<td>EFV versus ATV/r (n=124+62)</td>
<td>VF same, AEs same</td>
</tr>
<tr>
<td>PHIDISA (2010)</td>
<td>EFV versus LPV/r (n=888+883)</td>
<td>VF same, clinical endpoints same (South Africa &lt;200 CD4 T cells/AIDS)</td>
</tr>
<tr>
<td>Sierra-Madero 2010</td>
<td>EFV versus LPV/r (n=95+94)</td>
<td>Less VF under EFV than on LPV/r, better lipid profile on EFV (Mexico, &lt;200 CD4 T cells)</td>
</tr>
<tr>
<td>NEWART (De Jesus 2010)</td>
<td>NVP versus ATV/r (n=75+77)</td>
<td>VF same, but lipids better with NVP</td>
</tr>
<tr>
<td>OCTANE II (McIntyre 2010)</td>
<td>NVP versus LPV/r (n=249+251)</td>
<td>VF same, but more severe AEs with NVP (African women &lt;200 CD4 T cells)</td>
</tr>
<tr>
<td>Lubumbashi (Clumeck 2012)</td>
<td>NVP versus LPV/r (n=425)</td>
<td>Less VF under LPV/r, clinical endpoints comparable (Zaire)</td>
</tr>
<tr>
<td>004 (Markowitz 2009)</td>
<td>EFV versus RAL (n=38+160)</td>
<td>VF same, more AEs with EFV</td>
</tr>
</tbody>
</table>

Note: Different (partly randomized) NRTI backbones were utilized, in some cases there were other trial arms. VF=Virologic Failure, AE=Adverse Events. Note: The MERIT study is not mentioned here, as maraviroc is not licensed for first-line therapy in Europe. This is also the case for the new FDC Stribild®, consisting of TDF+FTC plus elvitegravir/c
These observations were confirmed in a systematic evaluation of 20 studies that included 7949 patients (see Table 6.5). All of the patients had been treated with either an NNRTI or a boosted PI, and had additionally received 3TC or FTC. Virologic failure was as frequent on NNRTIs as on PIs (4.9% versus 5.3% of patients, \( p=0.50 \)). However, major differences were observed in patients with virologic failure whose genotypic resistance testing was successful. Mutations were significantly higher with NNRTIs. This applied for NRTI key mutations like the M184 and K65R, and also for other resistance mutations.

Table 6.5: Rates of resistance mutations at therapy failure on first regimens containing NNRTIs or PIs, in percentages (Gupta 2008)

|                   | NNRTIs       | PIs            | \( p \)  
|-------------------|--------------|----------------|-----
| M184V             | 35.3 (29.3-41.6) | 21.0 (14.4-28.8) | <0.001 |
| K65R              | 5.3 (2.4-9.9)   | 0 (0-3.6)       | 0.01 |
| Resistance to third agent (NNRTI or PI) | 53.0 (46-60) | 0.9 (0-6.2) | <0.001 |

Data on resistance development for the integrase inhibitors raltegravir and elvitegravir in initial regimens is limited and long-term data lacking. There is evidence that resistance rates are somewhat lower than seen with NNRTIs but higher than with PIs. However, studies testing raltegravir versus efavirenz showed at least comparable efficacy with overall better tolerability over a period of more than three years (Rockstroh 2011).

Thus, the pros and cons for the different strategies continue, and controversy over the best first-line therapy persists. One should be warned against cross-trial comparisons, which are often used as marketing strategies to influence health providers on the effectiveness of a specific treatment ("we achieved over 90% tolerance rates in our study"). In a systematic evaluation of 10 large-scale randomized trials with 2341 therapy-naïve patients receiving AZT+3TC+efavirenz, the success rates (viral load in the ITT analysis <50/copies/ml at 48 weeks) ranged between 37% and 77%. This broad range was seen with use of the same combination in ART-naïve patients. Heterogeneous patient populations and study designs (definition of therapy failure), clinician experience and patient adherence may lead to variations (Hoffmann 2007). Below, various strategies or primary therapies are discussed. These include:

- Two NRTIs plus an NNRTI
- Two NRTIs plus a PI
- Two NRTIs plus an integrase inhibitor (INI)
- Three or four NRTIs (triple nuke, quadruple nuke)
- Experimental combinations (nuke-sparing, intensive approaches)
- Problematic primary therapies to be avoided
1. Two NRTIs plus an NNRTI

NNRTIs have an equal if not superior effect on surrogate markers compared to PI combinations. NNRTIs have performed well in numerous randomized studies: efavirenz-based regimens were superior to unboosted PIs such as indinavir or nelfinavir (Staszewski 1999, Robbins 2003) and at least equivalent to lopinavir/r (Riddler 2003), atazanavir (Daar 2010) or raltegravir (Rockstroh 2011). Nevirapine-containing regimens were roughly equivalent to atazanavir/r or lopinavir/r (McIntyre 2010, Soriano 2011).

Advantages of NNRTI regimens include the low pill burden and good long-term tolerability. In contrast to PIs, however, data with clinical endpoints is not available. Neither is there any long-term data or studies on severely immunocompromised patients. A disadvantage of NNRTI combinations is the rapid development of cross-resistance. This could result in failure, especially for highly viremic patients, although this has not been confirmed. Resistance upon virologic failure is generally more frequent on NNRTIs than on PIs (Gupta 2008, see above).

Allergies are frequent on all NNRTIs. The incidence is highest with nevirapine, but allergies are also seen with efavirenz, etravirine or rilpivirine. Hepatic adverse events requiring careful monitoring (nevirapine) but also central nervous system side effects and potential teratogenicity (efavirenz) should be considered. The 2NN trial showed no significant difference in efficacy between efavirenz and nevirapine in combination with d4T+3TC (van Leth 2004).

**TDF+FTC plus efavirenz** is one of the most frequently used combination at present and available as a fixed-dose regimen (FDC), Atripla®. In the Gilead 934 Study and in the large Switch trial, TDF+FTC plus efavirenz was more effective than AZT+3TC plus efavirenz (Arribas 2008, Fischer 2010). It should be noted that in Europe, approval for Atripla® is stricter than in the US. Although the bioequivalence with each individual substance has been shown, the EMA restricts the use of Atripla®. It is only approved for patients with virologic suppression under 50 copies/ml for at least three months on their current antiretroviral regimen. Furthermore, patients must not have experienced virologic failure with an earlier treatment combination or be known to have resistance to any of the three components in Atripla®. These slightly strange restrictions should be observed in Europe, as TDF+FTC (Truvada®) and efavirenz (Sustiva®) only require one more pill a day. Instead of FTC one can also use 3TC. In the double-blind, randomized Gilead 903 Study, this combination was effective and less toxic than d4T+3TC plus efavirenz (Gallant 2004). However, the combination of TDF+3TC is seldom used today in Europe and the US, as there is no FDC available. Moreover, there is no reason to use 3TC instead of FTC.

**TDF+FTC plus nevirapine** is also a frequently prescribed regimen. However, there is less data available than for efavirenz. Smaller trials observed an increased risk for therapy failure and for development of resistance, especially when viral load was high (Lapadula 2008, Rey 2009). The large ARTEN trial also showed a slightly higher risk for resistance with TDF+FTC plus nevirapine, but an altogether comparable efficacy to TDF-FTC plus atazanavir/r (Soriano 2011). In favor of nevirapine are its good lipid profile (Podzamczer 2012) and the excellent long-term tolerability, despite some risk for severe allergies and hepatotoxicity in the first few weeks. Since 2011, an extended-release tablet of nevirapine is on the market which can be taken once-daily.

**TDF+FTC plus rilpivirine** is a new option since the use of the FDC tablet Eviplera® was approved in November 2011. In a double-blind randomized trial (ECHO), this combination proved altogether as effective as TDF+FTC and efavirenz with slightly better tolerance regarding lipids and CNS side effects (Molina 2011, Cohen 2011). However, resistance mutations and virological failure rates were higher, especially in
highly viremic patients. This is why approval is limited to therapy-naïve patients with viral loads below 100,000 copies/ml. Eviplera must be taken with a meal in order to be absorbed properly.

**ABC+3TC plus efavirenz** is an alternative first-line therapy, if HLA testing to predict hypersensitivity to abacavir is available. The combination ABC+3TC plus efavirenz has been evaluated with success in numerous large trials such as CNA30024 (Dejesus 2004), ZODIAC (Moyle 2004) and ABCDE (Podzamczer 2006). More recent studies such as ACTG 5202 and ASSERT showed slightly less efficacy than on comparable regimens (Post 2010, Daat 2011). In ASSERT, less renal and bone side effects and were observed than with TDF+FTC (Post 2010, Stellbrink 2010). Data on ABC+3TC plus nevirapine or rilpivirine are so far limited.

**AZT+3TC plus efavirenz or nevirapine** were among those regimens most frequently used and have been evaluated in numerous milestone trials (006, Combine, ACTG 384, 5095, 934). Side effects may occur during the first weeks. In the 934 Study, anemia and gastrointestinal problems occurred frequently, which significantly compromised the efficacy of AZT+3TC in contrast to TDF+FTC (Arribas 2008). Side effects such as increased lipids and lipodystrophy are significantly reduced by switching to TDF+FTC (Fischer 2010). Another disadvantage is the fact that with these combinations (including AZT), QD dosing is not possible. This regimen can only be recommended if there are good reasons not to use tenofovir or abacavir.

### 2. Two NRTIs plus a PI

The combination of two NRTIs plus one protease inhibitor is the only three-drug combination ART that is supported by efficacy data from randomized studies with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). Given the high resistance barrier and the robustness of these regimens, many experts still prefer to use these combinations today, particularly in advanced patients or those with high viral load. Resistance on boosted PIs is significantly less than with NNRTIs or integrase inhibitors; PI/r resistance hardly exists (Gupta 2008). The slightly higher pill burden and frequent gastrointestinal side effects, which complicate adherence, are disadvantages of a PI-containing therapy. Often small factors are important when choosing the right PI, see Table 6.6.

<table>
<thead>
<tr>
<th>Pill number/day</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>ATV/r</th>
<th>SQV/r</th>
<th>FPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily dosing? yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no (US: yes)</td>
</tr>
<tr>
<td>Intake with food? Irrelevant</td>
<td>Irrelevant</td>
<td>Irrelevant</td>
<td>yes</td>
<td>yes</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Important side effects Diarrhea (mild)</td>
<td>Diarrhea</td>
<td>Hyperbilirubin., icterus</td>
<td>Diarrhea (mild)</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Main study ARTEMIS</td>
<td>Diverse</td>
<td>CASTLE</td>
<td>GEMINI</td>
<td>KLEAN</td>
<td></td>
</tr>
</tbody>
</table>

The following briefly describes the most common combinations:

**TDF+FTC plus darunavir/r** has been licenced for initial therapy since February 2009 and is one of the preferred first-line regimens in most guidelines. The combination proved at least as effective as TDF+FTC plus lopinavir/r in the ARTEMIS trial. With regard to tolerance it was even better (less diarrhea, less lipid changes) (Ortiz 2008). The effects remain stable out to 96 weeks (Mills 2009). Another advantage of this combination is the once-daily dosing. The resistance barrier is very high and resistance mutations are rarely seen.
TDF+FTC plus atazanavir/r was approved for first line in 2008. In the CASTLE trial, atazanavir/r proved virologically equal to lopinavir/r, but with better lipids and similar tolerance (Molina 2010). Although a randomized study showed no difference between unboosted and boosted atazanavir (Malan 2008, Squires 2009), boosting with ritonavir is recommended. The main arguments in favour of this combination are the low number of pills and the good lipid profile (compared to lopinavir/r). The major disadvantage is hyperbilirubinemia, which often manifests as harmless but disturbing icterus.

TDF+FTC or ABC+3TC plus lopinavir/r have been categorized in many guidelines as a preferred combination. However, after the results of CASTLE, ARTEMIS and ACTG 5142 (see above), lopinavir/r was down-graded in the US (by the DHSS) to an “alternative” regimen. More data is available for TDF+FTC as a backbone for lopinavir/r, although the HEAT study did not find significant differences compared to ABC+3TC (Smith 2008). Since 2009 lopinavir/r has also been licensed for once-daily use, after several studies showed similar efficacy and tolerability (Molina 2007, Gathe 2009). However, there is some evidence that the potency of once-daily dosing is slightly less than with BID (Ortiz 2008, Flexner 2010). Lopinavir/r lost its main disadvantage of requiring cool storage compared to other boosted PIs with the introduction of the Norvir® tablets in 2010.

ABC+3TC (or TDF+FTC) plus fosamprenavir/r: In the KLEAN study, this combination proved almost equal to ABC+3TC plus lopinavir/r in regard to both efficacy and tolerability. Better rates of diarrhea or cholesterol levels were, however, not achieved (Eron 2006). In the ALERT study, fosamprenavir/r was as effective as atazanavir/r, both combined with a TDF+FTC backbone (Smith 2006). In Europe, once daily use of fosamprenavir/r has not been licensed, although using a low booster of 100 mg ritonavir should be possible (Hicks 2009, Cohen 2010).

TDF+FTC plus saquinavir/r: Saquinavir was the first PI which showed a survival benefit (Stellbrink 2000). In the relatively small GEMINI study saquinavir/r with a TDF+FTC backbone proved to be non-inferior to lopinavir/r (Walmsley 2009). The even smaller BASIC study showed that a once-daily dosing (1000/100) was comparable to atazanavir/r with regard to lipid profiles (Vrouenraetes 2009). The main disadvantage of saquinavir-based regimens is the twice-daily dosing and the high pill burden, which is why the combination is rarely used today.

3. Two NRTIs plus one integrase inhibitor
Raltegravir was licensed as the first integrase inhibitor for first-line treatment in 2009. In 2012 elvitegravir was licenced by the FDA (European approval is pending). Tolerance and efficacy are both excellent. Convincing long-term data covering a period of 3–5 years, especially regarding tolerability, are lacking. Indication is especially adequate when NNRTIs or PIs are less favorable for primary therapy, i.e., when interactions are expected.

TDF+FTC (TDF+3TC) plus raltegravir: in the large STARTMRK trial, raltegravir proved at least as effective as efavirenz (Lennox 2010). Viral load decreased more rapidly in the raltegravir arm and CD4 T cell counts increased. In addition, tolerance was better and effects lasted over 196 weeks (Rockstroh 2011). It should be noted that data is available for raltegravir with TDF-based backbones while data for ABC+3TC or other backbones is still very limited. A pilot study with ABC+3TC plus raltegravir, however, showed no negative effects (Young 2010). Unfortunately, once-daily dosing of raltegravir is not possible (Vispo 2010, Eron 2011).
TDF+FTC plus elvitegravir/c: The combination of the four Gilead agents TDF+FTC, elvitegravir and the new pharmacoenhancer cobicistat in a single tablet regimen (STR, Stribild®) was approved by FDA in summer 2012. Two large Phase III trials yielded excellent results: In 236-0102 and 0103, Stribild® has shown at least comparable efficacy with Atripla® and TDF+FTC+atazanavir/r (Sax 2012, DeJesus 2012). Tolerability was good, except for some more cases of nausea and slight elevations of kidney enzymes. Approval in Europe is still pending.

4. Three or four NRTIs – triple nuke or quadruple nuke

Triple or quadruple nuke therapies have some theoretical advantages: fewer interactions, no side effects typical of PIs or NNRTIs, and the fact that all other drug classes can be spared for later. The major disadvantage of triple nuke therapies is that they are virologically less potent than other combinations. While this may not be the case with quadruple nukes, the increasing knowledge of the mitochondrial toxicity of NRTIs makes pure nuke therapies less attractive.

AZT+3TC+ABC in a single tablet Trizivir® (BID) is the classic triple nuke therapy. Since ACTG 5095, Trizivir® is no longer equivalent (Gulick 2004) and clearly less effective than AZT+3TC plus efavirenz. This also applies for developing countries, where Trizivir® is still occasionally propagated (Munderi 2011).

AZT+3TC+TDF: We have some experience with this approach (Mauss 2005). Given the different resistance pathways of AZT and TDF, the thymidine analog seems to be protective against tenofovir-associated mutations (Rey 2006, see chapter on resistance). However, larger studies have not been conducted. The use of this combination has also met with some criticism (Maggiolo 2009).

AZT+3TC+ABC+TDF: Some studies have reported good responses and low rates of virologic failure on this quadruple nuke therapy (Moyle 2006, Elion 2006, Gulick 2007, Ferrer 2008). However, these studies were not powered to demonstrate equivalence to other combination regimens. In two randomized studies, discontinuation rates were high, due to adverse events (Mallolas 2008, Puls 2010). In the ALTAIR study, it proved less effective than the standard ART regimen (Puls 2010). The long-term toxicity and efficacy of these combinations is still unknown.

TDF+3TC+ABC+ddl should be avoided (Jemsek 2004, Gallant 2005, Khanlou 2005). In up to 49% of patients, early virologic treatment failure was seen, probably due to a low genetic resistance barrier (Landman 2005). This is also true for treatment-experienced patients who want to simplify their therapy (Hoogewerf 2003, Perez-Elias 2005).

Conclusion: Pure NRTI combinations are not recommended for first-line therapy. Triple nuke is poorer in comparison to regimens of at least two classes and the results of some of the single-class combinations are truly not good. Data on quadruple nukes is too limited. However, triple and quadruple nuke therapy remains under consideration for maintenance therapy (see Chapter 7).

5. Experimental combinations

Antiretroviral therapies need to be more effective and tolerable. Although integrase and entry inhibitors offer new options, investigation with classic ART is still ongoing. Two approaches have attracted great interest: combinations without any NRTIs (nuke-sparing), and so-called induction therapies. Both approaches will be discussed below.
6.6. What to Start With?

Nuke-sparing

All classical ART regimens have to date included a backbone of two nucleoside or nucleotide analogs. This is mainly historical: nucleoside analogs were the first drugs on the market, and by the time NNRTIs and PIs were under development, treatment with two nucleoside analogs was standard. With growing knowledge of the mitochondrial toxicity of nucleoside analogs, nuke sparing, i.e., omission of NRTIs, is increasingly being investigated, even for first-line therapy. Nuke-sparing with pretreated patients will be discussed further on (see When to Switch).

Data for nuke-sparing as first-line is limited. As shown in Table 6.8, mostly smaller studies have been conducted so far.

**NNRTI plus PI:** ACTG 5142 was the first large study providing convincing evidence for the nuke-sparing strategy (Riddler 2008, Haubrich 2011, see above). This study showed that a combination of lopinavir/r and efavirenz was not inferior to two NRTIs with either lopinavir/r or efavirenz. This was also shown by a smaller study (Harris 2009). In contrast, a randomized African trial found that different nuke-sparing regimens (different NNRTIs plus PIs) were inferior to standard ART regimens (Duvivier 2008). It is still unclear whether side effects really improve with nuke-sparing regimens. A sub-study of HIVNAT 009 reported that lipoatrophy resolved, and that visceral fat and subcutaneous limb fat increased (Boyd 2005). In CTN 177 nuke-sparing regimens had a favorable effect on lactate levels (Harris 2005). In ACTG 5142 rates of lipoatrophy were lower in the nuke sparing arm (Haubrich 2009). However, adverse events in total were not reduced and dyslipidemia was observed even more frequently (Riddler 2008).

Poor response rates were observed with double PI therapies, which is why this nuke-sparing approach will probably not be further investigated for now (Landman 2009, Ulbricht 2011).

**INI/CCR5A plus PI:** Many studies are ongoing, especially with raltegravir and maraviroc, plus a PI: raltegravir is not only being looked at with lopinavir/r or atazanavir/r (PROGRESS, CCTG 589), but also with darunavir/r in treatment-naïve patients (RALDAR, NEAT 001). Maraviroc is also being combined with darunavir/r (MODERN). Is this the future? What does the current data say?

The randomized PROGRESS study evaluating 206 ART-naïve patients showed a more rapid and impressive reduction of viral load after 8 weeks with raltegravir and lopinavir/r than with the classic combination of TDF+FTC plus lopinavir/r. After 48 weeks, the antiviral effect was comparable (Reynes 2011). The results remained stable out until 96 weeks (Soto-Malave 2011).

In ACTG 5262, a single-arm study with darunavir/r plus raltegravir, many patients did not achieve a viral load to below detection level at week 48 and 5 out of 112 patients developed resistance to raltegravir (Taiwo 2011). Strikingly, these patients already showed several resistance mutations at baseline and there was some doubt whether all patients really were treatment-naïve. However, the SPARTAN study confirmed these results, where 4/63 (6.3%) patients developed raltegravir resistances on a combination of raltegravir and unboosted atazanavir (Kozal 2010). On account of these results, the study was discontinued prematurely. Unfortunately, PK data of patients showing virological failure was not available, which could have explained the therapy failure. Raltegravir, however, probably reduces the level of atazanavir (Zhu 2010). A striking observation in SPARTAN was the high rate of severe hyperbilirubinemia (grade 4), with 21% on atazanavir plus raltegravir, compared to no cases in the TDF+FTC plus atazanavir/r (Kozal 2010). This combination can therefore not be recommended now. In view of the rather low resistance barrier, a boosted PI as a partner seems necessary.
Table 6.7: Prospective studies on nuke-sparing regimens in treatment-naïve patients and patients with little prior treatment experience (intent-to-treat analyses)

<table>
<thead>
<tr>
<th>n ( naïve)</th>
<th>Combination</th>
<th>(Study)</th>
<th>Percentage &lt;50 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI + PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staszewski 1999</td>
<td>148 (126)*</td>
<td>EFV+IDV (006 Study)</td>
<td>47% at 48 weeks</td>
</tr>
<tr>
<td>Boyd 2003</td>
<td>61 (0)*</td>
<td>EFV+IDV/r (HIVNAT 009)</td>
<td>69% at 96 weeks</td>
</tr>
<tr>
<td>Allavena 2005</td>
<td>86 (65)*</td>
<td>EFV+LPV/r (BIKS)</td>
<td>73% at 48 weeks (&lt;400)</td>
</tr>
<tr>
<td>Riddler 2008</td>
<td>253 (253)</td>
<td>EFV+LPV/r (ACTG 5142)</td>
<td>83% at 96 weeks</td>
</tr>
<tr>
<td>Harris 2009</td>
<td>14 (14)</td>
<td>NVP+LPV/r (CTN 177)</td>
<td>78% at 48 weeks</td>
</tr>
<tr>
<td>Ward 2006</td>
<td>63 (63)</td>
<td>EFV+ATV/r (BMS 121)</td>
<td>63% at 48 weeks</td>
</tr>
<tr>
<td>INI/CCR5 + PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kozal 2010</td>
<td>63 (63)</td>
<td>RAL+ATV (Spartan)</td>
<td>81% at 24 weeks</td>
</tr>
<tr>
<td>Portsmouth 2011</td>
<td>60 (60)</td>
<td>MVC+ATV/r (A4001078)</td>
<td>74% at 48 weeks</td>
</tr>
<tr>
<td>Nozza 2011</td>
<td>19 (19)</td>
<td>MVC+LPV/r (VEMAN)</td>
<td>83% at 12 weeks</td>
</tr>
<tr>
<td>Reynes 2011</td>
<td>103 (103)</td>
<td>RAL+LPV/r (PROGRESS)</td>
<td>83% at 48 weeks</td>
</tr>
<tr>
<td>Taiwo 2011</td>
<td>112 (112)</td>
<td>RAL+DRV/r (ACTG 5262)</td>
<td>26% VF at 48 weeks</td>
</tr>
</tbody>
</table>

*Patients all PI-naïve. VF=Virologic Failure

Promising first results were shown with the combination atazanavir/r and low-dose maraviroc (Portsmouth 2011). Resistance mutations were not observed in this study; however, larger studies with maraviroc and darunavir/r such as MODERN are pending. It will be important to combine maraviroc with a boosted PI, as the tropism test does not always show valid results. There remains a risk for patients starting an insufficient monotherapy if non-R5 viruses are not recognized. In this setting, a monotherapy with a boosted PI would be less harmful than other drug classes.

With regard to the data available, it is still premature to be able to recommend nuke-sparing as an equal alternative in its own right.

Monotherapy, alternating therapy

Can it get any easier? Several studies introduced a very avant-garde concept in the summer of 2003: monotherapy with boosted PIs. With respect to the high resistance barrier of boosted PIs, success was considerable (Gathe 2009). Lipoatrophy can be avoided (Kolta 2011). However, in many studies, low-level viremia was found to be more frequent on monotherapies. In the MONARK study, only 64% (compared to 75% on AZT+3TC+lopinavir/r) of patients on lopinavir/r achieved a viral load of less than 50 copies/ml at 48 weeks (Delfraissy 2008). At 96 weeks it was only 47% (Ghosn 2009). Darunavir/r also started to show weaker effects in a small pilot study (Patterson 2009). According to one overview, the overall efficacy of monotherapy is slightly less effective to standard ART (Bierman 2009). This strategy is not recommended for treatment-naïve patients. In view of the constantly growing choice of well-tolerated combinations, it is difficult to find good arguments for monotherapy other than cost aspects and possibly as yet unknown long-term side effects.

Another approach is alternating therapy, which involves changing treatment every few weeks. In the SWATCH Study (Martinez-Picado 2003) a total of 161 patients were randomized to a regimen of d4T+ddd+efavirenz or AZT+3TC+nelfinavir. A third arm changed between the two regimens every three months when the viral load was below the level of detection. After 48 weeks, virologic failure in the alternating arm was significantly reduced. There was no difference for any other parameters (CD4 T cells, side effects, adherence, and quality of life). Considering the fact that several therapies are well-tolerated, alternating strategies, which can be very confusing for the patient, have never gained much attraction.
Induction with 4 or 5 drugs

Some experts speculate on whether more intensive approaches than conventional triple combinations are necessary for patients with high viral load. Because of fear of rapid development of resistance, some physicians give initial treatment with an induction of four or even five drugs, and then simplify to a triple combination once the viral load has dropped below the level of detection. This theoretical concept has not yet been validated, and is based on hypotheses or smaller proof-of-concept studies (Ramratnam 2004) in which it has been shown that the viral load falls faster under intensive combinations than under standard therapies with three active drugs. Approaches in which multiple individual drugs (usually nucleoside analogs) are given have to be distinguished from approaches in which three instead of two classes of drugs are used.

**Multiple individual drugs:** Current data indicates that there is no benefit to using this strategy. Giving two PIs or two NNRTIs instead of one sometimes produces even negative results (Katzenstein 2000, van Leth 2004). There is also no evidence in favor of giving three instead of two NRTIs (Staszewski 2003, Orkin 2004, Mallolas 2008, Hammer 2010). In ACTG 5095 with 765 patients, there was clearly no difference between Combivir® plus efavirenz and Trizivir® plus efavirenz, not even when the starting viral load was higher, or with regard to resistance (Gulick 2005).

**More drug classes:** The data on whether to use three or two drug classes is less clear. Large studies on this subject, such as ACTG 388 (Fischl 2003), ACTG 384 (Robbins 2003, Schafer 2003), INITIO (Yeni 2006) or FIRST (May Arthur 2006) were conducted with old combinations with nelfinavir as the main PI and ddI+d4T as the backbone. Therefore, validity of these studies is limited. A more recent randomized study with additional doses of T-20 in late presenters showed some effect on the viral load after 24 weeks, but these results were not sustained through week 48 (Joly 2010).

In summary, it is questionable whether intensification of therapy leads to any improvement at all and produces anything more than toxicity and cost. The studies above indicate that supposed improved efficacy (not shown in many trials) is counterbalanced by more side effects. Indeed, there is the risk of scaring patients away with the higher number of pills and side effects. It is unclear whether and in which patients such intensification of therapy is useful, and which drugs would be optimal.

### 6. Suboptimal first-line therapies

Combinations generally considered to be suboptimal include all forms of mono- and dual therapy, especially two nucleoside analogs. Even one nucleoside analog plus one NNRTI is not good as shown by the INCAS Trial (Montaner 1998). When using NRTIs, it is important to make sure that they are not competing for the same pocket. The thymidine analogs AZT and d4T are even antagonistic (Pollard 2002). The same is true for FTC and 3TC. According to a warning letter by the company BMS in March 2011, d4T should generally be avoided (not only in first-line).

Full dose ritonavir can be rejected as an active agent, as tolerability is very poor. There is no longer a reason to use ddI, indinavir, saquinavir or nelfinavir in a first-line regimen. Some drugs, such as T-20, etravirine, and tipranavir are not licensed for use in primary therapy. Drugs such as ddC (HIVID®), saquinavir-SGC (Fortovase®) and amprenavir (Agenerase®) have been taken off the market.

**NNRTI combinations** act non-competitively at the same site, and furthermore all can cause a rash, making differential diagnosis difficult. Efavirenz levels seem to be lowered considerably in combination with nevirapine (Veldkamp 2001). In the wake of the 2NN study, it seems clear that the combination of efavirenz and nevirapine
should be avoided. The study arm with this combination fared worse than the other arms, mainly due to toxicity (Van Leth 2004). NNRTIs should also not be combined with raltegravir alone – the resistance barrier is probably too low.

**TDF in a triple-nuke combination** should not be administered. Many studies have reported poor response rates, particularly in combination with ABC+3TC (Hoogewerf 2003, Jemsek 2004, Khanlou 2005, Gallant 2005) (see Triple Nukes).

**TDF+ddI**: at least five trials looking at TDF+ddI plus an NNRTI resulted in a high failure rate, and some were stopped prematurely (Leon 2005, Podzamczer 2005, Maitland 2005, van Lunzen 2005, Torti 2005). BMS even issued a warning letter concerning TDF+ddI. The combination of TDF+ddI no longer has a place in antiretroviral therapy.

**Starting gradually**: All drugs should be started simultaneously. Highly significant differences were shown between patients who had received three drugs immediately compared to those patients who were started on only two drugs (Gulick 1998, Ait-Khaled 2002). This is significant in the long-term. A large cohort study showed that the risk of virologic failure was doubled even years later if dual therapy had been the starting regimen, even for as little as a few weeks (Phillips 2002). Initiating triple therapy gradually, as is sometimes practiced due to concerns of side effects, is wrong and dangerous.

**Avoidable mistakes in first-line therapy**

- Mono- or dual therapy (except in controlled trials) as well as a gradual introduction of therapy – always start with a complete ART regimen
- Starting at a lowered dose (except for nevirapine)
- T-20, delavirdine, tipranavir, etravirine, maraviroc (not licensed for primary therapy in Europe)
- d4C (HIVID®), SQV-SGC (Fortovase®), amprenavir (Agenerase®) – distribution has been stopped
- Ritonavir (not tolerated – only for use as low-dose booster)
- AZT+d4T and 3TC+FTC (antagonistic effects)
- D4T in general
- TDF+ddI (diverse reasons), d4T+ddI (toxicities)
- TDF in triple-nuke therapy (especially without thymidine analogs)
- Simultaneous introduction of ABC and NNRTIs without prior HLA testing (allergy potential)
- Efavirenz+nevirapine (too toxic)
- Efavirenz or nevirapine+raltegravir (low resistance barrier)

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Kakuda TN, Anderson PL, Becker SL. CD4 cell decline with didanosine and tenofovir and failure of triple nucleoside/nucleotide regimens may be related. AIDS 2004;18:2424-2.


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6.7. When to Switch?

CHRISTIAN HOFFMANN

Antiretroviral therapy has to be modified frequently, even though the rates of modification and interruptions have declined during recent years. In EuroSIDA, among almost 1200 patients who began ART after 1999, at one year after initiation, only 70% of patients remained on their original regimen. 24% had changed, and 6% were off all treatment (Mocroft 2005). In an evaluation of the Swiss Cohort, 42% of 1318 patients beginning ART between 2005 and 2008 had modified therapy after one year, 22% of them due to side effects (Elzi 2010). In general, ART is switched for three main reasons (interruptions will be discussed separately):

- Acute side effects
- Long-term toxicity (or concerns regarding them)
- Virologic treatment failure

Switching due to acute side effects

Not every acute side effect requires immediate modification. Mild nausea or diarrhea at the beginning can and should be tolerated. Gastrointestinal side effects that occur during the first weeks are not dangerous and often improve spontaneously or can be treated symptomatically. The same is true for some allergic reactions and for relatively mild CNS disorders. Talking with the patient, suggestions on how to tolerate or palliate certain problems with the idea that these will not continue indefinitely will help. However, certain adverse drug events almost always require discontinuation or switch of ART (see box).

### Side effects that almost always require discontinuation/change of ART

- Severe diarrhea, which persists despite loperamide even after several weeks (usually with nelfinavir, lopinavir/r, fosamprenavir/r, saquinavir/r)
- Severe nausea, which persists despite metoclopramide, which requires continuous treatment or leads to significant weight loss (usually AZT, ddI)
- Persistent sleeping disorder (efavirenz)
- Polyneuropathy (d4T, ddI, possibly also 3TC), often resolves very slowly
- Severe anemia (AZT)
- Severe, progressive muscular weakness (d4T, ddI)
- Pancreatitis (ddI, ddI+TDF, d4T+ddI, in rare cases lopinavir/r)
- Lactic acidosis (most often d4T+ddI, but also all other NRTIs)
- Severe allergies with involvement of mucous membranes, fever (typically abacavir, all NNRTIs, more rarely fosamprenavir or darunavir)
- Renal failure (tenofovir, indinavir), nephrolithiasis (indinavir)
- Hepatotoxicity with transaminases >5 x normal values (nevirapine, tipranavir)
- Jaundice (nevirapine, atazanavir, indinavir, tipranavir)
- Rhabdomyolysis (raltegravir)
- Severe repetitive onychitis (indinavir, possibly also 3TC)
- Depression, psychosis (efavirenz, possibly also AZT)
Switching due to concerns over long-term toxicity

In the last few years, many clinicians have started to change virologically successful combinations out of concern for cumulative long-term toxicities, especially in cases of lipodystrophy and dyslipidemia. The switch strategy is based on the assumption that not all antiretroviral agents have similar toxicities. The most important switch studies are discussed below.

**PI replacement with other agents**

PIs may cause side effects in the long-term. Among these are lipodystrophy with abdominal fat accumulation and at the back of the neck, but also gastrointestinal side effects and dyslipidemia. The data on replacement of a successful PI with other classes, such as NNRTI, NRTI or more recently integrase inhibitors shows the following picture: replacement is virologically safe in most cases, provided viral load is constantly suppressed and no evidence of resistance exists (see Table 7.1).

### Table 7.1: Randomized studies on switching from PIs to other drugs

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Wk</th>
<th>VL Effect</th>
<th>Effect of switch on lipids (L) or lipodystrophy (LD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI → NVP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barreiro 2000</td>
<td>138</td>
<td>24</td>
<td>Advantage</td>
<td>L unchanged, LD better</td>
</tr>
<tr>
<td>Ruiz 2001</td>
<td>106</td>
<td>48</td>
<td>n.s.</td>
<td>L possibly better, LD unchanged</td>
</tr>
<tr>
<td>Arranz-Caso 2005</td>
<td>160</td>
<td>48</td>
<td>n.s.</td>
<td>L better, LD better</td>
</tr>
<tr>
<td><strong>PI → EFV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker 2001</td>
<td>346</td>
<td>48</td>
<td>Advantage</td>
<td>L unchanged</td>
</tr>
<tr>
<td>Molina 2005</td>
<td>355</td>
<td>48</td>
<td>Advantage</td>
<td>L/LD n.a., side effects similar</td>
</tr>
<tr>
<td><strong>PI → ABC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clumeck 2001</td>
<td>211</td>
<td>24</td>
<td>Advantage</td>
<td>L better, LD subjectively better</td>
</tr>
<tr>
<td>Opravil 2002</td>
<td>163</td>
<td>84</td>
<td>Disadvantage (trend)</td>
<td>L better, LD unchanged</td>
</tr>
<tr>
<td>Keiser 2002*</td>
<td>104</td>
<td>28</td>
<td>n.s.</td>
<td>L better, LD better</td>
</tr>
<tr>
<td><strong>PI → EFV vs NVP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negredo 2002</td>
<td>77</td>
<td>48</td>
<td>n.s.</td>
<td>L only better on NVP, LD unchanged</td>
</tr>
<tr>
<td>Calza 2005</td>
<td>130</td>
<td>48</td>
<td>n.s.</td>
<td>L actually worse if the PI arm contained lipid lowering drug</td>
</tr>
<tr>
<td><strong>PI → EFV vs NVP, ABC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez 2003</td>
<td>460</td>
<td>48</td>
<td>Trend against ABC</td>
<td>L only better on ABC, LD probably unchanged</td>
</tr>
<tr>
<td><strong>PI → RAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eron 2010</td>
<td>350</td>
<td>24</td>
<td>Disadvantage</td>
<td>L better</td>
</tr>
<tr>
<td>Martinez 2010+2012</td>
<td>139</td>
<td>48</td>
<td>n.s.</td>
<td>L better</td>
</tr>
</tbody>
</table>

In all studies (except Martinez 2003), randomization was against continuing PIs. All had an open-label design and all patients had been on PIs for several months at the time of the switch, with undetectable viral load. VL=viral load in the switch arm versus the continuing arm. Wk=weeks, LD=lipodystrophy, L=lipids, n.a.=not available, n.s.=not significant. *Here only 62% of patients were taking a PI, the rest were on NNRTIs or a triple nuke regimen.
Taken together, these studies show that lipid levels are most likely to improve after switching to other agents, in particular abacavir and raltegravir, and to a lesser extent, efavirenz. In cases of lipodystrophy the effects are clearly poorer. Quality of life and treatment satisfaction improved significantly in the switch arms of most studies, probably due to the reduced pill burden. A large study focused on investigating quality of life showed a clear improvement after switching from PIs to efavirenz (Campo 2010).

Switching from a PI to other drugs poses an increased risk of virologic failure, particularly with prior NRTI treatment and the associated resistance mutations. One example of what could happen when the drug is changed for strategic reasons is shown in Table 7.3. This case demonstrates how careful one must be when switching drugs, if there is a past history of inadequate treatment (i.e., dual therapy). There is a risk of a higher virological failure when switching from PI based regimens to triple nuke, especially in patients with prior NRTI pretreatment (Bommenell 2011). A higher failure rate was also seen in the SWITCHMRK trials in patients switching to the integrase inhibitor raltegravir (Eron 2010). In these two large-scale Phase II studies, a total of 702 patients on a stable and functioning lopinavir-containing regimen were randomized to change to raltegravir or to continue with lopinavir. Lipids improved with the switch, but after 24 weeks a non-inferiority of raltegravir compared to lopinavir/r in efficacy was not seen. In the ITT analysis, only 82% of patients on raltegravir compared to 88% on the continued PI maintained viral load below the limit of detection after 24 weeks. The viral load breakthrough applied especially for pre-treated patients with previous therapy failure. A smaller open-label randomized study in Spain did not make the same observations, however. Patients had been below detection for a longer period (Martinez 2010). Potential side effects also need to be considered with every switch. Although less frequently than with treatment-naïve patients, a rash or hepatotoxicity can be expected with nevirapine, and efavirenz may be associated with adverse CNS events. There is the risk of a hypersensitivity reaction with abacavir if HLA typing is not available. There is still no data on a change or a PI substitution with maraviroc yet, but it is being investigated.

Switching to atazanavir

Possibly the PI does not always have to be replaced with another drug class. In cases of dyslipidemia with lopinavir or fosamprenavir, switching to atazanavir could make sense as it is associated with a comparably good lipid profile (Gatell 2007, Soriano 2008, Mallolas 2009). Darunavir has a metabolic profile similar to atazanavir (Aberg 2011), however, there are no switch studies. Lipodystrophy and glucose metabolism may be improved if older PIs are replaced by atazanavir (Stanley 2009), although not endothelial function (Flammer 2010, Murphy 2010). There may be additional favorable effects on lipids if atazanavir is unboosted, which seems to work well with pre-treated patients with a viral load below detection (Sension 2009, Elion 2010, Ghosn 2010). Patients must be informed about the risk of jaundice, which is typical for atazanavir, with or without ritonavir.

Replacement of thymidine analogs with other NRTIs

The thymidine analog d4T, which plays a leading role in mitochondrial toxicity, is frequently replaced with other nucleoside analogs. Despite their heterogeneity, most studies show that lipoatrophy improves if d4T, and probably also AZT, is replaced (review: Curran 2011). In particular, the subcutaneous fat of the limbs increases, although at first the improvement is often unrecognizable clinically and can only be detected in DEXA scans (Martin 2004). Histological investigations have shown
6.7. When to Switch?

that the elevated rate of apoptosis in adipocytes normalizes when d4T is replaced (Cherry 2005, McComsey 2005). Based on the available data, it seems advisable to replace d4T with another nucleoside analog. According to a warning letter by the company BMS of March 2011, d4T should only be used if other antiretroviral substances cannot be used and duration of treatment should be as short as possible, and patients should change to a more suitable therapy alternative whenever possible. Unfortunately, it still plays a role in resource-limited regions for the time being. A dose reduction may be able to reduce adverse events (McComsey 2008). With regard to AZT, a replacement should be considered when lipoatrophy or anemia becomes manifest. To avoid a hypersensitivity reaction the patient’s HLA status should be known before switching to abacavir (Carr 2002).

Table 7.2: Controlled clinical studies on switching from d4T or AZT to other drugs (all were randomized, except McComsey 2004)

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Switch</th>
<th>Wk</th>
<th>Effect of switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr 2002</td>
<td>106</td>
<td>ABC instead of d4T or AZT</td>
<td>104</td>
<td>LA better, lipids unchanged</td>
</tr>
<tr>
<td>Martin 2004</td>
<td>106</td>
<td>ABC instead of d4T or AZT</td>
<td>104</td>
<td>LA better, lipids unchanged</td>
</tr>
<tr>
<td>John 2003</td>
<td>37</td>
<td>AZT instead of d4T and ABC instead of PI</td>
<td>48</td>
<td>LA of limbs slightly better, lipids and abdominal fat unchanged</td>
</tr>
<tr>
<td>Moyle 2003</td>
<td>30</td>
<td>ABC instead of d4T or PI/NNRTI, or AZT+ABC</td>
<td>48</td>
<td>LA better (when replacing d4T)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>instead of d4T+PI</td>
<td></td>
<td>Lipids better (when replacing PI)</td>
</tr>
<tr>
<td>Moyle 2005</td>
<td>105</td>
<td>TDF or ABC instead of d4T or AZT</td>
<td>48</td>
<td>LA better, lipids better on TDF</td>
</tr>
<tr>
<td>Valantin 2010</td>
<td>91</td>
<td>TDF+FTC instead of 2 NRTIs</td>
<td>16</td>
<td>Lipids better</td>
</tr>
<tr>
<td>Fischer 2009</td>
<td>234</td>
<td>TDF+FTC instead of AZT+3TC</td>
<td>48</td>
<td>LA better, lipids better</td>
</tr>
<tr>
<td>Martinez 2012</td>
<td>65</td>
<td>TDF+FTC instead of AZT+3TC</td>
<td>72</td>
<td>LA better</td>
</tr>
<tr>
<td>Ribera 2008</td>
<td>62</td>
<td>TDF instead of D4T</td>
<td>48</td>
<td>Lipids better, lactate better, LA slowly better</td>
</tr>
<tr>
<td>McComsey 2012</td>
<td>50</td>
<td>TDF or uridine instead of AZT or d4T</td>
<td>48</td>
<td>LA better, but reduction in bone density</td>
</tr>
<tr>
<td>Tebas 2009</td>
<td>101</td>
<td>ABC or nuke sparing instead of d4T or AZT</td>
<td>48</td>
<td>LA better</td>
</tr>
<tr>
<td>Milinkovic 2007</td>
<td>57</td>
<td>TDF or D4T reduction (30 mg) instead of d4T</td>
<td>24</td>
<td>LA, lipids better (TDF effects better than d4T reduction)</td>
</tr>
</tbody>
</table>

No study showed any difference with respect to virologic failure. Wk=weeks, LA=lipoatrophy. In McComsey 2004 and Moyle 2005, only patients with LA were investigated.

Switching to tenofovir

Studies on therapy-naive patients have shown that the short-term toxicity of tenofovir is lower than that of d4T or AZT (Gallant 2004+2006). In the 903 Study, lipids improved in patients that were switched from d4T to tenofovir. There was also an increase of the mean limb fat after three years (Madruga 2007). Several studies, some of them randomized trials, point in the same direction. Lipids, lipoatrophy, mito-

Recently, a double-blind, placebo-controlled, randomized study showed unexpected results. In ACTG A5206, the addition of tenofovir alone to existing virologically-suppressed ART regimens improved lipid parameters compared to placebo (Tungsiripat 2010). However, the mechanism of the lipid-lowering effect warrants further study. In a retrospective study, replacing d4T with tenofovir improved both lipids and liver enzymes (Schewe 2006).

It must be noted that negative effects may arise when switching too quickly to tenofovir. Randomized studies in treatment-naïve patients have observed a stronger reduction of bone density on tenofovir, compared to other NRTIs (Martin 2009, Stellbrink 2010). There is at least one randomized study showing large decreases in bone density after a switch to tenofovir (McComsey 2012). Bone turnover markers do improve when tenofovir is replaced by raltegravir (Bloch 2012). The potential nephrotoxicity of tenofovir is another point.

Switching to tenofovir-containing triple-nuke combinations must be avoided, as several studies have shown a high risk for an increase in viral load when switching to this combination (Hoogewerf 2003, Perez-Elias 2005), even after many years on successful ART. The resistance barrier is too low, as the following example shows.

Table 7.3: Example of what could happen on switching drugs (n.k.=not known)

<table>
<thead>
<tr>
<th>Date</th>
<th>ART</th>
<th>CD4 cells</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996–98</td>
<td>AZT+ddC</td>
<td>n.k.</td>
<td>n.k.</td>
</tr>
<tr>
<td>Since 1998</td>
<td>AZT+3TC+NFV (always under the limit of detection)</td>
<td>n.k.</td>
<td>n.k.</td>
</tr>
<tr>
<td>Nov. 2002</td>
<td>Findings: significant lipoatrophy. Decision to switch</td>
<td>688</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Feb. 2003</td>
<td>ABC+3TC+NFV</td>
<td>788</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Apr. 2003</td>
<td>ABC+TDF+NVP (=targeted regimen, notes below)</td>
<td>871</td>
<td>&lt;50</td>
</tr>
<tr>
<td>May 2003</td>
<td>Severe rash, ALT/AST &gt;500 U/l</td>
<td>n.k.</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Jun. 2003</td>
<td>ABC+TDF+3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sep. 2003</td>
<td>AZT+3TC+NFV</td>
<td>n.k.</td>
<td>59,100</td>
</tr>
<tr>
<td>Oct. 2003</td>
<td></td>
<td>n.k.</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Oct. 2004</td>
<td></td>
<td>743</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

Notes: On account of possible allergies to both ABC and NVP, ART was changed in February 2003 in two steps. Rash with hepatic involvement occurred on NVP, so in July 2003 NVP was replaced by 3TC – a triple nuke. The resistance mutations then detected were acquired almost certainly from the earlier treatment with AZT+ddC, but sufficiently suppressed while on PI therapy.

In practice, changes are often made that go further than PI and d4T/AZT, such as replacement of ddl, simply due to concerns over long-term toxicity. Such switching is based on laboratory studies showing a certain hierarchy with respect to mitochondrial toxicity (see chapter on Mitochondrial Toxicity).

A lot of attention is being drawn to simplification of therapy, in which mono- or nuke-sparing strategies are being used (see below). So far, there is no clear clinical evidence to show that this procedure has any benefit for the patient. If the patient has no complaints, a switch to monotherapy or nuke-sparing can not be justified and subjects the patient to unnecessary risks. Below, current data on this topic is discussed.
Switching to nuke-sparing

Nuke-sparing is the attempt to completely avoid NRTIs in antiretroviral therapy. In treatment-naive patients nuke-sparing proved virologically effective (see previous chapter) and is presently being investigated in treatment-experienced patients with well suppressed viral load (Table 7.4). Data, however, is still very limited.

PI+NNRTI: In ACTG 5116, the largest study so far with 236 patients on successful ART, the switch to lopinavir/r plus efavirenz compared to efavirenz plus NRTIs led to higher discontinuation rates due to increased virologic failure and other side effects (Fishl 2007). The results of this study are contrary to those of some other studies and to the results of lopinavir/r plus efavirenz with ART-naive patients (Riddler 2008). At this point in time, it seems too early to recommend nuke-sparing with PI+NNRTI as a transition strategy.

PI+INI/CCR5: Several studies are ongoing with raltegravir in combination with atazanavir/r (BATAR), darunavir/r (RALDAR, SPARE) and lopinavir/r (KITE). In the randomized KITE study on 60 virologically suppressed patients on ART, switching therapy to lopinavir/r/raltegravir produced similar sustained virologic suppression and immunologic profile as continuous ART. Adverse events were comparable between arms, but the nuke-sparing arm experienced higher triglyceridemia (Ofotukun 2012). In another pilot study, regimens comprising atazanavir plus raltegravir were efficacious and safe. However, PK data showing low trough levels were of concern (Carey 2012). Taken together, data is too limited to draw definite conclusions.

Table 7.4: Studies on switching to nuke-sparing regimens

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Switch to</th>
<th>Wks</th>
<th>Main effects of the switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI plus NNRTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Corles 2003</td>
<td>42*</td>
<td>SQV/r + EFV</td>
<td>48</td>
<td>Virologically effective</td>
</tr>
<tr>
<td>Boyd 2005 (HIVNAT 009)</td>
<td>26*</td>
<td>IDV/r+EFV</td>
<td>48</td>
<td>Virologically effective, but many side effects due to IDV, LA probably slightly better</td>
</tr>
<tr>
<td>Negredo 2009 (MULTINEKA)</td>
<td>16*</td>
<td>LPV/r + NVP</td>
<td>48</td>
<td>Virologically effective, lipids and mitochondrial DNA better</td>
</tr>
<tr>
<td>Tebas 2009 (ACTG 5110)</td>
<td>101</td>
<td>LPV/r + NVP</td>
<td>48</td>
<td>Virologically effective, lipodystrophy better</td>
</tr>
<tr>
<td>Tebas 2007 (ACTG 5125)</td>
<td>62</td>
<td>LPV/r + EFV</td>
<td>48</td>
<td>Many metabolic disturbances and LA better</td>
</tr>
<tr>
<td>Fischl 2007 (ACTG 5116)</td>
<td>118*</td>
<td>LPV/r + EFV</td>
<td>110</td>
<td>Trend towards more virologic failure, more side effects</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruane 2009</td>
<td>27</td>
<td>ATV 400+RAL</td>
<td>24</td>
<td>Virologically safe, but in 26% blips</td>
</tr>
<tr>
<td>Allavena 2009</td>
<td>22</td>
<td>DRV/r**+RAL</td>
<td>18</td>
<td>Virologically safe</td>
</tr>
<tr>
<td>Ripamonti 2009 (CARDS)</td>
<td>24</td>
<td>ATV 300+RAL</td>
<td>24</td>
<td>Virologically safe, good PK data also for ATV (unboosted)</td>
</tr>
<tr>
<td>Carey 2012</td>
<td>25</td>
<td>ATV 300 + RAL, ATV/r + RAL OD</td>
<td>8</td>
<td>No virological breakthroughs, PK data of concern</td>
</tr>
<tr>
<td>Ofotokun 2012 (KITE)</td>
<td>60</td>
<td>LPV/r + RAL</td>
<td>48</td>
<td>Virologically safe but more dyslipidemia</td>
</tr>
</tbody>
</table>

LA=lipodystrophy, *in Switch Arm (these studies were randomized) **7 patients received other PIs, among them 4 atazanavir
Switching due to virologic failure

Any change in treatment due to virologic failure requires experience, a certain degree of finesse and decisiveness. There are many possibilities for mistakes here. On the one hand, there is a threat of acquiring more resistance (if they have not already developed), but on the other hand, young physicians often want to quickly change treatment, which is not always necessarily the right solution. In many cases a frequent change of therapy confuses the patient and causes anxiety. If the problem is adherence, switching the regimen without talking about adherence may not be the solution. A switch only brings up more misunderstandings and, consequently, may generate later resistance. It is always important to explain to patients, who often tend to be skeptical (“should I save the other drugs for later?”) when and why treatment changes must be made.

As a rule of thumb, ART should be changed quickly with insufficient viral suppression and/or a rise in plasma viremia, as otherwise future options could be limited. One speaks of insufficient viral suppression or virologic failure if the viral load is repeatedly above the level of detection. A switch is not recommended with temporary viremia (blips – more on this topic in the chapter Principles of Therapy). Even single point mutations can be a problem. Abacavir, 3TC, FTC and ddI lose their efficacy in the presence of the K65R mutation, which is often selected by tenofovir-containing triple-nuke therapies. Viral replication with insufficient plasma levels is the best breeding ground for resistance. Therefore, it is recommended to act fast if a clear virologic failure occurs. The longer one waits, the more complicated it becomes. An insufficient viral suppression means, as stated before, a repeated viral load above 50 copies/ml. Some clinicians tolerate levels of up to 500 or even 1000 copies/ml for months. We believe such hesitation is not justified in most cases when patients have good options and good adherence. A patient’s frequent assertions of not having symptoms should not count too much, either. Obviously, such thoughts do not always play a role in clinical reality. In an analysis in Great Britain 34% out of 694 patients remained on a virologically unsuccessful combination for over 6 months. Factors associated with an early switch were low CD4 T cells, a high viral load and older age (Lee 2008).

Arguments for a rapid switch in the case of virologic failure

<table>
<thead>
<tr>
<th>Arguments for a rapid switch in the case of virologic failure</th>
<th>Arguments for a later switch in the case of virologic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>The virus becomes incapable of generating more resistance</td>
<td>New therapies bear the risk of new toxicities/intolerance, which can lead to a termination of therapy</td>
</tr>
<tr>
<td>Options are maintained</td>
<td>Most patients are immunologically stable for a long time with low viremia (clinically)</td>
</tr>
<tr>
<td>The switch is more successful with less resistance</td>
<td>Replication fitness is reduced on failing treatment</td>
</tr>
<tr>
<td>The lower the viral load at time of switch, the better the response to the new therapy</td>
<td>Resistance testing is often not possible with low viral load, even though they are there, so you may switch “blindly”</td>
</tr>
<tr>
<td>The following regimens do not have to be as complex as the present one – some things can be simplified (QD, no more d4T/ddI, etc.)</td>
<td>It is sometimes difficult to explain to the patient why change of a well-tolerated and simple regimen is necessary</td>
</tr>
</tbody>
</table>
To date, only a few randomized trials have investigated strategies in patients in whom several ART combinations have failed: either the patients change immediately or when the viral load reaches a certain level (early versus deferred switch). The preliminary results of some small randomized studies indicate that even in such cases one can wait a short time (Nasta 2006, Tenorio 2009). However, these trials were small. It seems difficult to recruit physicians and patients to participate in such strategy trials.

With failing PI therapies there is more time. In the prospective Johns Hopkins Cohort there was no association between a deferral of ART modification and mortality in the course of treatment in patients on a PI showing virologic failure (Petersen 2008). This is why in the TITAN study, the number of acquired PI mutations had no effect on the success of darunavir/r, although it did play a role for lopinavir/r (De Meyer 2008).

In cases of clinical treatment failure (disease progression) or immunological failure (stagnation or decrease in the level of CD4 T cells) where the viral load remains below 50 copies/ml, the value of a change in therapy is unclear. Some combinations such as TDF+ddI are clearly unfavorable for immunological reconstitution (Negredo 2004). This may also be the case for AZT-containing regimens; such combinations should be changed.

It is important that when virologic failure occurs, the individual situation of the patient is carefully analyzed. In particular, several questions need to be addressed:

**What are the reasons for the measurable viral load?** A viral load above 50 copies/ml does not necessarily mean that resistance mutations have developed. A frequent cause may be a blip (see section on Goals and Principles of ART). These transient and, almost always, small increases in viral load usually have no relevance. However, a measurable viral load may be due to treatment failure. It may indicate insufficient plasma drug levels (measure these if possible). This may be due to drug malabsorption, drug interactions or simply insufficient dosing (e.g., in larger, heavy patients).

**How is the patient’s adherence?** Adherence is critical. Any difficulties related to the regimen should be openly addressed. Is it the number of pills? Do restrictions in food intake cause problems? Would once-daily treatment be better? Are there other reasons, such as depression? Any misunderstanding on how to take the drugs? The risks of resistance development as a result of non-compliance should be reiterated. If plasma levels are sufficient and viral load remains detectable (monitor blips at short intervals – within a few weeks), treatment should be changed as soon as possible.

**How vulnerable is the present combination?** NNRTI regimens are extremely sensitive, and cross-resistance can develop particularly rapidly for the class. A prompt change in therapy is more vital than with the other drug classes. Delaying this by even a few days or weeks may be too long. Rapid development of resistance can also be expected with 3TC/FTC and probably with the integrase inhibitor raltegravir. A PI-containing regimen without an NNRTI may allow a little more time, but the credo still applies. The higher the viral load at the time of modification, the lower the chance of success. One should not wait too long.

**What options does the patient have, and what are the consequences of the change in therapy?** The more options that remain available the sooner they should be utilized. Therapy can often be intensified quite easily (e.g., adding abacavir plus an NNRTI). In such cases, the decision to change or intensify a regimen is less difficult. On the other hand, it may be advisable in certain circumstances to continue therapy in a patient, even if the plasma viremia is not completely suppressed. Often, the viral load does not rise above the baseline value, and the CD4 T cells remain
stable or even increase. Some experts advocate waiting in these cases. Resistance to nucleoside analogs are to be expected, so NNRTIs and PIs can be saved by waiting. Even when multiple resistance mutations are already present, one is probably able to wait (see above). Especially in patients with adherence problems, it does not make sense to run through new drug classes. Adherence will not automatically be better with newer regimens. One should talk with the patient, find out what needs to be made better, and clarify if they are really ready for intensification or modification of therapy.

**Virologic failure: to be considered before changing therapy**

- How resistance-sensitive is the present therapy? NNRTIs, 3TC/FTC, raltegravir: rapid development of resistance, change quickly
- The lower the viral load, the greater the prospect of success with a change
- Are you sure it is virologic failure and not a temporary blip?
- Are there other reasons for a detectable virus load? What about malabsorption/drug uptake?
- Do you know all the other therapies the patient is taking? Ask. Whether a gastric stimulant prescribed by the family doctor (i.e., PPIs) or herbal agents prescribed by an alternative practioner, it should all be laid out
- Has the patient been adherent to current ART or have there been misunderstandings? Was the therapy discontinued *ad hoc*?
- What do the plasma levels say and what does the patient say?
- What options are there and what does a change mean for the patient? Is the patient able to start a new therapy?
- Does a reasonably up-to-date resistance test exist? (if not, do one)
- If relevant mutations to the current agents have already developed, calmly wait and prepare the patient for a new regimen, possibly with more adherence counseling
6.8. How to Switch ART?

CHRISTIAN HOFFMANN

Changing a regimen that is successful but intolerable due to side effects is usually easy. The suspected drug is replaced with another drug of the same class. It becomes more difficult if alternate drugs are contraindicated because of potential toxicity or if resistance mutations to these drugs are suspected. In such cases, changes need to be individualized.

This is particularly true in those subjects with a treatment history of 10 or 15 years, who probably harbor multi-resistant viruses. Even physicians with lots of experience in treatment should discuss these complex individual cases with their colleagues. In many large centers, so-called weekly ART meetings have been established. At these meetings, both virologists (to translate resistance testing) and clinicians (with personal experience of the individual patient’s situation) can discuss these complex cases.

This chapter discusses two important reasons for switching where certain principles should apply: changing due to virologic failure, and changing to simplify the regimen. Switching due to possible side effects has been discussed in previous chapters.

Switching due to virologic failure

The same principles apply as when initiating therapy: compliance, dosing issues, concurrent diseases, co-medications and drug interactions. It is also essential to consider treatment history and possible existing resistance mutations. Although desirable before any change in treatment, resistance tests in cases of virologic failure are not always practical. It is therefore useful to become familiar with the most important resistance mutations, particularly for nucleoside analogs:

<table>
<thead>
<tr>
<th>Failing nuke backbone</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT/d4T+3TC</td>
<td>M184V and then successive TAMs, the more one waits</td>
</tr>
<tr>
<td>AZT+3TC+ABC</td>
<td>K65R and/or M184V</td>
</tr>
<tr>
<td>TDF+3TC/FTC</td>
<td>K65R and/or M184V</td>
</tr>
<tr>
<td>ABC+3TC</td>
<td>L74V, less frequently K65R and/or M184V</td>
</tr>
<tr>
<td>AZT/d4T+ddI</td>
<td>TAMs, Q151M, T69ins</td>
</tr>
<tr>
<td>TDF+ABC/ddI</td>
<td>K65R</td>
</tr>
</tbody>
</table>

The basic principles for changing therapy in cases of virologic failure apply: the faster the change, the better; the virus should be given as little time as possible to generate more resistance mutations. Resistance patterns become more complex the longer one waits (Wallis 2010). In addition, the more drugs that are changed, the higher the likelihood of success for the new regimen.

The situation with NNRTIs is more straightforward. There is usually complete cross-resistance with efavirenz and nevirapine. Continuation in the presence of these resistance mutations is of no use as they have no impact on the replicative fitness of the virus. Moreover, accumulation of further resistance mutations may compromise the efficacy of second generation NNRTIs such as etravirine. Therefore, NNRTIs should be discontinued if resistance occurs or quickly be replaced by etravirine if the situation allows (etravirine is only approved for use in combination with boosted PIs). Reduction of etravirine activity seems to take longer in patients experiencing therapy...
failure on nevirapine vs. efavirenz (Cozzi-Lepri 2011). Rilpivirine is not approved for treatment-experienced patients, although it is probably effective for 80% of NNRTI-resistant isolates (Anta 2012).

There are also relevant cross-resistance mutations for PIs. For switching and sequencing PIs refer to the salvage section of the next chapter. Table 8.2 provides a rough guide on how to proceed without knowing the specific resistance mutations. One must note that data is not sufficiently available for all options. On account of the promising monotherapy studies with lopinavir/r and darunavir/r, the regimen need not be totally changed in cases of limited resistance mutations is switch to these boosted PIs happens quickly. One study showed that if the frequent NRTI mutation M184V is detected alone, cytidine analogs 3TC or FTC can be continued, provided a boosted PI is initiated. The effect of the boosted PI is enough to achieve virological success – 3TC seems to be able to conserve M184V that in turn lowers viral fitness (Hull 2009). Presently there are ideas about developing a fixed combination of a boosted PI and 3TC.

Table 8.2: Changing first-line therapy without knowledge of resistance mutations*

<table>
<thead>
<tr>
<th>Failing initial therapy</th>
<th>Potentially successful change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 NRTI</td>
<td>Instead of 3rd NRTI one PI/r (rapid switch) or 1–2 new NRTIs plus NNRTI or RAL</td>
</tr>
<tr>
<td>2 NRTI + NNRTI</td>
<td>Instead of NNRTI, one PI/r (rapid switch) or 1–2 new NRTIs plus RAL or MVC*</td>
</tr>
<tr>
<td>2 NRTI+ 1 PI/r</td>
<td>1–2 new NRTIs plus NNRTI plus new PI/r or RAL or MVC**</td>
</tr>
</tbody>
</table>

*In individual cases, other modifications or simply waiting may be advisable. All PIs should be boosted (PI/r). **Maraviroc only with tropism test. For complex cases, see chapter on Salvage Therapy.

In some cases of virologic failure, the addition of one agent alone can make sense. Whether this applies to abacavir is under discussion. In contrast to a placebo-controlled study (Katlama 2001), in clinical practice there was no sustained virologic effect with the addition of abacavir alone to a failing regimen (Cabrera 2004). Addition of tenofovir also seems possible in certain cases (Khaykin 2008, Schooley 2002). Our experience with this approach has been good in cases with minimal increases in the viral load (up to 500 copies/ml) and in the absence of TAMs.

In patients who have been treated exclusively (and over a prolonged period) with NNRTIs, the above strategy has mostly not been successful. Extensive resistance mutations usually exist and a complete change of ART is necessary. In all patients previously treated with NRTIs or NNRTIs over a longer period, a boosted PI must be used. In the presence of a failing PI regimen, a new NNRTI alone is often not sufficient (Abgrall 2007, Khaykin 2008). With respect to resistance mutations and prior ART exposure, the addition of a new drug such as raltegravir and maraviroc should be considered. For complex resistance situations see the next chapter.

**Simplification – do maintenance therapies work?**

Can HIV infection be treated in a similar fashion to mycobacteria, with a sequence of intense induction therapy followed by less toxic (and less expensive) maintenance therapy? The idea is appealing, and has circulated almost since the existence of combination ART. Between 1998 and 2003, the answer was clearly that maintenance therapies do not work. Three randomized studies (Triîlée, ADAM, ACTG 343) destroyed any hope that ART might be reduced to two or even one drug. By today’s standards, one could object that outdated agents such as saquinavir, indinavir or nelfinavir were used (Havlir 1998, Reijers 1998, Flander 2002).
In the last few years better drugs have been licensed. In particular, lopinavir and darunavir with high resistance barriers cast a different light on the negative image of maintenance therapies. Randomized studies already exist for lopinavir/r and darunavir/r, but other boosted PIs have also been investigated as PI/r monotherapy (see Table 8.3).

The studies show that in most cases virologic suppression remains when simplifying to a PI/r monotherapy. In the OK04 study with lopinavir/r, a reduction of lipoatrophy rates was achieved. The observation period has now been extended to four years (Cameron 2007, Pulido 2008). However, some patients on lopinavir/r show low levels of viremia, especially in combination with low CD4 T cells and as expected, they show poor compliance (Campo 2007, Pulido 2008, Gutmann 2010). The same was observed with therapy-naïve patients (see above).

Table 8.3: Newer studies on maintenance therapies (PI/r monotherapy)

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Maintenance</th>
<th>Wks</th>
<th>Less than 50 copies/ml?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nunes 2009 (KalMo)</td>
<td>60</td>
<td>LPV/r versus 2 NRTIs+LPV/r</td>
<td>96</td>
<td>80% vs 87% (ITT, VL &lt; 80)</td>
</tr>
<tr>
<td>Campo 2009 (M03-613)</td>
<td>155</td>
<td>LPV/r versus CBV+EFV</td>
<td>96</td>
<td>60% vs 63% (ITT), but low-level viremia more frequently</td>
</tr>
<tr>
<td>Pulido 2008 (OK04 Study)</td>
<td>205</td>
<td>LPV/r versus 2 NRTIs+LPV/r</td>
<td>48</td>
<td>85% vs 90% (ITT), Non-inferiority shown, but more frequent low-level viremia</td>
</tr>
<tr>
<td>Meynard 2010 (KALESOLO)</td>
<td>186</td>
<td>LPV/r vs ART-continuation</td>
<td>48</td>
<td>84% vs 88% (ITT), Non-inferiority not shown, more frequent low viremia</td>
</tr>
<tr>
<td>Gutmann 2010</td>
<td>60</td>
<td>LPV/r vs ART-continuation</td>
<td>24</td>
<td>21% VF on Mono. Especially those with low CD4 nadir, study discontinued.</td>
</tr>
<tr>
<td>Cahn 2011</td>
<td>80</td>
<td>LPV/r vs ART-continuation</td>
<td>48</td>
<td>98% vs 95% (LOCV, VL &lt; 200)</td>
</tr>
<tr>
<td>Clumeck 2011 (MONET)</td>
<td>256</td>
<td>DRV/r versus 2 NRTIs+DRV/r</td>
<td>96</td>
<td>78% vs 82% (ITT), Non-inferiority not shown completely</td>
</tr>
<tr>
<td>Valentin 2012 (MONOI)</td>
<td>225</td>
<td>DRV/r versus 2 NRTIs+DRV/r</td>
<td>96</td>
<td>84% vs. 88%, Non-inferiority not clearly shown (low viremia more frequently)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahlert 2004</td>
<td>12</td>
<td>IDV/r</td>
<td>48</td>
<td>92%, 1 discontinuation, no failure</td>
</tr>
<tr>
<td>Patricia 2010</td>
<td>17</td>
<td>SQV/r</td>
<td>48</td>
<td>94%, 1 case of VF</td>
</tr>
<tr>
<td>Karlstrom 2006</td>
<td>15</td>
<td>ATV/r</td>
<td>16</td>
<td>VF 33%, study discontinued prematurely</td>
</tr>
<tr>
<td>Vernazza 2007 (ATARITMO)</td>
<td>28</td>
<td>ATV/r</td>
<td>24</td>
<td>92%, no resistance or VF</td>
</tr>
<tr>
<td>Wilkin 2009 (ACTG 5201)</td>
<td>36</td>
<td>ATV/r</td>
<td>48</td>
<td>88%, no resistance</td>
</tr>
<tr>
<td>Pulido 2009 (OREY)</td>
<td>63</td>
<td>ATV/r</td>
<td>48</td>
<td>79% under 400 copies/ml, however at least 14% VF</td>
</tr>
<tr>
<td>Saumoy 2011 (FONT)</td>
<td>20</td>
<td>FPV/r</td>
<td>48</td>
<td>VF 45%, study discontinued prematurely</td>
</tr>
</tbody>
</table>

All patients had less than 50 (75) copies/ml for at least six months. VF=Virologic failure, ITT=Intent-to-treat
For darunavir, the results of two large randomized studies MONET and MONOI with identical design are published (Clumeck 2011, Valentin 2012). In MONET, non-inferiority of the monotherapy could not completely be shown after 96 weeks, at least regarding the primary endpoints (Clumeck 2011). In total, 82% of patients were below 50 copies/ml in the standard arm at week 96, compared to 78% on darunavir monotherapy. At week 144, the difference was 6% (Arribas 2012). When virologically successful therapies were not evaluated as failure, a difference was not observed. The results can be explained by a possibly low adherence in the mono-arm (with significantly more HCV-coinfected patients). In MONOI, transient viremia was more frequent on monotherapy and a permanent control under 50 copies/ml without blips was observed in 59% versus 70% of patients at week 96 (Valentin 2012). Virologic failure was associated with levels of proviral DNA at baseline (Marcelin 2011), but also with low adherence (Lambert-Niclot 2011). Of note, darunavir mutations were not observed either in MONET or in MONOI (Lambert-Niclot 2012, Pulido 2012). Possibly, darunavir levels are lower without NRTIs (Garvey 2010). In MONOI, lipoatrophy improved in some patients (Valentin 2012).

Less data is available for other PIs. For atazanavir/r and fosamprenavir/r there are one-arm pilot studies with weak results. Some of them were prematurely interrupted due to high failure rates (Karlstrom 2006, Saumoy 2011). The Ataritmo study observed an elevated viral load in cerebrospinal fluid within some patients on atazanavir with otherwise well suppressed viral loads. In the OREY study, 9/63 patients developed virological failure (Pulido 2009). There is also a pilot study for saquinavir (Patricia 2010).

Conclusion: Monotherapies with boosted PIs such as lopinavir/r and darunavir/r are slightly less effective than classic therapies (review: Mathis 2011). Lower viremia without resistance appears that does disappear upon intensification. Risk factors for monotherapy failure are poor adherence and low CD4 T cell nadir. Monotherapies as a strategy can not be justified at this time. In individual cases, however, they may be able to reduce adverse events.

Switching to simplify – triple-nukes revisited

Triple nuke therapy, though now fairly obsolete for first-line therapy, may be justifiable in maintenance therapy. Several randomized studies have not detected any virologic disadvantage.

In the ESS40013 study, a total of 448 patients were treated with AZT+3TC+ABC plus efavirenz. After 36 or 44 weeks, 282 patients with undetectable viral load were randomized to continue with the same therapy or to stop efavirenz. After 96 weeks, 79% versus 77% of patients were still below 50 copies/ml, proving that triple nuke was not inferior (Markowitz 2005). In a Spanish study, 134 patients with an undetectable viral load for at least 24 weeks were randomized to receive either Trizivir® or Combivir® plus nevirapine (Bonjoch 2005). At 48 weeks, the percentage of patients with an undetectable viral load was comparable across arms (71% versus 73%, ITT). Similar results were also seen in the TRIZAL and FREE study, in which 209 patients were randomized (Katlama 2003, Sprenger 2010). In the Swiss Cohort, the failure rate was low in 495 patients with suppressed viral load and switch to Trizivir®. Patients with earlier exposure to mono- or dual-NRTI therapy, low CD4 T cell count at time of switch, or AIDS were at increased risk of treatment failure, limiting the use of Trizivir® in these patient groups (Wolbers 2007). Some long-term data for the quadruple-nuke strategy with Trizivir® plus tenofovir (d’Ettore 2007, Llibre 2008) also exist. The approach taken in the French COOL Study failed. In this trial, 140 patients were randomized to TDF+3TC+efavirenz or TDF+efavirenz for 48 weeks. Inclusion criterion was ART with a viral load below 50 copies/ml for at least three months; patients
with prior treatment failure were excluded. There were no restrictions on CD4 T cell counts. An analysis showed a significantly worse outcome for patients on the dual therapy. Moreover, there were no differences in the toxicity rates between arms. Thus, 3TC seems to be important in maintaining viral suppression. Its discontinuation, however, has no effect on tolerability (Girard 2006).

Maintenance therapy using Trizivir® seems feasible. However, the benefit remains questionable. Three or four NRTIs are possibly more toxic than other strategies. Strategies such as monotherapy with boosted PIs are not yet justifiable outside clinical trials.

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6.8. How to Switch ART?


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6.9. Salvage Therapy

CHRISTIAN HOFFMANN

Background

The term “salvage therapy” is not clearly defined in HIV medicine. As in oncology the term is currently used to refer to varying situations. Some speak of salvage only if all drug classes have failed, whereas others employ the term from second-line therapy onward. Today, many clinicians talk about salvage when there is resistance to at least two or three antiretroviral drug classes. Triple class resistance (TCR) is present when viral resistance mutations against the three conventional drug classes NRTIs, NNRTIs and PIs have developed. Triple class failure (TCF) means that the viral load remains detectable although these three drug classes have been used. Analogous to MDR tuberculosis, triple class resistant viruses with additional resistance mutations are also referred to as MDR, multi-drug resistant viruses. However these terms are not uniformly defined.

Significant progress has been made for patients with TCR and/or MDR viruses over the last few years, changing therapy dramatically within a few months. For years lopinavir, T-20 and tipranavir/r were the only TCR drugs; then, within a short period in 2007/08, four new drugs were licensed. Darunavir, maraviroc, raltegravir and etravirine all have remarkable effects in the presence of multiple resistance mutations, which allows for optimism and maintaining the goals. Even in intensely pretreated patients all efforts should be made to get viral loads to below the limit of detection.

The number of patients with TCR viruses is in decline and not, as often presumed, increasing (Lohse 2005+2006). Today, TCR is mainly observed in patients who were treated with mono- or dual therapy in the 90s (Napravnik 2007). In an analysis of almost 92,000 patients in Europe, the TCF rate was only 3.0% during the years 2000–2009. Since 2005, the rate of patients who do not achieve a viral load of less than 50 copies/ml due to TCF has plateaued (Plato 2012). New cases of TCF are rare. Given that this patient group is small, it is difficult to do studies with sufficient power. Homogenous populations do not really exist and every patient has his own individual therapy history and resistance pattern. In larger centers as many as 50 different combinations are used. This makes it difficult to test new salvage agents in Phase II/III studies. The design of these studies is another problem: as the single use of an experimental drug within a failing regimen is ethically questionable, ART must always be optimized (OBT, optimized background therapy). If the OBT is too good, the effect of the new drug may be hidden, as many patients achieve a good viral suppression just on OBT. If the OBT is poor, the effect of the new drug may only be temporary or too weak – the window through which the efficacy of a new salvage drug can be seen is small.

The failure of the CCR5 antagonist vicriviroc (Gathe 2010) is only one of many examples. This shows how difficult it has become to bring a new drug to market.

Preface

First a few words about daily practice: it should not be forgotten that patients with TCF, who often have a long history of being on treatment and who now find themselves once again on the precipice, need encouragement. It is important not to leave these patients without hope. It usually takes years to progress from virologic treatment failure to immunologic and finally clinical failure (see Principles of Therapy). Fortunately these patients – most having been treated for ten or fifteen years, having
experienced a lot – are often not nearly as nervous as the often young HIV doctor. They have learned that there is almost always more to come.

Much is possible now in individual cases. Table 9.1 shows an example illustrating the history of antiretroviral therapy – although treatment always remained up to date, viral load of less than 100,000 copies/ml was not always achieved. Finally, with the application of a new agent the patient experienced their first success after more than a decade of having a high level plasma viremia. Viral load has now been below the limit of detection for four years.

Table 9.1: Case report showing what is possible today

<table>
<thead>
<tr>
<th>Date</th>
<th>ART</th>
<th>CD4 cells</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jun 95</td>
<td>AZT (later, ddl, ddC, ddI)</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>Jun 96</td>
<td>AZT+ddC+RTV</td>
<td>25</td>
<td>62,000</td>
</tr>
<tr>
<td>Oct 96</td>
<td>D4T+3TC+IDV</td>
<td>10</td>
<td>167,000</td>
</tr>
<tr>
<td>Jul 97</td>
<td>D4T+ddl+3TC+NVP+IDV</td>
<td>173</td>
<td>69,000</td>
</tr>
<tr>
<td>Jan 99</td>
<td>D4T+ddl+ABC+3TC+SQR+VR</td>
<td>212</td>
<td>106,000</td>
</tr>
<tr>
<td>Sep 99</td>
<td>D4T+ABC+3TC+DLV+LPV/r</td>
<td>231</td>
<td>74,000</td>
</tr>
<tr>
<td>Dec 01</td>
<td>TDF+ddl+DLV+HU</td>
<td>174</td>
<td>84,000</td>
</tr>
<tr>
<td>Jun 03</td>
<td>TDF+3TC+FPV/r</td>
<td>143</td>
<td>145,000</td>
</tr>
<tr>
<td>Oct 03</td>
<td>TDF+3TC+ddl+TPV/r</td>
<td>77</td>
<td>733,000</td>
</tr>
<tr>
<td>May 04</td>
<td>AZT+3TC+TDF+LPV/r+T-20+DLV</td>
<td>43</td>
<td>123,000</td>
</tr>
<tr>
<td>Dec 04</td>
<td>AZT+3TC+TDF</td>
<td>32</td>
<td>204,000</td>
</tr>
<tr>
<td>Dec 07</td>
<td>AZT+3TC+TDF+DRV/r+RAL+T-20</td>
<td>7</td>
<td>&gt;1,000,000</td>
</tr>
<tr>
<td>Jan 08</td>
<td></td>
<td>54</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Apr 09</td>
<td>AZT+3TC+TDF+DRV/r+RAL+ETV</td>
<td>83</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Mar 12</td>
<td></td>
<td>134</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

Comment: Not all treatment modifications are shown. The switch in 2007 was deferred until DRV and RAL were available in order to use both agents simultaneously. T-20 was recycled when resistance testing did not clearly show if darunavir was still active. Although not foreseeable how long this therapy success will last, the complete and durable suppression of the patient’s viral load is remarkable after so many years. A de-escalation of the current treatment (13 pills, 7 agents) seems too risky at present.

Patients with TCF probably have a worse prognosis than patients without TCF (Lohse 2007). In a population-based study from the Danish HIV Cohort on all patients who experienced TCF between 1995 and 2004 (n=179), the total number of genotypic resistance mutations and specific single mutations predicted mortality. In a regression model adjusted for CD4 T cell count, HIV RNA, year of TCF, age, gender and previous ART regimen, harboring at least 9 (versus less) mutations was associated with increased mortality (Lohse 2007). However, things have changed. There are new options for patients with TCF. Moreover, other studies did not find an association between number of resistance mutations and mortality (Lucas 2004). With good CD4 T cell counts, even despite TCR viruses, the risk of developing AIDS is relatively small (Ledergerber 2004). TCR viruses have less ability to replicate and are probably less aggressive (Prado 2005).

So, in cases of TCR or MDR, be patient. It is, however, important that patients with MDR viruses are very carefully monitored and undergo regular (monthly) full-body exams – something that is often neglected these days in the discussions on blood values and resistance testing, etc. Loss of weight, Stage B symptoms, oral candidiasis, OHL and cognitive worsening are early signs of disease progression that need to be watched for. If possible, these patients should be treated in large centers that have access to clinical studies.
Salvage with the newer drugs

A wide range of agents for the treatment of patients with limited options has been licensed in the last few years. These agents include the PIs tipranavir/r and darunavir/r (which now also has an indication for naïve patients), the NNRTI etravirine, the CCR5 antagonist maraviroc and the integrase inhibitor raltegravir (also with an indication for naïves). They have revolutionized salvage therapy and have become indispensable in the struggle against resistant viruses. Other strategies have proved less effective. The most important results on salvage therapy from large-scale studies within the last few years are shown in Tables 9.2 and 9.3.

Table 9.2: Large randomized studies in salvage therapy

<table>
<thead>
<tr>
<th>References</th>
<th>Study (Agent)</th>
<th>Main inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lalezari 2003, Lazzarin 2003, Nelson 2005</td>
<td>TORO 1+2 (T-20)</td>
<td>TCF or TCR or both, VL &gt;5000</td>
</tr>
<tr>
<td>Hicks 2006</td>
<td>RESIST 1+2 (tipranavir/r)</td>
<td>TCF and 1–2 primary PI-resistance, VL &gt;1000</td>
</tr>
<tr>
<td>Clotet 2007</td>
<td>POWER 1+2 (darunavir/r)</td>
<td>TCF and ≥1 primary PI-resistance, VL &gt;1000</td>
</tr>
<tr>
<td>Lazzarin 2007, Madruga 2007, Katlama 2009</td>
<td>DUET 1+2 (etravirine)</td>
<td>≥1 NNRTI-resistance and ≥3 primary PI-resistance, VL &gt;5000</td>
</tr>
<tr>
<td>Gulick 2008, Fätkenheuer 2008</td>
<td>MOTIVATE 1+2 (maraviroc)</td>
<td>TCR or TCF or both, VL &gt;5000 (prior treatment interruption at baseline allowed), only R5-tropic viruses</td>
</tr>
<tr>
<td>Cooper 2008, Steigbigl 2008</td>
<td>BENCHMRK 1+2 (raltegravir)</td>
<td>TCR, VL &gt;1000</td>
</tr>
</tbody>
</table>

TCR=Triple Class Resistance, TCF=Triple Class Failure, VL=Viral load

Table 9.3: Large randomized studies in salvage therapy, main results

<table>
<thead>
<tr>
<th>Agent tested</th>
<th>POWER</th>
<th>RESIST</th>
<th>MOTIVATE</th>
<th>BENCHMRK</th>
<th>DUET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>DRV</td>
<td>TPV</td>
<td>MVC</td>
<td>RAL</td>
<td>ETV</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>1509</td>
<td>1049</td>
<td>701</td>
<td>612</td>
</tr>
</tbody>
</table>

Baseline characteristics

<table>
<thead>
<tr>
<th>Median VL, log RNA/ml</th>
<th>4.5–4.6</th>
<th>4.7</th>
<th>4.9</th>
<th>4.5–4.7</th>
<th>4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 active drug, %</td>
<td>49–55</td>
<td>43–45</td>
<td>38–44</td>
<td>48–51</td>
<td>54</td>
</tr>
</tbody>
</table>

Background-Therapy

| With de novo T-20, % | 29–33 | 18–23 | 40–44 | 20 | 25 |
| With darunavir, %   | 100 | 0 | 0 | 25–50 | 100 |
| With tipranavir, %  | 0 | 100 | 14–16 | 19–23 | 0 |

Response at 48 Wks*

| In total, % | 45 vs. 10 | 23 vs. 10 | 44 vs. 17 | 64 vs. 34 | 61 vs. 40 |
| With de novo T-20, % | 58 vs. 11 | 28 vs. 14 | 61 vs. 27 | 84 vs. 62 | 71 vs. 59 |
| 0-1 active drug, % | 37 vs. 1 | n.a. | 37 vs. 6*** | 48 vs. 12 | 57 vs. 24 |

*Definition of an active drug varied considerably (different resistance scores were used); **Response at 48 weeks defined as viral load <50 copies/ml; ***Data at week 24. n.a.=not applicable
Of note, inclusion criteria for these studies varied widely. In some studies inclusion was coupled to certain resistance mutations, others included triple-class failure. There were great differences in patient populations and the definition of TCF was not consistent. The proportion of patients additionally receiving T-20 ranged from 20–44%. Different resistance scores were also used in order to determine the number of active agents in background therapy. Accordingly, response rates vary considerably even in the placebo arms. The rates of all patients with a plasma viremia less than 50 copies/ml at 48 weeks ranged from 10% to 40%, with addition of T-20 from 11% to 62%. The response rates of patients who had received only one active agent and placebo varied from 1–24%.

Cross-trial comparisons regarding the efficacy of the new agents need to be avoided, although this is attempted for marketing reasons. According to these trials, darunavir/r is not better than tipranavir/r. Raltegravir does not have a higher efficacy than maraviroc. The individual study matters greatly.

**What to do in patients with TCR**

First of all, a resistance test should be available that was not done during a treatment interruption. Older resistance tests should also be reviewed. Resistance mutations detected earlier presumably still exist even if they are no longer detected. It is also important to check incompatibilities of the last years to spare the patient unnecessary side effects and dangerous re-exposure.

Some pilot studies report success when only new drugs are used. In the French TRIO study, 103 extensively pre-treated patients with TCF were treated with the combination RAL+ETV+MVC, out of which 86% achieved plasma viremia below 50 copies/ml at 48 weeks (Yazdanpanah 2009). In a smaller Italian study with 28 patients on the same combination RAL+ETV+MVC, this got to 92% (Nozza 2010+2011).

Does it necessarily have to be new drugs? Before switching, physicians should go over the classes, one by one, depending on the individual resistance profile, even the old ones. Table 9.4 shows an overview of the major salvage strategies with regard to each class.

**Table 9.4: Salvage strategies in patients with TCR to NRTIs, NNRTIs and PIs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible strategies, remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>Try to conserve mutations that reduce replication fitness, such as M184V with 3TC or FTC. Consider AZT and TDF simultaneously, due to diverging resistance pathways</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>At &lt;3 NNRTI mutations, consider etravirine (approved only with a boosted PI/r), otherwise discontinue NNRTIs</td>
</tr>
<tr>
<td>PIs</td>
<td>Darunavir/r (good data with etravirine) or tipranavir/r</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Tropism test? Due to non-detected dual-tropic viruses, use 2 definitively active agents such as raltegravir and T-20 (if nothing else works), remember dose adaption when boosting with PIs</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>At least 1-2 active agents additionally needed, be aware of rapid resistance development</td>
</tr>
<tr>
<td>T-20</td>
<td>Consider when uncertain that at least one other agent beyond raltegravir and maraviroc is active</td>
</tr>
</tbody>
</table>
NRTIs: Even if 3TC or FTC are no longer effective according to the resistance test, it might make sense in many cases to continue treatment with them. In this way, HIV is forced to conserve the M184V mutation, which reduces the replication fitness (Eron 2004, Campbell 2005, Castagna 2006). Due to diverging resistance pathways, another consideration may be to use AZT and TDF. This also applies when patients have already been treated with these agents. By adding AZT, viral load can be decreased to below detection in the presence of resensitising K65R (Stephan 2010). However, recent studies evaluating if partially active or inactive NRTIs contribute to treatment response have yielded conflicting results (Imaz 2011, Scherrer 2011).

NNRTIs: In the case of NNRTIs, with less than three NNRTI resistance mutations, etravirine seems to be a good option in combination with a boosted PI (most effective with darunavir/r). In other cases it is recommended to discontinue NNRTIs. There is little doubt that once generated, resistance remains. However, with pregnant women who have received nevirapine once for transmission prophylaxis there was no elevated rate of treatment failure on nevirapine-containing regimens if ART was initiated more than 6 months after delivery – at least theoretically, it seems possible for NNRTI resistances to disappear provided one waits a long enough time (Lockman 2007). However, there is no other data on recycling NNRTIs besides those for transmission prophylaxis.

PIs: In the case of PIs, the boosted PIs darunavir and tipranavir are strongly recommended. These PIs probably have distinct resistance profiles. When resistance findings are unclear, they should be discussed with the virologist. If darunavir/r and tipranavir/r are not available or if they are not tolerated, one can try lopinavir/r; other PIs are probably not suitable.

INIs: With elvitegravir and dolutegravir, two new integrase inhibitors are on the horizon (in August 2012, elvitegravir was approved in US but not yet in Europe). A large double-blind randomized Phase III Trial with over 700 pre-treated patients with resistance showed comparable effects between elvitegravir and raltegravir (Molina 2012). However, cross-resistance exists (Garrido 2012). A small trial, in which patients switched from elvitegravir to raltegravir, showed no virologic response. It seems that sequencing of these two integrase inhibitors makes no sense (DeJesus 2007). This could be different with dolutegravir. Cross-resistance with raltegravir does not appear to be complete (Kobayashi 2011). Clinical pilot projects such as the VIKING trials show that higher doses of dolutegravir may help to overcome raltegravir resistance. In VIKING II, 13/24 patients with raltegravir resistance reached viral loads below 400 copies/ml with 10 days of monotherapy with 100 mg dolutegravir daily showing better results than in VIKING I, where 50 mg were given (Eron 2011).

Maraviroc, T-20: If at least one other agent is still active, it seems sufficient to treat with only one of the new agents, either maraviroc or raltegravir, to reduce the viral load to below the limit of detection. That way, one could keep the option with the other drug that could be then combined with T-20 in the future. In the case of maraviroc, a recent tropism test should be available. If maraviroc or raltegravir are the only active agents according to the resistance test, they could and should be administered together. Fortunately, there is no relevant interaction (Baroncelli 2010). If maraviroc can not be used due to tropism, one should consider T-20. It is also important to strategize. What comes after the current regimen, and what can you do if that fails? To what extent is the patient standing with his back against the wall, immunologically? How high is the risk of progression to AIDS? The lower the CD4 T cells and the higher the viral load the more active agents are required to control the virus. If CD4 T cells are very low, it may be better to put all stakes into one option with as many active agents as possible (at least two), instead of saving up for future options.
Such complex decisions should be discussed in a team of experienced HIV physicians with a virologist who can shed some light onto the resistance situation. The treating physician should be present as well, as they are familiar with the individual situation, know the patient's adherence history and understand what can be expected from the patient.

**Practical tips for salvage therapy**
- First question: what is the treatment history, what level of success was there and for how long? Perform resistance testing (not during treatment interruption).
- Choose as many new active drugs as possible when changing therapy.
- Do not add one new drug to a failing regimen. If the clinical and immunological situation allows, wait for a second active drug.
- Do not wait too long to switch, thus giving the virus the opportunity to develop further mutations – the higher the viral load at the time of switch, the more difficult the chances for success.
- Do not be too demanding toward the patient! Not everyone is suitable for MegART.
- Patients should be treated in larger centers where new drugs and experience are available.
- Encourage the patient. New treatments may become available soon. A “watch and wait” approach may be possible.
- Do not allow reversion to wild-type virus – even a failing regimen should be continued in the absence of further options.

The following strategies were used with some success. Today, after the introduction of new drugs, however, they play a minor role.

**Double PI salvage regimens**

Since the introduction of darunavir/r and tipranavir/r, double PI regimens have lost their standing in salvage therapy. They will briefly be discussed because some patients are still being treated with double PI regimens.

**Lopinavir/r + saquinavir/r:** *in vitro* they have synergistic effects (Molla 2002). In the LopSaq study, 128 treatment-experienced patients were treated for different reasons (resistance, toxicity) with a nuke-free combination consisting of lopinavir/r plus saquinavir. At week 48, 61% had reached a viral load below 400 copies/ml. However, the response in patients with numerous PI resistance mutations and low CD4 counts was poor (Staszewski 2006).

**Atazanavir/r + saquinavir/r:** PK parameters for saquinavir are significantly improved by atazanavir. Response in pretreated patients was good (von Hentig 2007, Manosuthi 2008). Despite the fact that saquinavir levels are elevated by atazanavir, this combination must be given with ritonavir (Johnson 2005). Given the poor results in treatment-naïve patients, this combination is unlikely to play any further role (Landman 2008). Table 9.5 gives an overview of other double PI combinations.

**Conclusion:** There is no longer any reason to put a patient on a double PI. Simplifying therapy should be considered for patients on a double PI. One newer study showed that patients with stable viral suppression on a double PI can change to darunavir/r monotherapy without risk (Cohen 2009). This would also save costs as darunavir, albeit a more expensive PIs, is still less expensive than two older PIs together.
Table 9.5: Double PI combinations with supporting data

<table>
<thead>
<tr>
<th>Combination</th>
<th>Daily Dose/comment</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More favorable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r + saquinavir</td>
<td>800/200/2000</td>
<td>Staszewski 2006</td>
</tr>
<tr>
<td>Saquinavir/r + fosamprenavir</td>
<td>2000/200/1400</td>
<td>Boffito 2004</td>
</tr>
<tr>
<td>Lopinavir/r + indinavir</td>
<td>800/200/1600</td>
<td>Staszewski 2003</td>
</tr>
<tr>
<td><strong>Less favorable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r + fosamprenavir</td>
<td>Poor PK data</td>
<td>Kashuba 2005</td>
</tr>
<tr>
<td>Lopinavir/r + atazanavir</td>
<td>Poor activity</td>
<td>Ulbricht 2011</td>
</tr>
<tr>
<td>Lopinavir/r + nelfinavir</td>
<td>Poor PK data, diarrhea</td>
<td>Klein 2003</td>
</tr>
<tr>
<td>Atazanavir + indinavir</td>
<td>Elevated bilirubin</td>
<td>Chisolm-Burns 2007</td>
</tr>
<tr>
<td>Atazanavir + fosamprenavir</td>
<td>Poor activity</td>
<td>Landman 2009</td>
</tr>
<tr>
<td>Atazanavir + saquinavir without /r</td>
<td>Poor activity</td>
<td>Johnson 2005</td>
</tr>
<tr>
<td>Tipranavir + LPV/APV/SQV</td>
<td>Poor PK data</td>
<td>Walmsley 2004</td>
</tr>
<tr>
<td>Indinavir + nelfinavir</td>
<td>Relatively poor activity</td>
<td>Riddler 2002</td>
</tr>
</tbody>
</table>

**Mega-ART with T-20, treatment interruptions**

Intensified treatment combinations with more than three drugs – often described as mega- or giga-ART – may indeed be effective. Only well-informed and highly motivated patients can be considered for mega-ART regimens, and such approaches are often unrealistic in clinical practice. There is some evidence from the small INTENSE study that, in some cases, induction with T-20 is of benefit (Clotet 2008). So, do structured treatment interruptions (STI) before initiation of such intensified regimens provide additional benefit? The answer is clearly no. After some encouraging results from the early GIGHAART Study (Katlama 2004) there is an overwhelming amount of data showing that STIs do not have a positive effect in heavily pretreated patients. In the CPRC064 Study in which patients interrupted treatment for four months prior to going on a salvage regimen, no differences were found between patients who took an STI and those who did not (Lawrence 2003). However, it was disconcerting to see that patients who interrupted treatment not only had worse CD4 counts but also had a significantly higher frequency of severe clinical events during the follow-up period. Other randomized studies did not find any virologic benefit by interrupting treatment prior to starting an intensified salvage regimen (Ruiz 2003, Beatty 2006, Benson 2006, Walmsley 2007, Holodiny 2011). This approach is no longer an option.

**Utilizing NNRTI hypersusceptibility**

Viral strains are considered “hypersusceptible” to certain drugs if the IC50 (50% inhibitory concentration) for the drug is lower than that of the wild-type in phenotypic resistance tests. NNRTI hypersusceptibility was first described in January 2000 (Whitcomb 2000). It generally occurs very rarely with NRTIs but quite frequently with NNRTIs, and mostly in viruses that have developed resistance mutations against NRTIs (Albrecht 2001, Haubrich 2002). In an analysis of more than 17,000 blood samples the prevalence of hypersusceptibility in NRTI-naïve patients to efavirenz and nevirapine was 9% and 11%, respectively. In NRTI-experienced patients, it was 26% and 21% (Whitcomb 2002). Studies show that NRTI mutations, predominantly at codons 215, 208 and 118, are independently associated with NNRTI hypersusceptibility (Shulman 2004, Clark 2006).
There seems to be some evidence that patients with NNRTI hypersusceptibility have better virologic response. Of 177 highly treatment-experienced (but NNRTI-naïve) patients, 29% exhibited this type of lowered IC50 for one or several NNRTIs (Haubrich 2002). Of the 109 patients who received a new NNRTI-containing regimen, those with NNRTI hypersusceptibility achieved better results. Viral load was significantly lower even after 12 months, and the CD4 T cell count was higher. The replicative fitness, however, does not seem to be important here (Clark 2006). Even if the real significance and molecular correlates for NNRTI hypersusceptibility remain uncertain, the consequence is clear: patients with NRTI mutations and without NNRTI resistance should receive an NNRTI if possible.

Watch-and-wait or even simplifying ART

Sometimes even the most intensified salvage regimen is not effective. Viral load cannot be suppressed to undetectable levels. What should be done in these cases? The answer is to keep going as long as the patient can tolerate the therapy. Multidrug resistant viruses are typically slightly less aggressive than wild-type, at least for a certain period of time. A drug such as 3TC also has a positive effect on the viral load even in the presence of a confirmed M184V resistance. In a small study, in which 6 patients with MDR virus stopped only 3TC, the viral load increased by 0.6 logs (Campbell 2005). An Italian study enrolled 50 patients with a viral load of at least 1000 copies/ml on a 3TC-containing regimen, with evidence of the M184V mutation and at least 500 CD4 T cells/µl (Castagna 2006, Gianotti 2008). Patients were randomized to completely interrupt treatment or to continue with 300 mg 3TC alone because the M184V mutation reduces the replicative fitness of HIV. Patients on 3TC indeed had a significantly lower increase in viral load (0.6 versus 1.2 logs) and lost significantly less CD4 T cells (73 versus 153/µl). The M184V mutation was maintained in all patients on 3TC, and no other mutations accumulated. In contrast, a shift to wild-type was observed in all patients without 3TC. The benefit was sustained until week 144 (Castagna 2007) when 3TC was continued on a daily basis. Regarding FTC, daily doses also seems to be effective, but not when given weekly (Soria 2010).

However, ART should not be stopped completely in very immunocompromised patients who are then at risk of developing opportunistic infections. In fact, all efforts should be made in such cases to at least partially control the virus. Waiting, even on a suboptimal regimen, is a strategy that can be used to gain valuable time until new drugs are available. In such cases, ART is not being taken in vain: suboptimal ART is better than none at all, and some suppression of viral load better than none. Patients benefit even with only a slight reduction in viral load (Deeks 2000). A trial of patients with at least 2500 copies/ml on ART who were randomized to interrupt or continue ART for at least 12 weeks showed an immunological benefit for those who remained on their regimen. CD4 T cells dropped only by 15, compared to 128 cells/µl in patients on an STI (Deeks 2001). In a large cohort study, CD4 T cell counts did not drop as long as the viral load remained below 10,000 copies/ml, or at least 1.5 logs below the individual set point (Lederberger 2004).

How intensively should treatment be continued? Which drugs can be discontinued in this watch-and-wait setting? Quadruple nukes seems to be safe, as indicated by a retrospective study (Llibre 2008). NNRTIs such as nevirapine or efavirenz can be stopped if resistance mutations are found, because replicative fitness is not influenced by NNRTI mutations (Piketty 2004). Moreover, accumulation of further resistance mutations should be avoided as these may compromise newer NNRTIs such as etravirine. The same is probably true for integrase inhibitors (Wirden 2009).
Table 9.6: Example of a successful watch-and-wait strategy over almost three years

<table>
<thead>
<tr>
<th>Date</th>
<th>(HA)ART</th>
<th>CD4 T cells</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>until 1997</td>
<td>AZT, AZT+ddC, AZT+ddl</td>
<td>40 (nadir)</td>
<td>107,000</td>
</tr>
<tr>
<td>Mar 97</td>
<td>AZT+3TC+SQV-HGC</td>
<td>84</td>
<td>259,000</td>
</tr>
<tr>
<td>Oct 97</td>
<td>d4T+3TC+SQV+NFV</td>
<td>211</td>
<td>67,000</td>
</tr>
<tr>
<td>Jun 98</td>
<td>d4T+3TC+NVP+IDV/r</td>
<td>406</td>
<td>1,200</td>
</tr>
<tr>
<td>Jan 00</td>
<td>AZT+3TC+ABC+NVP+IDV/r</td>
<td>370</td>
<td>1,030</td>
</tr>
<tr>
<td>Mar 02</td>
<td>AZT+3TC+ABC+TDF+NVP+IDV/r</td>
<td>429</td>
<td>3,350</td>
</tr>
<tr>
<td>Sep 02</td>
<td>d4T+ddl+3TC+NVP+LPV/r</td>
<td>283</td>
<td>5,000</td>
</tr>
<tr>
<td>Nov 02*</td>
<td></td>
<td>348</td>
<td>7,600</td>
</tr>
<tr>
<td>Jan 03</td>
<td></td>
<td>315</td>
<td>16,400</td>
</tr>
<tr>
<td>Feb 03</td>
<td>AZT+3TC+ABC</td>
<td>379</td>
<td>6,640</td>
</tr>
<tr>
<td>May 03</td>
<td></td>
<td>241</td>
<td>2,400</td>
</tr>
<tr>
<td>Dec 04</td>
<td>AZT+3TC+ABC+TDF**</td>
<td>298</td>
<td>4,200</td>
</tr>
<tr>
<td>Jan 06</td>
<td></td>
<td>323</td>
<td>5,800</td>
</tr>
</tbody>
</table>

*Resistance testing showed a total of 20 mutations, with genotypic resistance against all drugs tested. Compliance was very good and plasma levels were always adequate. **TDF was added because of chronic HBV infection. Note: the patient's viral load has been below the limit of detection since April 2006, when he started AZT+3TC+TDF+TPV/r+RAL.

What about PIs? There is data from a small pilot study showing that PI discontinuation may be safe (Deeks 2005). 18 patients, in whom the viral load remained high despite more than 6 months on ART (good compliance, appropriate efficacy), had the PIs removed from their respective ART regimens while the NRTIs were continued. Within the first two weeks, none of the patients had an increase of more than 0.5 logs, and even after 16 weeks, no increase was observed in most patients (in only 5/18 patients was there an increase of between 0.5 and 1.0 logs; in the others there was no increase, maybe even a fall). A negative immunological effect was also seen in a few patients, but this was only moderate. Repeated resistance tests showed that all PI mutations persisted in all patients in the first 12 weeks, although PIs were not being taken. One retrospective study on HIV-infected children, in which the PIs had been discontinued, was based on the same idea as the Deeks study. Here, it was also seen that on continuous NRTI therapy, there was no increase in viral load (LeGrand 2005). Another study, however, showed that PIs maintained activity (Opravil 2009). Results from one of our own patients where this approach has been successful for almost three years are shown in Table 9.6. Resistance testing after two years showed that there were no changes in the MDR virus. Watch-and-wait on a simple NRTI regimen seems feasible in some patients for a limited period of time. The reasons for this phenomenon, however, are still not understood but it is possible that multiresistant viruses cannot easily mutate back. With PI therapy alone, this does not appear to be effective – in 5/5 patients, in whom only the nucleoside analog was stopped, viral load increased significantly (Deeks 2005). As total patient numbers are still very small in the data presented to date, many observers remain skeptical. The main question is how long and in which patients these strategies might be successful. It is thus advisable to monitor CD4 T cells at short intervals.

References


6.10. When to Stop ART?  
A review of treatment interruption  

CHRISTIAN HOFFMANN

Treatment interruptions are common. They are an important part of antiretroviral therapies whether as a clinician one approves of them or not. In the ART Collaboration Cohort (25,500 patients from Europe and North America), the probability of treatment interruptions was 11% after three years of ART (Abgrall 2012). Rates of interruption were markedly higher for intravenous drug users (than men who have sex with men) and in patients younger than 30 years of age. The following chapter provides an overview of the current knowledge in this area.

Viral load and CD4 T cells during treatment interruptions

Almost all patients who stop treatment experience a rebound in viral load within a few weeks, even patients in whom this has been undetectable for several years. Viral load is usually detectable again within 10–20 days (Chun 1999, Davey 1999, Harrigan 1999). The viral load in compartments such as the CNS, as well as in semen and vaginal fluids, parallels that in the plasma (Garcia 1999) and is detectable in semen within only a few weeks (Ananworanich 2011). Patients should therefore be informed about the higher risk of transmitting HIV (Burman 2008). Some cases report infections during interruption (Bernasconi 2001). There may be an increased risk of maternofetal transmission, even if ART is interrupted in the first trimester (Galli 2009). Frequently, an initial overshooting rebound is observed (De Jong 1997), and only after a few weeks does the viral load settle to its original, pre-treatment level (Hatano 2000). The rebounding virus evidently does not originate from latent reservoirs; other cell populations must exist from which this new virus is produced so quickly (Chun 2000, Ho 2000, Imamichi 2001).

Treatment interruptions can have serious immunological consequences. Often, CD4 T cell counts drop within a short time to pre-treatment levels. The ground that has been gained on ART is rapidly lost. The drop is bi-phasic, and the drop more pronounced in the first few months (Fagard 2005, Wit 2005, Skiest 2006). CD4 T cell losses vary greatly between patients but may reach -200 or -300/µl within a few weeks. The higher and faster the CD4 T cells increase on ART, the more rapid their decline (Tebas 2002). The CD4 nadir is also important. The lower it was and the older the patient, the more rapidly the count drops again (Maggiolo 2004, Molina 2006, Skiest 2006, Touloumi 2006). Probably there is also an association with high proviral DNA level at treatment interruption (Piketty 2010).

The loss of CD4 T cells during an interruption may not be regained as quickly. In a prospective study, we saw a significant disadvantage for patients undergoing treatment interruptions. After a follow up of 18 months, CD4 T cells were more than 120/µl less in these patients than in matched patients who had not interrupted treatment (Wolf 2005). This has also been seen in other studies (Kaufmann 2011).

The risks: resistance, clinical problems, AIDS

Viral resistance always has to be anticipated whenever there is viral replication in the presence of suboptimal drug levels, and thereby resistant mutants gain a selective advantage over the wild-type virus. As a result, there are concerns that resistance could develop both during the washout phase of medication (increasing viral replication with insufficient plasma levels) and on re-initiation of treatment (continued replication despite sufficient plasma levels).
However, in the case of single treatment interruptions, the probability of this does not appear to be particularly high, as shown in 1999 by the small French COMET Study, one of the first studies on treatment interruption (Neumann 1999). But there is no certainty as to whether interruptions might not eventually lead to development of resistant isolates, which merely require more time until they are able to dominate. Mathematical models show that this risk – at least theoretically – is not low, especially if viral load rises to high levels (Dorman 2000, Bonhoeffer 2000). The risk of resistance is probably higher for repeated treatment interruptions. In several studies, these have led particularly to NNRTI- or 3TC-resistance (Martinez-Picado 2002, Schweighardt 2002, Ruiz 2007). The risk seems particularly high for strategies involving stopping and starting at fixed intervals (see below). Table 10.1 describes the example of a patient who was clinically well and who interrupted treatment. It was probably the repeated stopping and starting of ART that ultimately led to resistance in this case.

Table 10.1: Example of the development of resistance due to repeated ART interruptions*

<table>
<thead>
<tr>
<th>Date</th>
<th>ART/comments</th>
<th>CD4 T cells</th>
<th>Viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jun 97</td>
<td>AZT+3TC+SQV</td>
<td>288</td>
<td>67,000</td>
</tr>
<tr>
<td>Oct 99</td>
<td>ART stopped, patient feeling well</td>
<td>540</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Dec 99</td>
<td>Diagnosis of autoimmune hyperthyroidism</td>
<td>400</td>
<td>63,000</td>
</tr>
<tr>
<td>Jan 00</td>
<td>AZT+3TC+NVP (+ carbimazole)</td>
<td>260</td>
<td>74,000</td>
</tr>
<tr>
<td>Feb 00</td>
<td>Diagnosis of anemia (Hb 7.3 g/dl)</td>
<td>ART stopped again</td>
<td>347</td>
</tr>
<tr>
<td>Mar 00</td>
<td>d4T+3TC+NVP (+ carbimazole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apr 00</td>
<td>Resistance mutations K103N, M184V</td>
<td>360</td>
<td>2,400</td>
</tr>
</tbody>
</table>

*During the first treatment interruption the patient developed autoimmune hyperthyroidism, the treatment of which led to anemia after re-initiation of ART, so ART was interrupted again. As a result, resistance developed against NNRTIs and 3TC. Autoimmune phenomena in the context of treatment interruption as seen in this patient have not previously been described.

The sharp increase in viral load that may often occur can present as a retroviral syndrome. The symptoms are similar to acute HIV infection, with lymphadenopathy, fever, asthenia and malaise (Colven 2000, Zeller 2001). Thrombocytopenia occurs in 25% of cases, especially when low thrombocytes existed previously (Ananworanich 2003, Bouldouyre 2009). The blood count needs to be monitored, especially in patients with a history of thrombocytopenia.

Finally, attention should be paid to patients who are coinfected with hepatitis B. If the HBV treatment with 3TC, FTC or tenofovir is interrupted, HBV rebound can result in fulminant and life-threatening hepatitis (Sellier 2004, Dore 2010). It is therefore advisable to monitor these patients very carefully and read the liver enzymes at least every two weeks.

The risk of AIDS seems to be low for single interruptions provided the immune defect is only moderate. In the Swiss Cohort, the risk of progression was not increased (Taffe 2002). In 133 patients who interrupted treatment we observed no increased risk of AIDS after 24 months compared to 262 matched controls (Wolf 2005). However, almost all patients in this study were immunologically stable throughout. The risk is probably higher in patients with severe immunodeficiency (Deeks 2001, Lawrence 2003). The CPRC064 Study in which 270 patients with MDR virus and clear immunodeficiency (median 144 CD4 T cells/µl) were randomized before a salvage regimen either to a four-month treatment interruption or not was stopped because of high risk of progression. In comparison with the control group, a significantly higher progression to AIDS (17 versus 5) occurred in the group interrupting therapy. In a mul-
tivariate analysis, two factors were predictive for death or progression: treatment interruption and the CD4 T cell count at the time of interruption. The risk increased by 1.4 with every drop of 50 CD4 T cells. This study demonstrates that severely immunocompromised patients are particularly at risk of developing AIDS during treatment interruptions of several months. Treatment interruptions should be avoided in such patients. Data from the SMART Study show that even with higher CD4 T cells treatment interruptions can lead to the development of AIDS (see below).

**STI for immunologic reasons: no effects**

Hardly any patient became as famous as the acutely-infected man treated in a Berlin practice a few years ago who, with a viral load of approximately 80,000 copies/ml, began an ART regimen consisting of ddI, indinavir and hydroxyurea. The virus rapidly became undetectable. After several problems – and two short treatment interruptions – ART was completely stopped after 176 days. Surprisingly, even without drugs plasma viremia remained below the level of detection for more than five years. Although virus was still detectable in lymph nodes, thus excluding eradication, the immune system in this case – referred to as the Berlin Patient (Lisziewicz 1999) – was obviously capable of durable control of infection. Why? Was it the early initiation of therapy, the hydroxyurea, or the treatment interruptions? No one knows the answer, even today. There may be a completely different explanation: it is possible that certain host factors in this patients that have not yet been elucidated could have influenced the course of disease – completely independently of ART, STI or hydroxyurea (Bloch 2006).

STIs have been extensively investigated in acutely-infected patients (see chapter on Acute HIV Infection). The theory of “endogenous vaccination” seems plausible. Transient increases in viral load could strengthen HIV-specific immune responses, which decline with increasing viral suppression on ART.

In several pilot studies from 2000/2001 successive interruptions seemed to indeed prolong the time to viral rebound or decrease the rate of rebound and, in parallel, there were measurable improvements in HIV-specific CD4 or CD8 T cell immune responses (Haslett 2000, Garcia 2001, Lori 2000, Ortiz 1999, Papasavvas 2000, Ruiz 2000). However, almost none of these studies included more than 2–6 patients, and a control group was usually missing.

STIs were finally put to the test in the Spanish-Swiss SSITT Study (Oxenius 2002, Fagard 2003): 133 patients were monitored throughout four ten-week treatment cycles, each consisting of eight weeks ART and two weeks of treatment interruption. After this, ART was permanently interrupted. Treatment success – defined as a viral load below 5000 copies/ml without ART after 52 weeks – occurred in 21/99 patients. However, 5/21 patients had a low viral load even before the initiation of ART. Most importantly, none of the 32 patients with a pre-ART viral load above 60,000 copies/ml achieved a viral load of less than 5000 copies/ml. The viral load set point was lowered in only a few patients, usually those with low initial viral load, despite repeated STIs. In contrast to acute infection, improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection. SSITT clearly showed that treatment interruptions on immunological grounds alone are not justified and are dangerous. Approaches with immunomodulatory drugs such as hydroxyurea (Foli 2004), mycophenolate (Garcia 2004), steroids (Ulmer 2005) or IL-2 (Henry 2006, Kilby 2006, Angus 2008) took place to lengthen the period of STIs. These approaches have not delivered positive results or are still in the experimental phases and are not justified outside studies. The same holds true for vaccination strategies (Harrer 2005, Jacobson 2006, Goujard 2007, Harrer 2008).
STI as a salvage strategy for MDR virus: no effects

In most patients with MDR virus, treatment interruption leads to a gradual shift back to wild-type and a loss of resistance. Resistance testing during treatment interruption is often of little use since mutations disappear from the blood as early as two weeks after treatment interruption (Devereux 1999). In modestly immunosuppressed patients, this shift is observed more frequently and faster. In more advanced stages of disease and with a longer duration of treatment, it lasts longer (Miller 2000, Izopet 2000), and sometimes after a longer interruption of therapy, no shift can be seen (Halfon 2005). When the shift is visible, PI mutations are the first to disappear, while NNRTI mutations are more protracted because they hardly affect viral fitness (Deeks 2001, Birk 2001). It is assumed that the wild-type merely dominates the resistant mutants. Special PCR methods can detect low quantities of resistant virus during STI (Izopet 2000) and when treatment is restarted resistance mutations rapidly re-dominate (Delaugerre 2001). Only a few cases have been described in which resistance mutations were apparently flushed out completely. There is one patient (Walter 2002) who was not able to attain sufficient viral suppression despite intensified ART, who then interrupted treatment. During the following seven months of treatment interruption there was a gradual reversion to wild-type, and after re-starting ART (which, according to previous resistance testing, should have had no effect) the viral load was successfully suppressed for several years.

Can patients with MDR improve the effect of the salvage regimen if they have had a previous interruption of treatment? At least two studies have shown that the shift resulting from treatment interruptions can be beneficial for salvage strategies (Miller 2000, Katlama 2004). However, this data is in contrast to that of numerous other studies in which an increased risk of AIDS was occasionally seen during treatment interruptions (Lawrence 2003, Lawrence 2006, Ruiz 2003, Ghosn 2005, Beatty 2006, Benson 2006, Walmsley 2007, Holodny 2011). In view of the risk of AIDS and the lack of evidence regarding the benefits, treatment interruptions are no longer justified.

STI for reduction of toxicity

Every antiretroviral therapy can cause side effects. Is it possible to reduce toxicity by treatment interruptions? Increased transaminases or lipid levels can drop quite rapidly after stopping treatment (Hatano 2000, Wolf 2005). However, it is not clear whether this is relevant in reducing the risk of cardiovascular disease. In SMART (see below), the risk of cardiovascular and metabolic complications during STIs was actually higher. In contrast to other studies, no relevant improvement of lipids was observed (Lampe 2010). In SMART but also in other trials, biomarkers for cardiovascular events were even elevated during treatment interruptions (Baker 2011, Olmo 2012). Thus, it seems questionable that, through solitary or repeated interruptions, the cardiovascular risk profile can be improved.

What about lipodystrophy and mitochondrial toxicity? At least two studies have shown that, after a few months, mitochondrial DNA can regenerate itself following a treatment break (Cote 2002, Mussini 2005, Kim 2007). In contrast, another study showed no effect (Negredo 2006). Whether or not a clinically manifest lipodystrophy improves, remains to be seen. At least short treatment interruptions have not had any effect on morphological changes (Hatano 2000). A six-month ART interruption markedly improved adipose tissue function, although fat distribution did not visibly change (Kim 2007). Substudies from the SMART trial (see below), so far the largest, showed a moderate positive effect on peripheral fat, lipids and bone mineral density during CD4-guided treatment interruptions (Martinez 2010).
Another subtrial showed more reduction of bone density on continued therapy than during interruption – however, numbers of a slightly reduced fracture risk during interruptions are still small (Grand 2009).

**Conclusion:** Although a treatment interruption is theoretically the solution to long-term toxicity on ART a convincing argument has not been provided by the data so far. Nevertheless, we will try to outline some relevant data. It is essential to distinguish between structured intermittent treatment with fixed intervals and interruptions that are individualized based on CD4 T cell count, in which case the interruption period depends on the patient’s immunological situation.

**Structured Intermittent Treatment (SIT, Fixed Intervals):** In the initial phase immediately following ART interruption the viral load usually remains low. Plasma viremia only reaches pre-treatment levels after about four, sometimes six weeks. The risk of developing resistance is presumably small at lower levels of viral replication (Bonhoeffer 2000). Does this indicate that ultra-short treatment interruptions could be utilized to reduce drug use, costs and long-term toxicity? In two NIH pilot studies on SIT in chronically infected patients ART was administered as seven days of treatment and seven days interruption (7-on-7-off). At 44–84 weeks, neither the viral load nor the proviral DNA increased (Dybul 2001+2004). CD4 T cells and HIV-specific immune responses remained unchanged suggesting that the immune system is probably unaffected by such ultra-short breaks in treatment. A significant reduction in lipid levels did, however, occur. Some patients experienced several blips (temporary increases in viral load) to above 100 copies/ml. It is impossible to predict whether this treatment strategy might result in a higher risk of resistance in the long term. There are still no larger studies, and it has become suspiciously quiet in this area. In addition, patients in the NIH studies were carefully selected, with good immune status and many years of viral suppression. This strategy is probably only applicable to a select group of patients. A three-arm study from Thailand showed a negative experience with the 7-on-7-off approach (Cardiello 2005). In this study, 19/36 patients experienced virologic treatment failure within a short period of time, and this treatment arm was consequently stopped prematurely. The main reason for this appears to lie in the fact that the majority of patients were NRTI-experienced. This means that if NRTIs are unstable, such on-off strategies are problematic.

ART only on weekdays? This approach was taken by the randomized FOTO Study (Five On, Two Off) in which TDF+FTC plus efavirenz was either given daily or from Monday to Friday and stopped at the weekends (i.e., saving 28% of the treatment and the costs). 60 patients were enrolled who showed an undetectable viral load for at least three months prior to the study. After 48 weeks, viral load increased in one patient despite low trough levels (Cohen 2007+2009).

In contrast, longer interruptions, over several weeks, with fixed intermittent treatment seem to be unfavorable. Results from a randomized NIH study with fixed intervals (each with one month of STI, two months of treatment) were disconcerting (Dybul 2003). The SIT arm contained significantly more patients with virologic treatment failure. Resistance mutations developed particularly against NNRTIs and 3TC, so that the study was stopped early. In the SSITT Study (2 weeks STI, 2 months ART) some resistance was seen (Yerli 2003), likewise in an Italian study (Palmisano 2007), but not in the French WINDOW Study (two months each of STI and therapy) (Marchou 2006). In the DART trial, the risk of AIDS was increased during the three months of treatment interruption (DART 2008).

**CD4 T cell driven interruptions:** Beside fixed intervals, whether short or long, there is another approach whereby interruptions are individualized based on CD4 T cell count. In other words, in patients with a good CD4 count, ART is interrupted until
the CD4 count drops below some immunological cut-off and only then is it resumed. Over the last few years, many non-randomized studies with differing cut-off points and very heterogeneous patient populations came to the conclusion that this approach is safe and allows for a considerable reduction in drug exposure (Maggiolo 2004, Skiest 2004, Fernandez 2005, Mussini 2005). In the meantime, a few randomized studies compare such CD4-driven intervals with continuous administration of ART. The relevant data and results of these studies are given in Table 10.2. It is clear that the results of these randomized studies differ considerably. While TIBET, Staccato or ACTG 5170 produced the verdict that CD4 T cell-driven interruptions are safe, two other studies, Trivacan and SMART came to other conclusions. In particular, the results of the SMART Study, which started in 2002, caused a sensation. In this, the largest randomized HIV study of all time, the cut-off levels for stopping ART were 350 cells/µl, and 250 cells/µl for re-initiating it. In the end, 318 centers in 53 countries recruited a total of 5472 patients. In 2006 an independent data safety monitoring board concluded that therapeutic interruptions result in an increased risk of AIDS – in the interruption arm, approximately twice as many AIDS illnesses were observed at follow-up, over an average of 18 months. This included severe opportunistic infections as well as malignant tumors. In fact, the overall risk was low, but so significantly elevated that the decision was made to end the study by the DSMB.

Table 10.2: Randomized studies of CD4 T cell-guided structured treatment interruptions

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>CD4 BL</th>
<th>CD4 Restart</th>
<th>Clinical findings in the STI arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIBET, Ruiz 2007</td>
<td>201</td>
<td>&gt;500</td>
<td>&lt;350 or VL  &gt;100,000</td>
<td>Some retroviral syndromes, some de novo NNRTI resistance, otherwise clinically safe (not a single AIDS case)</td>
</tr>
<tr>
<td>SMART, El Sadr 2006</td>
<td>5472</td>
<td>&gt;350</td>
<td>&lt;250</td>
<td>Morbidity and mortality risk low, but significantly raised. See Table 10.3.</td>
</tr>
<tr>
<td>Trivacan, Danel 2006</td>
<td>326</td>
<td>&gt;350</td>
<td>&lt;250</td>
<td>Morbidity significantly raised (double) due to invasive bacterial infections.</td>
</tr>
<tr>
<td>Staccato, Ananworanich 2006</td>
<td>430</td>
<td>&gt;350</td>
<td>&lt;350</td>
<td>Clinically safe (slightly more side effects in ART arm; more candidiasis in STI arm). No evidence of resistance.</td>
</tr>
<tr>
<td>ACTG 5170, Skiest 2007</td>
<td>167</td>
<td>&gt;350</td>
<td>&lt;250</td>
<td>In general safe, with risks only elevated when CD4 nadir was low.</td>
</tr>
</tbody>
</table>

FU=follow up; Mo=months; BL=baseline

Table 10.3: Different events occurring in SMART, per 100 patient years (El Sadr 2006)

<table>
<thead>
<tr>
<th>Event</th>
<th>STI (n)</th>
<th>Control (n)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of disease or death</td>
<td>3.7 (120)</td>
<td>1.3 (47)</td>
<td>2.6 (1.9-3.7)*</td>
</tr>
<tr>
<td>Death</td>
<td>1.5 (55)</td>
<td>0.8 (30)</td>
<td>1.8 (1.2-2.9)*</td>
</tr>
<tr>
<td>Cardiovascular/renal/hepatic events</td>
<td>1.8 (65)</td>
<td>1.1 (39)</td>
<td>1.7 (1.1-2.5)*</td>
</tr>
<tr>
<td>Grade IV toxicity</td>
<td>5.0 (173)</td>
<td>4.2 (148)</td>
<td>1.2 (1.0-1.5)*</td>
</tr>
</tbody>
</table>

* Significant difference. ** 95% Confidence interval
In addition it was observed that cardiovascular incidents in the interruption arm did not become less frequent, but actually increased. The clinical incidents in SMART (http://www.smart-trial.org/news.htm) are shown in the Table 10.3. Quality of life did not improve with therapy interruptions – it even declined (Burman 2008). More recent studies showed that clinical and immunological disadvantages remained, even when ART was resumed (El Sadr 2008). However, even after SMART, not all questions were answered. A striking fact was the high incidence of clinical occurrences compared to Staccato, a study involving 430 patients. As measured by the AIDS/mortality rates of ART, there should have been at least 17 cases in Staccato – instead there was not one. Moreover the significantly higher risk of an AIDS-defining malignancy during therapy interruption (Silverberg 2007) was questionable as the majority of the patients who developed KS or lymphoma in SMART had already suffered from AIDS illnesses before. Why were these patients enrolled in the SMART study?

Most of the deaths in the interruption group were not ascribed to AIDS (only 4 compared to 3 cases in the control group) but to cancer which is normally not associated with HIV infection (11 versus 5), and to cardiovascular incidents (7 versus 4). Cases of death of unknown cause were also more frequent in the interruption group (15 versus 3). One can only speculate about the increased cardiovascular, renal and hepatic incidents in the interruption group. How many patients interrupted therapy that should not have? How many patients with chronic hepatitis B experienced a HBV rebound during interruption, how many patients with previous HIVAN developed renal problems, how many patients decided to stop concomitant medications (statins) that led to a cardiovascular event? However, there are some newer studies that show an increase of inflammatory or coagulation parameters during therapy interruption (Kuller 2008, Calmy 2009, Baker 2011, Olmo 2012). Cystatin C, a parameter for renal dysfunction, also increases (Mocroft 2009).

### Practical tips for treatment interruptions

- If there are no problems with ART, there is no reason to stop it.
- To reverse resistance or for immunologic reasons, i.e., from a strategic point of view, STIs are not useful.
- A positive effect on cardiovascular incidents or lipodystrophy has not been confirmed. From the SMART Study, this seems highly unlikely.
- The patient’s wish for a break should be respected. The interruption will happen whether the clinician agrees or not. A supervised treatment interruption is always better than one undertaken without the awareness of the clinician.
- Beforehand, information should be provided on possible clinical (retroviral syndrome, AIDS), immunologic (loss of CD4 T cells) and virologic (resistance) consequences.
- Patients must be aware that the risk of infection increases – even after a longer suppression, viral load returns to initial levels after 4–6 weeks without ART.
- Beware of HBV coinfection (danger of hepatitis flare-ups).
- CD4 T cells (including percentage), viral load, and blood count (i.e., thrombocytes) should be monitored monthly during interruptions.
- Risk of resistance is possibly higher with NNRTIs (choose robust regimens and stop NNRTIs several days earlier if possible – consider the half-life of the drugs).
- Patients who started ART “too early” according to current standards can probably interrupt safely.
- Resistance testing during treatment interruptions is not useful – it usually only measures the wild-type.
- Start with ART again, but not too late.
6.10. When to Stop ART?

Despite all these questions, the conclusion remains that it is difficult to find a reasonable argument for treatment interruption. Especially the argument that therapy interruptions improve quality of life is no longer acceptable. One can discuss higher values for initiation and interruptions, but there will certainly not be any second SMART with new starting/stopping values for some time. Patients should always be encouraged to continue ART. Thanks to the new classes, the options have widened, enabling us to react to many side effects. If the patient, after discussion, still wishes to interrupt therapy the wish should be respected. The interruption will happen anyway with or without the doctor’s agreement. A monitored interruption is better than one done secretly behind the physician’s back. Under strict surveillance the risk for complications is rather low.

References


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6.11. Monitoring

CHRISTIAN HOFFMANN, CHRISTIAN NOAH

Which parameters should be included in routine laboratory monitoring of HIV-positive patients? What results can be expected? This section deals with viral load, CD4 T cells, routine checks, and plasma levels. Resistance and tropism tests are the subject of a separate chapter (see HIV Resistance Testing). For the tests to be performed on initial presentation see The New Patient.

Viral Load

Viral load is the amount of HIV RNA in the blood. Alongside the CD4 T cell count, viral load has become the most important surrogate marker for HIV infection (Hughes 1997, Mellors 1997, Lyles 2000, Ghani 2001, Phillips 2004). It provides information on how high the risk is for disease progression and whether antiretroviral therapy is indicated; it is the critical value in determining the success of therapy. Viral load assays measure the amount of HIV RNA (viral genetic material), which correlates directly with the number of virions. The units are viral copies/ml (or genome equivalents). This is reported either as a direct whole number or as a logarithmic number. A change of one or more logs refers to the change in viral load by one or more decimal powers. Many labs provide both values, the number and the log. There is no standardized international unit/ml as in used in hepatitis B or C.

<table>
<thead>
<tr>
<th>Number of copies</th>
<th>Log_{10}</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>50</td>
<td>1.7</td>
</tr>
<tr>
<td>100</td>
<td>2.0</td>
</tr>
<tr>
<td>500</td>
<td>2.7</td>
</tr>
<tr>
<td>1,000</td>
<td>3.0</td>
</tr>
<tr>
<td>10,000</td>
<td>4.0</td>
</tr>
<tr>
<td>50,000</td>
<td>4.7</td>
</tr>
<tr>
<td>100,000</td>
<td>5.0</td>
</tr>
<tr>
<td>1,000,000</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Assessment

The higher the viral load, the higher the risk of decrease in CD4 T cells, with subsequent disease progression or occurrence of AIDS-related illnesses (Mellors 1997, Lyles 2000, Phillips 2004). A viral load above 100,000 copies/ml (sometimes even above 50,000 copies/ml) is considered to be high; a value below 10,000 copies/ml (sometimes below 5000 copies/ml), low. However, these thresholds are not absolute and only provide points of reference.

The effects of plasma viremia on immune status can vary greatly between individuals. There are some patients whose CD4 T cells remain stable for relatively long periods despite having a high viral load, while others experience a rapid drop, although the viral load is relatively low. Even in the so-called elite controllers in which the viral load is undetectable without ART a slow but constant drop in the CD4 cells can be observed (Stellbrink 2008).

Viral load is probably lower in women than in men. In a meta-analysis, the difference was 41% or 0.23 logs (95% CI 0.16–0.31 logs) (Napravnik 2002). The reason for this phenomenon remains unclear and whether it should have an impact on the indication for treatment is still the subject of debate.
Methods

Three methods or assays are currently used to measure viral load: Reverse Transcription-Polymerase Chain Reaction (RT-PCR); branched-chain DNA (bDNA); and, occasionally, Nucleic Acid Sequence-Based Amplification (NASBA). These three methods differ both in levels of detection and in the linear range within which measurement is reliable or reproducible (see Table 11.1). In the case of PCR and NASBA, the viral RNA is transformed into several enzymatic steps and then amplified to measurable amounts. Detection occurs after binding of marked DNA fragments. bDNA does not require an enzymatic step; signal amplification occurs via binding of branched DNA fragments to viral RNA.

Table 11.1: Methods of measurement

<table>
<thead>
<tr>
<th>Company</th>
<th>Test</th>
<th>Technology</th>
<th>Detection limit (copies/ml)</th>
<th>Linear Range (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Diagnostics</td>
<td>COBAS TaqMan HIV-1 Test; v2.0</td>
<td>RT-PCR</td>
<td>20</td>
<td>20–10,000,000</td>
</tr>
<tr>
<td>Siemens Healthcare Diagnostics</td>
<td>Versant HIV-1 RNA 1.0 Assay (kPCR)</td>
<td>RT-PCR</td>
<td>37</td>
<td>37–11,000,000</td>
</tr>
<tr>
<td>Abbott Molecular</td>
<td>Abbott RealTime HIV-1</td>
<td>RT-PCR</td>
<td>40</td>
<td>40–10,000,000</td>
</tr>
<tr>
<td>Siemens Healthcare Diagnostics</td>
<td>Versant HIV-1 RNA 3.0 Assay (bDNA)</td>
<td>bDNA</td>
<td>65</td>
<td>50–500,000</td>
</tr>
<tr>
<td>Biomérieux</td>
<td>NucliSENS EasyQ HIV v. 2.0</td>
<td>NASBA</td>
<td>250</td>
<td>25–7,900,000</td>
</tr>
</tbody>
</table>

The market for assay systems is very dynamic. New assay systems will become available, existing ones further developed. Siemens, for example, offers an RT-PCR in addition to bDNA technology. Roche concentrates on RT-PCR and is working on additional functions such as “dual-target detection” for more successful results. This means that not one section of the viral RNA, like before, but two sections can be duplicated at the same time. If duplication fails in one section on account of the high variability of the HIV genome (the result in this case would be incorrect negative), it will be duplicated in the second section. Besides already established manufacturers, newer companies such as Qiagen are trying to gain market share. Experience will show whether their testing systems are reliable or not.

Recent further developments also concern a reduction below detection level which is at 20 copies/ml in the most sensitive tests. Clinical relevance of a viral load below 50 copies/ml is questionable due to lack of data. It should be noted that a higher sensitivity can lead to insecurity in patients and clinicians and to more frequent control tests.

Although intra-assay variability is fairly good for all three methods, methodological variations should be carefully considered. Differences of less than 0.5 logs are not considered significant. A decrease from 4.3 to 3.9 logs, for example (corresponding to a decrease from approximately 20,000 to 8,000 viral copies/ml) does not necessarily signify a drop in viral load. The same holds for increases in viral load. Changes of up to threefold can therefore be irrelevant. Patients should be made aware of this. Considerable differences exist between the methods (Coste 1996) and to change from one method to another is generally not advisable. The results obtained by bDNA are usually lower than the PCR by a factor of 2. Different subtypes are also detected with varying success according to the method employed (Parekh 1999). One should be
particularly cautious in patients from Africa and Asia with non-B subtypes in whom the viral load at first presentation can be unexpectedly low. In such cases, use of a different assay may actually be indicated. However, newer versions with improved primers are probably superior in measuring even unusual HIV subtypes with adequate sensitivity.

All assays have a linear dynamic range, outside of which precise numbers are not so reliable. The following rule applies: use one method, one laboratory. The laboratory should be experienced and routinely perform a sufficiently large number of tests. Measurement should take place as soon as possible after blood withdrawal, and correct collection and shipping of centrifuged plasma is also important (contact the laboratory ahead of time on these issues).

**Influencing factors**

Apart from methodological variability a host of other factors may influence levels of viral load including vaccinations and concurrent infections. During active OIs viral load is often high. One study showed a 5- to 160-fold elevated viral load during active tuberculosis (Goletti 1996). Viral load can also increase significantly during syphilis and declines after successful treatment (Buchacz 2004, Kofoed 2006, Palacios 2007). In a large retrospective study, 26% of transient viremia in patients on ART were caused by intercurrent infections (Easterbrook 2002). In these situations, determining the viral load does not make much sense.

Following immunizations, i.e., for influenza (O’Brien 1995) or pneumococcus (Farber 1996), the viral load may be transiently elevated (Kolber 2002). As the peak occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization. It should be noted that not every increase is indicative of virologic treatment failure and resistance. Slight transient increases in viral load, or blips, are usually of no consequence, as numerous studies in the last few years have shown (see chapter on *Goals and Principles of Therapy*). The possibility of mixing up samples always has to be considered. Unusually implausible results should be double-checked with the laboratory, and if no cause is found there, they need to be monitored – people make mistakes. Should there be any doubt on an individual result; the lab should be asked to repeat the measurement from the same blood sample.

**Viral kinetics on ART**

The introduction of viral load measurement in 1996–1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant *in vivo* dynamics (Ho 1995, Perelson 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the process of viral production and elimination. The concentration of HIV-1 in plasma is usually reduced by 99% as early as two weeks after the initiation of ART (Perelson 1997). In one large cohort, the viral load in 84% of patients was already below 1000 copies/ml after four weeks. The decrease in viral load follows biphasic kinetics. In the first phase, i.e., within the first three to six weeks, an extremely rapid drop occurs, followed by a longer phase during which the viral load gradually decreases further (Wu 1999). The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection. In one study, the range was between 15 days with a baseline viral load of 1000 and 113 days with a baseline of 1 million viral copies/ml (Rizzardi 2000). The following figure shows a typical biphasic decrease in viral load after initial high levels.

Numerous studies have focused on whether durable treatment success can be predicted early (Thiebaut 2000, Demeter 2001, Kitchen 2001, Lepri 2001). In a study
on 124 patients, a decrease of less than 0.72 logs after one week was predictive of virologic treatment failure in more than 99% of patients (Polis 2001). According to another prospective study, it is possible to predict virologic response at 48 weeks even after 7 days (Haubrich 2011). However, this has little clinical relevance, and in our opinion it is pointless to start measurement of viral load only one or two weeks after initiation of therapy.

We recommend measuring viral load every four weeks until it has dropped to below detection of 20–50 copies/ml. Once that is achieved, measurement every three to four months is enough. Eventually, longer intervals are possible (Chaiwarith 2010). In case of rebound, closer monitoring becomes necessary. Within the first 4 weeks of therapy initiation the viral load should be reduced by a factor of 100, after 3–4 months (6 months if viral load was high) it should be below the level of detection. Viral load can also be measured fairly reliably in body fluids other than blood or plasma (for example cerebrospinal, vaginal or seminal fluid). However, such tests are usually performed for scientific purposes and are not officially licensed for other reasons.

**Practical tips for dealing with viral load** (see chapter Goals and Principles of Therapy)

- Use only one assay, if possible.
- Use only one experienced laboratory, if possible, no home-brewed assays.
- Watch for assay variability (up to half a log) and explain this to the patient.
- Monitor viral load every four weeks with new ART until the viral load is below the level of detection (50 copies/ml).
- Measure viral load sparingly – on successful ART, every three months may be sufficient.
- Not on ART, measurement every three months is usually sufficient.
- Do not measure shortly after vaccinations or with concurrent infections.
- Implausible results should be rechecked after 2–4 weeks.
- Consider differences between subtypes (in some cases it may be useful to use another method).
CD4 T cells

CD4 T cells are T lymphocytes that express the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as T helper cells. Alongside viral load, measurement of the CD4 T cell level is the most important parameter or surrogate marker in HIV medicine. It allows for a reliable estimate of the individual risk of developing AIDS. All HIV-positive patients should have a CD4 T cell measurement every six months. Two reference values are generally accepted: above 400–500 CD4 T cells/µl, severe AIDS-related diseases are very rare; below 200 CD4 T cells/µl, the risk of AIDS-related morbidity increases significantly with increased duration of immunosuppression. Most AIDS-related illnesses occur below 100 CD4 T cells/µl.

Several points should be considered when measuring CD4 T cells (usually by flow cytometry). Blood samples should be processed within 18 hours. The lower normal values are between 400 and 500 cells/µl, depending on the laboratory. Samples should always be sent to the same (experienced) laboratory. The same applies for viral load as for CD4 T cells: the higher the level, the greater the variability. Differences of 50–100 cells/µl are not unusual. In one study, the 95% confidence intervals with a real value of 500 cells/µl were between 297 and 841 cells/µl. At 200 CD4 T cells/µl, the 95% confidence interval was between 118 and 337 cells/µl (Hoover 1993).

Measurement of CD4 T cells should only be repeated in the case of highly implausible values. As long as the viral load remains below the level of detection, there is no need to be concerned even with decreases in CD4 T cells. In such cases, the relative values (CD4 percentages) and the CD4/CD8 ratio (ratio of CD4 to CD8 T cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference, with values above 500 CD4 T cells/µl, fluctuations of more than 29% are to be expected, with less than 200 CD4 T cells/µl fluctuations of up to than 14%. Individual laboratories may define the normal ranges for the relative values and the ratio differently. If there are considerable discrepancies between absolute and relative CD4 T cells, any decisions involving treatment should be carefully considered – if in doubt, it is better to check the values again. The remaining differential blood count should also be scrutinized carefully – is leukopenia or leukocytosis present? Clinicians sometimes forget that the result of the CD4 T cell count is of existential importance for the patient. To go to the doctor and discuss the test results can involve a great deal of stress for many patients. Insensitively informing the patient of a sup-

Figure 2. Slow decline of the absolute (solid line) and relative (dashed line) CD4 T cells/µl over almost ten years in a treatment-naïve patient. Note the variations in the absolute numbers.
posedly bad result can lead to further negative results. From the start, patients must be informed about the possible physiological and method-related variability of laboratory tests. In the case of unexpectedly good results, every effort should be made to contain euphoria. In the long run, this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results. Once CD4 T cell counts within the normal range are reached in addition to adequate viral suppression, measurements every six months should suffice, in our opinion. The probability of CD4 T cells dropping to values below 350/µl is extremely low in such cases (Phillips 2003). Patients who might sometimes insist on more frequent monitoring of immune status can be assured that there are usually no detrimental changes in the CD4 T cell count as long as HIV remains suppressed.

Influencing factors
Several other factors can influence CD4 T cell counts apart from laboratory-related variables. These include concurrent infections, leucopenia of varying etiology and steroids or other immunosuppressive therapies. Extreme exertion, surgical procedures or pregnancy can also lead to lower values. Even diurnal variation occurs; CD4 T cells are lower at noon, and highest in the evening around 8 p.m. (Malone 1990). Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Kinetics of CD4 T cells on ART
Similarly to viral load, a biphasic increase in CD4 T cells occurs following the initiation of ART (Renaud 1999, Le Moing 2002), with a rapid increase within the first three to four months and a much slower rise thereafter. In a study of almost 1000 patients, the CD4 T cell count increased by 21/µl per month during the first three months. In the following 21 months, this rate was only 5.5 CD4 T cells/µl per month (Le Moing 2002). The initial rapid increase in CD4 T cells is probably due to redistribution, which is followed by the new production of naïve T cells (Pakker 1998). Diminished apoptosis may also play a role (Rober 2002).
It is still being debated whether the immune system steadily continues its recovery even after a long period of viral suppression, or whether a plateau is reached after three to four years beyond which there is less improvement (Smith 2004, Viard 2004).
Several factors can influence the extent of immune reconstitution during ART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moin 2002). The absolute increase is higher if CD4 T cell counts were high at the start of ART (Kaufmann 2000). Naïve T cells still present at initiation of therapy are a particularly important factor for long-term immune reconstitution (Notermans 1999).
Age is also important (Grabar 2004). The larger the thymus and the more active the process of thymopoiesis, the more significant the rise in CD4 T cells is likely to be (Kolte 2002); due to age-related degeneration of the thymus, CD4 T cells in older patients do not increase as much as those in younger ones (Viard 2001). However, we have seen both 20-year-old patients with very poor CD4 T cell count recovery and 60-year-old patients with very good, above average increases in CD4 T cells. The regenerative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.
It is possible that some antiretroviral therapies such as ddi+tenofovir are associated with less immune reconstitution than others. In addition, current studies are evaluating if immune reconstitution is better during treatment with CCR5 antagonists. Immunosuppressive concurrent medications should also be considered (see chapter on Goals and Principles of Therapy).
Practical tips for dealing with CD4 T cells

- As with viral load, use only one (experienced) laboratory.
- The higher the values, the greater the variability (consider numerous factors) – compare the relative (percentage) values and CD4/CD8 ratio with previous results.
- Do not disconcert the patient when there are apparent decreases – if viral suppression is sufficient, the drop is usually not HIV-related. Only highly implausible results should be repeated.
- If the viral load is below the level of detection, three-monthly measurements of CD4 T cells are sufficient.
- In the presence of good viral suppression and normal CD4 T cells, CD4 T cells (not viral load) may also be checked less frequently.
- The patient should have time to discuss the CD4 count and viral load with the physician.

Beyond the measurement of the CD4 T cell count and lymphocyte subpopulations, a number of other assays allow detailed testing of the qualitative or functional capacity of the immune system, for example in response to specific antigens (Telenti 2002). These often cumbersome methods are not currently necessary for routine diagnostics and their use remains questionable. However, they could one day help to better describe individual immune status and, for example, identify those patients who are at risk of developing opportunistic infections despite good CD4 cell counts.

Routine checks – What else should be monitored?

Besides the CD4 T cell count and viral load several other parameters should be monitored in the HIV-positive patient. The following recommendations apply to clinically asymptomatic patients with normal results on routine laboratory evaluation, who have been on stable treatment for several months or who are not taking antiretroviral therapy. Of course, if treatment is started or changed or if the patient develops complaints more frequent monitoring is required. Depending on the problem additional tests may be necessary. On the other hand, the rate of new lab abnormalities decreases as more time elapses post-ART initiation (Taiwo 2012). This suggests that as time on initial ART increases, monitoring frequency may be reduced in subgroups without early abnormalities.

A complete physical examination should be performed regularly, and this often leads to the discovery of important findings such as Kaposi’s lesions or mycoses (thrush). The lower the CD4 T cells, the more frequently patients should be examined. In patients with less than 200 CD4 T cells/µl, we usually perform fundoscopies every three to six months to exclude CMV retinitis. Close cooperation with an HIV-experienced ophthalmologist is essential. The better the CD4 T cells, the less often fundoscopies are necessary – in our opinion when CD4 counts have normalized these can be stopped completely. In contrast, regular gynecological examinations with PAP smears are recommended regardless of CD4 count. Many experts now also recommend rectal examination (including proctoscopy) for the early detection of precancerous lesions and anal cancer.

However, such guidelines or recommendations can be interpreted very differently. In our opinion, in cases of good immune status unless there is a specific suspicion, routine X-rays, ultrasound examinations (exception: patients with chronic hepatitis, as hepatocellular carcinoma is not rare in such cases), multiple serologies or lactate measurements are not necessary. An annual ECG is only indicated in our view in patients with a specific risk profile (see chapter on HIV and Cardiac Disease). The
tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

With regard to the growing age of the HIV population, it is essential not to forget cancer screening. In many countries, for example, colonoscopy is recommended for early detection of colorectal cancer for every individual older than 50–55 years (colonoscopy should be performed every 10 years). For further information see WHO website, http://www.who.int/cancer/detection/en/

<table>
<thead>
<tr>
<th>Table 11.2: Minimal evaluations per year in stable asymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient on ART per year</strong></td>
</tr>
<tr>
<td>Blood count, LDH, ALT, AST, creatinine, bilirubin, AP, lipase, GGT, glucose</td>
</tr>
<tr>
<td>Viral load</td>
</tr>
<tr>
<td>CD4 T cells</td>
</tr>
<tr>
<td>Lipids</td>
</tr>
<tr>
<td>Physical examination, urine status</td>
</tr>
<tr>
<td>Gynecological examination</td>
</tr>
<tr>
<td>Fundoscopy if CD4 T cells &lt; 200/μl</td>
</tr>
</tbody>
</table>

**Therapeutic Drug Monitoring (TDM)**

Plasma levels of many antiretroviral drugs may vary considerably for diverse reasons (e.g., adherence, metabolism, absorption). Measurement of drug concentrations in serum or plasma is also referred to as therapeutic drug monitoring (TDM).

Sufficient plasma levels are essential for success of virologic treatment (Acosta 2000). In the VIRADAPT Study adequate PI concentrations were even more crucial than knowledge of resistance mutations (Durant 2000). The importance of sufficient plasma levels has also been shown for NNRTIs (Marzolini 2001, Veldkamp 2001). This information however dates to the early years of ART.

Whether TDM improves virologic response today is not clear (Kredo 2009). Only a few large randomized studies exist that have provided data regarding this question. One randomized trial showed no benefit in 183 patients experiencing therapy failure, who had switched to a new PI and had either adjusted or not adjusted the dose of PIs when their levels were low. After 48 weeks the number of patients with viral loads below the limit of detection did not increase with TDM. A positive effect on viral load was merely restricted to a small subgroup of patients with only partial PI effects (Albrecht 2011). Another randomized trial also showed no positive effects on viral suppression (Best 2007). Favorable effects of TDM continue to remain questionable and the method is still regarded as experimental (Review: Liu 2010).

On the other hand, very high plasma levels correlate with a higher rate of side effects. Reported renal problems with indinavir (Dielemann 1999), gastrointestinal disturbances with ritonavir (Gatti 1999), hepatotoxicity with nevirapine (Gonzalez 2002) or CNS problems with efavirenz (Marzolini 2001) were all associated with high plasma levels. For this reason, TDM will remain a tool for therapy observation: not every interaction between antiretroviral drugs or with concomitant drugs has been investigated.

Measurement of plasma levels may currently be reasonable in the following situations (German-Austrian ART guidelines):
- Complex drug combinations including boosted PIs
- Patients with very high or low body weight
- Side effects
• Treatment failure (resistance?)
• Suspected absorption or adherence problems
• Severe liver or renal diseases
• ART in children, pregnancy
• Use of new drugs (unknown interactions)

Several problems associated with TDM limit its broader use. The measurement of NRTIs, for example, is not possible since they are converted to the active metabolites only intracellularly. Intracellular measurements are difficult and are not available in routine clinical practice. There is no valid data available for newer antiretroviral agents such as raltegravir, maraviroc, etravirine, rilpivirine or elvitegravir. Measuring NNRTIs or PIs may therefore currently determine levels of only one component of a failing combination. Further problems include not only viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, and time-dependent variability of plasma levels, but also methodological problems with the assays, as well as lack of clearly defined limits. Many uncertainties thus remain in the assessment of therapeutic drug plasma levels. Until data from randomized studies is available, proving the clinical value of TDM, both the measurement and interpretation of results should be left to specialized centers.

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Approximately 30 years after AIDS was first described, a prophylactic vaccination remains a distant prospect. In 2007 two highly promising vaccine studies were prematurely interrupted. Only a few trials are ongoing. It seems doubtful now that a vaccine to effectively prevent HIV infection will be discovered anytime soon – the moderate but surprisingly successful RV144 vaccine study will not change that (Rerks-Ngarm 2009, see chapter on Preventive Vaccination). Several experts believe that a promising vaccine candidate does not exist presently.

The finding that HIV superinfection occurs at approximately the same rate as primary HIV incidence (Redd 2012, Ronen 2012) has significant implications for HIV vaccine research. When HIV itself does not provide any protection from re-infection – how to find a protective vaccine in uninfected persons? Some experts believe that a vaccine may never come. Neither blind hope nor time schedules have proved very helpful. Some vaccine studies up until now can in fact be regarded as counterproductive, fatiguing both sponsors and the community.

Considering all this, prevention will continue to be the central means of controlling the HIV epidemic. However, common prevention strategies focused on the ABC guidelines (abstinence, be faithful, condom use) have reached their limits. In 2010 UNAIDS declared a worldwide increase of 2.7 million new infections. In every major city in the US or in Europe syphilis endemics in HIV-infected patients have been reported. Acute hepatitis C among MSM is common. It seems clear that advertisements and brochures alone are not the solution, especially when these simple publicity mechanisms are not maintained. High-risk groups are not being reached effectively. Prevention remains an arduous business and success is not immediately visible nor is it profitable in economic terms, although the savings in people needing treatment, i.e., people not becoming infected, could be enormous. In any case, sexual behavior is not easily modified by a few advertisements or brochures.

For some time, preventive medicine in HIV has been taking completely new and sometimes unusual paths to reach focus groups. Terms such as serosorting, seropositioning, dipping or strategic positioning show that the medical world is learning to face sexual reality. People have sex and not everyone cares about, follows, or can follow guidelines. Recent studies with serosorting, choosing sexual partners according to perceived HIV serostatus, show that new prevention strategies can be developed (Morin 2008).

The following focuses mainly on medical prevention strategies. In 2010 there were groundbreaking new findings in this area regarding PrEP and microbicides. In 2011, the protective effect of ART, which had been expected for a while, finally became evident and could have a substantial impact on HIV prevention.

**Treatment as prevention**

Little in HIV medicine of the last few years has met with such wide response as the results of the HTPN 052 Trial. Spontaneous, standing ovations as seen during the International AIDS Conference in Rome in July 2011 are seldom seen in the world of science. The reputable journal “Science” described the results as “the breakthrough in 2011” and “The Economist” even wrote about the “end of AIDS”. What caused this commotion? Results of a trial had been published in the summer of 2011, which had investigated the protective effect of ART (Cohen 2011). HTPN-052 was a trial with 1763 HIV-discordant couples in the US, India, Brazil, Thailand and five African
countries. The HIV-infected partners had to be treatment-naïve and show CD4 T cell counts between 350 and 550/µl. Approximately 97% of the couples were heterosexual and most of the volunteers were between 26 and 40 years. The couples received thorough instructions and the use of condoms was counseled at monthly sessions. Then the HIV-infected partners were randomized to start ART, either immediately or after CD4 T cells fell to below 250/µl or when AIDS had manifested. The primary endpoint was defined with new infections of the negative partners clearly originating from the infected partners (“linked infections”). In a first evaluation in February 2011 after a follow-up of 1.7 years, 39 infections were observed, among them 28 identified as “linked”. Dramatic differences were observed. There was only one infection in the arm in which infected partners had received ART immediately. Later investigations showed that the infection was probably caused before or just after the infected partner had started ART. Even when counting this case, the results gave evidence for a 96% protection with ART, a result unachieved up to then by any of the other prevention strategies, including PrEP or vaccination (Karim 2011).

Thus, antiretroviral therapy is an important contribution to prevention, possibly the most important. However, this was already suggested by a large number of uncontrolled studies prior to the HTPN trial. These studies are here discussed briefly:

- In a group of 415 HIV-discordant couples in Uganda 90 new infections were diagnosed over a period of 30 months. Not a single infection was caused by an infected partner with a viral load below 1500 copies/ml. With every additional log of HIV RNA, infection risk increased by a factor of 2.45 (Quinn 2000).
- In a study in Thailand with 493 HIV-discordant couples, the factor was 1.81. No infection from a partner with less than 1094 copies/ml was recorded (Tovanabutra 2002).
- In a study in Spain with 393 heterosexual HIV-discordant couples, a transmission rate of 8.6% was observed between 1991 and 2003. No infection was recorded when infected partners were receiving combination ART (Castilla 2005).
- Among 534 MSM in San Francisco, infectiousness based on the probability of transmission per couple decreased by 60% between 1994 and 1998 (Porco 2004). The HIV incidence decreased in spite of the reported higher number of partners and risk contacts, even though not all of the HIV-infected partners were on antiretroviral therapy.
- In a Spanish study with 62 HIV-discordant couples (22 HIV-infected women, 40 HIV-infected men, all of them on ART), 76 “natural” pregnancies were diagnosed. Not a single HIV infection of a non-infected partner was recorded (Barreiro 2006). The above-mentioned clinical studies show clearly that the lower the viral load in the plasma, the less infectious the patient. In a meta-analysis of 11 cohorts with 5021 heterosexual couples (and 461 HIV transmissions) the transmission rate of patients on ART was 0.46 per 100 person years (5 cases). No transmission was detected from anyone who was below 400 copies/ml (Attia 2009).

**Test and treat?**

At the end of 2008 a statistical paper caused great discussion. A research group led by the Director of WHO Kevin De Cock calculated how to, at least theoretically, curtail and even eliminate the worldwide HIV epidemic (Granic 2008). For this ambitious goal they concentrated totally on the preventive effect of antiretroviral therapies. They compared the common treatment strategy used today, beginning ART only on symptomatic patients or on those who have less than a certain number of CD4 T cells, to a theoretical strategy that seems simple enough. Every person is tested for HIV once a year and if found positive, starts ART immediately, irrespec-
tive of CD4 T cells or viral load. The study was based on population data in South Africa, where 17% of the adult population is HIV-infected and on data from a successful intervention in Malawi. Other preconditions of the calculation model are that infectiousness of treated versus not-treated patients was estimated at 1%. The case-reproduction number, the so called R0 number of new infections caused by one infection, was crucial for this calculation. The corresponding simple assumption that R0 of <1 is required in order to reduce the incidence and to eventually eliminate HIV means that an incidence rate of less than one new case per 1000 person years was determined in order to eliminate HIV.

At present, every untreated HIV-infected individual causes another 7 HIV infections (R0=7) in the course of their lifetime. R0 could be reduced to 4 if every person received regular treatment with therapy starting at 200 CD4 T cells/µl, or even to 3 if therapy starts at 350 CD4 T cells/µl. However, an R0 reduction to less than 1 is impossible by this method and curtailing the epidemic with ART alone remains unrealistic. This could change however, with regular testing and immediate treatment of positively-diagnosed individuals – elimination of the epidemic could be possible by 2020, even in a country as severely affected as South Africa. Compared with common practice today where ART is begun only at a certain level of CD4 T cells, immediate treatment could reduce AIDS mortality to half today’s number by 2050. Calculations showed that this initially more expensive strategy could start to be cost-saving by around 2032.

The comments to the WHO publication ranged from “provocative” (Cohen 2008) to “extremely radical” (Garnett 2008). Critics raised concerns over the risks and the absence of ethics (would all actors agree? Could a restricted individual autonomy be achieved? Can changes in sexual habits be maintained?), medical (compliance problems, the dangers of possible resistance, the side effects and “overtreatment” – starting too early) as well as financial (South Africa would have to triple their financial commitments) considerations.

Such calculations are not new. Other groups have arrived at similar results in the past (Velasco-Hernandez 20002, Montaner 2006). What is new is that antiretroviral therapies today are potentially more user-friendly and such programs are probably easier to put into practice than just a few years ago.

In addition, people are realizing that the current preventive measures can only improve slowly and that neither vaccines nor microbicides can be expected in the near future. At present, approximately 80% of the population in sub-Saharan Africa is not aware of their infection. More than 90% do not know if their sexual partners are infected – an invitation for further spread of the epidemic.

Juggling figures like this may seem unhelpful at first. Despite all objections regarding methodological, ethical, financial or logistic considerations, etc., facing 2.7 million new infections per year, a number that is not likely to decline much (if at all) in the near future, and the failure of several vaccine and prevention studies, one thing has become clear. Antiretroviral therapy has turned into one of the most important components of prevention.

Initiatives like this one of WHO must continue, and new and unusual strategies must be continually developed. It cannot do harm to bring more therapy to the 6.7 million people, worldwide, the number who by the end of 2007 desperately needed ART and were not receiving it (see chapter on Global Access).

**ART & viral load in other body fluids**

Do viral load in plasma and viral load in other body fluids correlate? Here are some data:

- In a study from Italy the viral load on PI-containing ART regimens decreased by several logs in plasma as well as in semen (Liuzzi 1999).
In a Swiss study with 114 male patients with plasma viremia under 400 copies/ml on ART, only 2 (2%) isolated viral loads were detected in semen, compared to 67% in untreated control groups.

In 205 HIV-infected women with plasma viremia under 400, 400–9999 and over 10,000 copies/ml, the rate of detectable HIV-1 RNA in the genital tract was 3, 17 and 48%, respectively (Cu-Uvin 2000). In 7 ART-naïve women, the viral load decreased by 0.7–2.1 logs within the first 14 days of ART. Similar results were achieved with 11 Brazilian female patients (Vettore 2006).

In a group of 290 women with plasma viremia under 500 copies/ml, 44 (15%) had detectable HIV-1 RNA in cervical smears (Neely 2007). In comparison to PI-containing ART the risk with NNRTIs was double.

In a study with 34 females with plasma viremia below 80 copies/ml, all treated with ART for at least 6 months, only one woman showed a viral load over 80 copies/ml in cervical vaginal fluid (CVF) compared to 7 rebounds in plasma (Kwara 2008).

Out of 122 samples of cervical vaginal lavage the viral load in the lavage correlated highly with plasma viral load (Fiore 2003). However, in 25% of cases, virus was found in the lavage even when plasma viremia findings proved negative.

In a study with 233 MSM (1996–1997), far less virus was found in anorectal smears of those treated with ART. Among those patients with less than 50 copies/ml in plasma, 1/54 (2%) HIV-1 RNA was detected in the anorectal smear. However, in 14/50 (28%) HIV-1 DNA was detected.

Among 255 MSM receiving ART with a plasma viral load below 40 copies/ml, 7 patients (3%) showed an isolated viral load in semen (Marcelin 2009). These 7 patients had been on ART for some time and treated with agents detected in semen.

In a prospective study on 25 Canadian patients on ART, a viral load in semen was found in 19/116 (14%) samples (Sheth 2009). There was no reference to drug concentration in seminal fluid.

In conclusion, in most cases, viral load in plasma parallels viral load in other bodily fluids. If the viral load in plasma decreases, so does the RNA in semen or the vaginal fluid within a short time. “Below the limit of detection in plasma” also means “below the limit of detection in other bodily fluids”. In most cases. There are exceptions: in the studies above the variation was between 1 and 14%. Although there are implications that the detected virus in semen is not completely infectious (Nunnari 2002), one cannot rule out the patient being potentially infectious even on successful ART. Putting together these facts with clinical data, transmission with a low viral load seems unlikely. To date, only a few cases have been recorded in which transmission has taken place despite effective ART (Stürmer 2008). These cases show that there is in fact a residual risk. The question is how to manage that risk.

The EKAF paper

In January 2008 a paper was released by the “Eidgenössische Kommission für Aids-Fragen” (EKAF), the Swiss AIDS commission. Just the title of this paper caused a great stir: “HIV-infected individuals without other STDs on effective antiretroviral therapy are not sexually infectious.” The original manuscript can be found at http://www.saez.ch/pdf_d/2008/2008-05/2008-05-089.PDF.

EKAF concluded that HIV-infected individuals do not transmit the disease under three conditions:
1. ART is adhered to and monitored by a clinician
2. The viral load has been below detection for at least six months
3. There is no other STD
This first official statement from public authorities on this subject had a major impact. Despite its caveats, critics feared that this publication could be misunderstood as an all-clear signal resulting in people being less careful and unnecessarily exposing themselves to risks of HIV infection.

Critics say that the data is not sufficient, especially for the risk of anal sexual contacts. The probability of infection is certainly under 1:100,000, but nevertheless not zero (Wilson 2009). The preventive effect of ART may be endangered by higher risk taking. According to mathematical models, a 10% rise in risk behavior could counter the effects of ART (Blower 2001, Law 2001). However, a meta-analysis came to the conclusion that ART does not increase risk behavior of the patient, even if the viral load is below detection (Crepaz 2004).

HIV clinicians must be prepared for this discussion. Patients are asking more questions: do I have to use a condom for the rest of my life? Here, it is better to give individualized advice. It depends greatly on the non-infected partner as well, as he or she should not be pressured. On the other hand, information of this type can be a relief for many patients and their partners. The EKAF paper may also motivate high-risk patients to finally start antiretroviral treatment (preventing more infections rather than causing new ones initially feared by the release of the paper).

However, it must be repeated that the EKAF statement refers only to stable relationships. Safer sex is still recommended, especially with occasional sexual contacts to avoid other sexually transmittable diseases.

**Medical prevention strategies besides ART**

**Circumcision**

Circumcision of the male foreskin reduces the risk of infection for several diseases in unprotected sexual intercourse (Weiss 2006). At least three randomized trials with heterosexual males in Uganda, Kenya and South Africa demonstrated this in recent years for HIV as well. Remarkably similar results were achieved (Table 12.1).

Table 12.1. Large randomized studies on circumcision

<table>
<thead>
<tr>
<th>Place (Reference)</th>
<th>n</th>
<th>Main Results</th>
<th>Reduction of Transmission risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya (Bailey 2007)</td>
<td>2,784</td>
<td>Two-Year HIV Incidence 2.1% (95% CI 1.2–3.0) vs 4.2% (95% CI 3.0–5.4)</td>
<td>53–60%</td>
</tr>
<tr>
<td>Uganda (Gray 2007)</td>
<td>4,996</td>
<td>Over 24 months HIV incidence 0.66 vs 1.33/100 person years</td>
<td>51–60%</td>
</tr>
<tr>
<td>South Africa (Auvert 2005)</td>
<td>3,274</td>
<td>Over 18 months HIV incidence 0.85 vs 2.10/100 person years</td>
<td>60–61%</td>
</tr>
</tbody>
</table>

TR=Transmission Risk, partly different definition/calculation

A meta-analysis of these studies shows a relative risk of 0.44 for circumcision (Mills 2008). The NNT (number needed to treat) required to prevent an event reached a relatively low number of 72.

The effect of circumcision is explained by the presence of CD4-positive Langerhans cells and primary HIV target cells in the male foreskin. Circumcision reduces the frequency of genital HSV-2 infection (Tobian 2008), which however does not explain the protective effect (Gray 2009). An estimated 2 million HIV infections in Africa alone could be prevented in the next few years (Williams 2006). The WHO recommends circumcision as a preventive means for heterosexual men. A favourable side effect is that circumcision has also a protective effect against HPV-infections (Serwadda 2010).
Circumcision, however, is not without risk. Complications (infections, postoperative bleeding) occur in 3–4% of cases (Gray 2007). Sexual behavior after circumcision, ethics and logistical problems are only a few aspects (Lie 2006). It must be noted that circumcision reduces the risk for male but not for female partners. The randomized study in Uganda showed a slight increase in infections of the female partners of circumcised males (Waver 2008). This can be mainly explained by couples probably having sexual intercourse earlier than recommended. Several weeks of no-sex are stipulated after the operation.

Is there a protective effect for MSM after circumcision? If there is, the data is less clear compared to the results for heterosexual men. A meta-analysis of 15 greatly varying studies with 53,567 MSM (52% with circumcision) showed no significant difference between circumcised and uncircumcised males (Millet 2008). Another newer study confirms these results (Sanchez 2011).

Preventive treatment of HSV and other diseases
Genital infections clearly increase the risk of acquiring HIV. This applies especially to the human herpes virus 2 (HSV-2). According to a meta-analysis, the risk of HIV increases with HSV-2-seropositivity: when HSV-2 antibodies are detected in the blood, the risk increases in male patients 2.7-fold and in female patients 3.1-fold (Freeman 2006). A considerable amount of new HIV infections are due to HSV coinfection, with an estimated 38–69% in female patients and 8–49% in male patients. Considering these data, several studies have been conducted in which the protective effect of HSV therapy has been evaluated both in HIV-negative and HIV-positive populations.

**HIV-negative:** Is a reduction of the HIV transmission rate in HIV-negative persons possible by suppression of HSV-2? HPTN 039, a double-blind, randomized, Phase III trial investigated this question (Celum 2008). In total, 1871 MSM from the USA and Peru and 1,380 women from Zimbabwe, Zambia and South Africa received 400 mg acyclovir or placebo twice daily. Enrolled subjects were all HIV-negative and HSV-2-positive at the beginning of the trial. Although less HSV ulcers were observed in the active group, the trial failed to show a decline in HIV incidence in the acyclovir-group, with 3.9/100 person-years compared to 3.3/100 in the placebo group. These disappointing results were confirmed by the Mwanza trial with 821 women in Tanzania, in which again no decline was observed (Watson-Jones 2008). It is still not clear why, however, resistance to acyclovir is unlikely (Watson-Jones 2010). Another study showed that short bursts of subclinical genital HSV reactivation are frequent, even during high-dose anti-herpes therapy, and probably account for continued transmission of HSV during suppressive antiviral therapy (Johnston 2012). Taken together, preventing HIV infection with HSV therapy using acyclovir in HIV-negative individuals has proven unsuccessful. The prophylactic use of azithromycin, to prevent bacterial STDs also showed no protective effect against HIV (Kaul 2004).

**HIV-positive:** Can the transmission rate be reduced if the HIV-infected partner is treated with acyclovir? A huge study enrolling 3408 discordant African couples showed no effect on the transmission rate, although there was a clearly reduced rate of genital HSV ulcers (Celum 2010). However, this study did show an interesting side effect, that there is a slight but measurable effect with acyclovir and its derivatives regarding HIV viral load. Compared to placebo, a decline of 0.25 logs was observed. This effect slightly decreased the risk of HIV progression in therapy naïve patients (Lingappa 2010). The transmission rate was obviously not influenced by the reduction in viral load. Resistances were not induced by acyclovir (Baeten 2011). Antiviral effects were also observed in several other randomized studies. The viral
load in blood and cervicovaginal fluids was reduced by 0.26 to 0.53 logs by using acyclovir or valacyclovir (Delany 2009, Nagot 2007, Zuckermann 2007, Baeten 2008, Dunne 2008, Paz-Bailey 2009). Valacyclovir also significantly decreased early breast milk HIV-1 RNA among women receiving PMTCT (Drake 2012). In a meta-analysis of seven randomized trials conducted between 2000 and 2009 in which acyclovir or valacyclovir were used as prophylaxis among individuals coinfectected with HIV-1 and HSV-2, the summary treatment effect estimate was -0.33 logs, an approximate halving of plasma viral load (Ludema 2011).

These studies may possibly lead to the development of new acyclovir derivatives with improved antiviral potency, provided they respond well to HIV (Vanpouille 2010).

**Microbicides, lubricants, diaphragms**

Microbicides are chemical agents, mostly of topical application, in the form of gels that kill or immobilize HIV and other diseases. Presently heterogenic mechanisms are being examined. Among them are agents that inhibit docking to the target cell or antiviral agents. It is required that microbicides are not only inexpensive, easy to apply and non-toxic, but also effective against other STDs, as these increase the risk of HIV transmission. The CAPRISA trial (see below) has led to a noticeable revival in this field of research.

**Classical microbicides:** Up to now, there is no product that has delivered convincing protective effects in clinical studies. HIV transmission risk in fact increased with nonoxynol-9 (Van Damme 2002) or cellulose sulfate (van Damme 2008). PRO 2000, which initially seemed promising (Abdool Karim 2011), had no effect (McCormack 2010). Application of diaphragms and/or lubricants in addition to condoms had no protective effect, as one randomized study showed (Padian 2007).

**Antiretroviral microbicides:** A breakthrough in research of microbicides was achieved in the CAPRISA trial in September 2010. CAPRISA was a double-blind study in which 889 HIV-negative women in South Africa used 1% tenofovir gel (Abdool Karim 2010). Compared to placebo, HIV incidence was reduced from 9.1 to 5.6/100 years. Transmission risk for women applying the gel regularly was reduced by 54%.

According to newer estimations (Williams 2011), over 20 years, the use of tenofovir gel in South Africa could avert up to 2 million new infections and 1 million AIDS deaths. Even with low rates of gel use, it is highly cost-effective and compares favorably with other control methods.

This first success (“proof of concept”) has led to a focus on antiretroviral agents in the research of microbicides, such as tenofovir and even the more experimental NNRTIs dapivirine and MIV-150, as well as maraviroc and raltegravir (Review: Mertenskötter 2011).

**PrEP (Pre-exposure Prophylaxis)**

In the HIV setting, PrEP is an oral prophylactic antiretroviral treatment. Like malaria prophylaxis, it is taken before exposure. PrEP trials are currently being conducted in high-risk groups (i.e., commercial sex workers). Most trials use tenofovir, either alone or in combination with FTC. Many of these studies were regarded with skepticism. Pressured by activists and others, a study with Cambodian sex workers was interrupted in 2004 and others in Cameroon and Nigeria in 2005 (Cohen 2004, Sing 2005). The researchers involved were accused of not providing sufficient information to the participants and of discontinuing treatment once the study was over. A similar breakthrough, like the one with microbicides by the CAPRISA trial, was seen with PrEP at the end of 2010. In the iPrEx study, 2499 MSM from six countries
received either TDF+FTC or placebo. After a median of 1.2 years, 36 versus 64 infections were observed and the risk for infection was reduced by 44% (Grant 2011). Apart from slightly more cases of nausea and weight loss in the active arm, there were no differences. Of note, only in 3/34 patients of those infected in the active group was tenofovir or FTC detected in plasma. Protective effects were also proven in the Partners PrEP Trial, a large trial involving 5000 heterosexual couples in Kenya and Uganda, and the TDF2 trial (Thigpen 2011, Baeten 2012). In the Partners PrEP trial, the placebo arm was stopped in July 2011 and randomized again to tenofovir or TDF+FTC.

This success, however, has not been without setbacks. In the FEM-PrEP Trial on African woman, 35 infections in the placebo arm were observed compared to 33 with TDF+FTC. Due to lack of efficacy, this large trial was discontinued in April 2011. The three-armed VOICE Trial investigating women from three African countries also showed no benefit with different interventions. The arms with oral tenofovir and tenofovir gel also lacked the expected results and were discontinued by the end of 2011. The following table shows an overview of the ongoing large trials:

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Risk groups, region, PrEP regimen</th>
<th>Protective effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>2,400</td>
<td>IDU in Thailand: TDF</td>
<td>Fully enrolled, no data yet</td>
</tr>
<tr>
<td>PARTNERS PrEP (Baeten 2012)</td>
<td>4,758</td>
<td>Heterosexual couples in Africa: TDF, TVD</td>
<td>67% with TDF, 75% with TVD</td>
</tr>
<tr>
<td>iPREX (Grant 2011)</td>
<td>2,499</td>
<td>MSM, world-wide: TVD</td>
<td>44% with TVD</td>
</tr>
<tr>
<td>CAPRISA 004 (Abdool 2010)</td>
<td>889</td>
<td>Women in South Africa: Vaginal TDF gel</td>
<td>39% with TDF gel</td>
</tr>
<tr>
<td>TDF 2 (Thigpen 2011)</td>
<td>1,200</td>
<td>Young women and men in Botswana: TVD</td>
<td>62% with TVD</td>
</tr>
<tr>
<td>Africa, FEM-PrEP (van Damme 2012)</td>
<td>2,064</td>
<td>Women, Kenya, South Africa, Tanzania: TVD</td>
<td>None (Study stopped)</td>
</tr>
<tr>
<td>Africa, VOICE/ MTN 003</td>
<td>5,000</td>
<td>Women in South Africa, Uganda and Zimbabwe: TVD, TDF, vaginal TDF gel</td>
<td>None with TDF (oral or gel, both arms stopped 2011), TVD ongoing</td>
</tr>
</tbody>
</table>

To date it remains unclear why some trials were successful and others not. Adherence certainly has a strong influence. Simple truth: You can not expect a protective effect if you don’t take the agent. Trials such as iPREX or PARTNERS showed a clear correlation between blood levels and infection risk. Protection was highest in volunteers with detectable tenofovir levels (Anderson 2012, Donnel 2012). Adherence was poor in the FEM-PrEP trial, as the young women considered their risk of acquiring HIV infection as minimal. The VOICE trial also showed poor adherence as probably the application of gel was considered annoying.

What has become clear, however, is that PrEP is not always beneficial and that success depends on several factors, first adherence, but also viral load of the infected sexual partner, other STDs, different biological factors, sexual behavior and sexual practices, to name just a few. Hormonal contraceptives seem to have no influence on the transmission rates (McCoy 2012).

Physicians must be prepared to talk about PrEP, although some questions remain that have not been answered by the above mentioned studies.
How should PrEP be administered? Who will receive the treatment? And who will cover the expense? Is the dose studied and the form (every day) the best way? Is TVD the only option? Who should distribute it (ambulances, doctors, pharmacists?) and how to make it more accessible to risk groups? Other questions regarding long term tolerance, safety during pregnancy, administration in young people or patients with hepatitis B remain unanswered. Some results indicate that tenofovir as PrEP significantly reduces bone density (Liu 2011, Mulligan 2011). What about development and transmission of resistance in an unidentified HIV infection? Will this decrease the use of condoms? Will PrEP be sold on the black market in the near future (and so, with limited adherence programs)? These are only a few aspects to be considered. In Switzerland as well as at the EMA, a commission dealing with these questions has already been set up, although the benefits of PrEP have not yet been scientifically proven.

In conclusion, with dramatically high numbers of continuing infections worldwide, prevention must strike new paths. Strictly propagating safer sex alone is not enough. Among medical approaches, the use of antiretroviral therapy is the most imaginative strategy right now. The EKAF paper will continue to be discussed. Like it or not, microbicides and PrEP will have a lasting effect on HIV prevention. Patients and their partners will be asking for it.

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We all know this data, which we see every time we go to an international meeting:

- Some 6,860 people become infected with HIV every day, 2,400 of whom are under 25 years of age.
- Approximately 8 million people are currently receiving ART, while at least 8 million people are still in need, depending on the guidelines of when to start (i.e., <500, <350, <200 CD4).
- There are some 34.2 million people infected, 2.5 million newly infected in 2011. 1.7 million people died of AIDS-related causes in 2011.
- Based on global goals and targets for 2015, it is estimated that an investment of $23 billion/yr will be required for the global AIDS response in low- and middle-income countries (www.who.org, accessed 19.04.10).

In the developing world, the price of ART has fallen drastically in recent years. Even so, cost remains an obstacle to access for many millions. Moreover, the health infrastructure required to deliver ART and maintain adherence and retention is lacking in many places. Access to drugs depends not only on financial and human resources. It depends also on people being aware of their HIV status, knowledgeable about treatment, and empowered to seek it. Thus public information and education are important elements in widening access, alongside efforts to build or strengthen health services. Stigma has been and remains a major stumbling block in wanting, seeking and taking the treatment regimen correctly. The campaign for universal access to life-saving drugs for HIV and AIDS, started originally by grassroots AIDS activists, is today a major focus of attention of UN agencies and most all influential organizations at national and global levels.

The Declaration of Commitment on HIV/AIDS, unanimously endorsed by the UN General Assembly in 2001, embraced equitable access to care and treatment as a fundamental component of a comprehensive and effective global HIV response. Since then many countries, through the support of intergovernmental organizations and donors, have definitively demonstrated the ability to deliver HIV treatment in very resource-limited settings. Access to treatment has helped mobilize communities in response to HIV, preserved the health and viability of people and households vulnerable to HIV, and strengthened HIV prevention efforts in many parts of the world. In the goal to reach universal access to HIV prevention, treatment, care and support, leadership at a national level is required to establish policies that support treatment scale-up by:

- increasing the number of people who choose to know their HIV status;
- reducing HIV stigma;
- building human capacity to sustain treatment through education and training and better use of human resources;
- improving supply management and integrating HIV care with other health services.

In 2011, the international community recommitted to the goal of universal access. This time, countries committed to achieving universal access by 2015. The goal of universal access is also part of Millennium Development Goal (MDG) 6 which includes halting and beginning to reverse the spread of HIV/AIDS by 2015.

The updated 2011–2015 global health strategy was released in June 2011. This strategy outlines four key targets that countries need to achieve if universal access and MDG 6 are to be realised: reduce new infections by 50 percent among young people (15–24 years), reduce TB-related mortality by 50 percent, eliminate new infections in children, and reduce HIV-related mortality.
Major Players

PEPFAR Update

The President’s Emergency Plan for AIDS Relief (PEPFAR) was launched in 2003 to combat global HIV/AIDS, and is the largest commitment by any nation to combat a single disease in history. During PEPFAR’s initial phase in 2004–2008, the United States invested nearly $19 billion in PEPFAR (which includes bilateral HIV/AIDS and tuberculosis programs, as well as contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria). For 2011, $5.56 billion was enacted for bilateral HIV/AIDS programs, $1.05 billion for the Global Fund; the line item for bilateral TB programs is requested at $285M (see chart; all $ in this chapter are US$).

PEPFAR is now the cornerstone of the US Global Health Initiative, which commits $63 billion over six years to support countries in improving and expanding access to health services. PEPFAR is moving from its initial emergency focus to a heightened emphasis on sustainability, and serves as a platform for expanded responses to a broad range of global health needs. As of March 2012, PEPFAR directly supported ART for over 4.5 million men, women and children. PEPFAR partnerships in more than 70 countries have directly supported care for nearly 13 million people affected by HIV/AIDS.

In 2011, PEPFAR supported prevention of mother-to-child transmission programs that allowed nearly 200,000 infants of HIV+ mothers to be born without HIV. In 2012, of course, one wonders if treating all HIV+ women, pregnant or otherwise, as women, might not be a more human strategy. Still, far from all pregnant HIV+ women get the care they need (beyond point-of-care transmission prevention). In 2011, PEPFAR directly supported HIV counseling and testing for nearly 40 million people, including community-based services and rapid tests, providing what may be an important entry point to prevention, treatment, and care.

FY 2006 – FY 2012 PEPFAR Funding ($ in millions)

<table>
<thead>
<tr>
<th>Programs</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2012</th>
<th>Total</th>
<th>2013 Req’d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral HIV/AIDS Programs¹</td>
<td>2,654</td>
<td>3,699</td>
<td>5,028</td>
<td>5,503</td>
<td>5,574</td>
<td>5,333</td>
<td>37,137</td>
<td>4,537</td>
</tr>
<tr>
<td>Global Fund</td>
<td>545</td>
<td>724</td>
<td>840</td>
<td>1,000</td>
<td>1,050</td>
<td>1,046</td>
<td>7,149</td>
<td>1,650</td>
</tr>
<tr>
<td>Bilateral TB Programs</td>
<td>91</td>
<td>95</td>
<td>163</td>
<td>177</td>
<td>243</td>
<td>239</td>
<td>256</td>
<td>232</td>
</tr>
<tr>
<td>TOTAL PEPFAR (w/o Malaria)</td>
<td>3,290</td>
<td>4,518</td>
<td>6,031</td>
<td>6,680</td>
<td>6,867</td>
<td>6,725</td>
<td>45,731</td>
<td>6,419</td>
</tr>
</tbody>
</table>

¹ Bilateral HIV/AIDS Programs includes funding for bilateral country/regional programs, UNAIDS, IAVI, Microbicides and NIH HIV/AIDS research.
² FY 2011 Enacted level includes across-the board and HHS agency-wide rescissions.
³ Includes enacted funding for FY 2004-2012

Note: All funding amounts have been rounded to the nearest million, so the numbers shown in the table may not sum to the totals. *As of February 2012

PEPFAR will have dispersed more than 1 billion condoms in the years 2012 and 2013. Also new this year is the commitment to voluntary male circumcision that will reach 4.7 million men in the next two years, within a VMC goal of 20 million men by 2015. They speak more intelligently than in the past on prevention, vis-a-vis most at-risk populations, risk reduction, STI screening and treatment and comprehensive services for drug users, criminalization and stigma. They talk about having invested, but do not give specific budget indications.
The Global Fund
The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international financ-
ing institution that invests the world’s money to save lives. To date, it has commit-
ted $22.9 billion in 151 countries to support large-scale prevention, treatment and care programs against the three diseases. Round 11 of the grants cycle was cancelled in 2011 and instead a Technical Funding Mechanism was launched at the end of the year. The Fund did provide $2.64 billion in disbursements in 2011 from earlier rounds. A new call for “Rounds” should be put forth by 2014.

Along with a realignment of how to fund projects, a concern was raised from within the Global Fund that certain countries and implementers were misappropriating funds. When this was re-broadcast via the world press, it became another reason to reconsider how to do business. The new GF business model will basically include an effective management strategy (vs. what might be considered a more “hands off” approach up until now – that each country would be able to do what they needed to do with the money, according to the project submitted). 3 countries were raised as problematic in the 2011 annual report, only one of which looks unresolvable (for a loss of less than $1 million).

To operate effectively, the Global Fund requires strong and consistent financial com-
mitments from all of its stakeholders. It is thus essential that pledges are renewed to finance additional grants and to continue successful programs. By the end of 2011, The Global Fund had received $3 billion in contributions, as all nations who had been hesitant to continue due to the misappropriations scandal were satisfied by the internal and transparent investigations as well as the new forward-looking mechanism of grant management. The Fund’s architecture of application, funding structure, management of performance and future planning will be rewritten before the next Call.

Finally, their former (and first) CEO left, and they put into place a General Manager who, while transforming the methods of the Fund, is also looking for a new CEO. Pledges and contributions from donors are received on an ad-hoc voluntary pledge basis (http://www.theglobalfund.org/en/about/donors/public/, accessed 30.08.12). And due to the economic downturn that started in 2008 and that shows little sign of abating in many places, Spain and Italy have not even pledged post-2010, which leaves a funding gap of close to half a billion dollars (Italy still owes from 2009!). Other European countries with less commitments (Portugal, Ireland, Belgium, Greece, Hungary) have also stopped pledging.

Interestingly, the GF uses a pooled procurement procedure to buy medicines and other commodities, which has been a useful tool when negotiating purchases.

The World Bank
The World Bank supplies more than just money for drugs – large chunks of its investment is intended for infrastructure of health systems (i.e., child health, health system performance, etc). This money, at least that specifically under AIDS, started to fall in 2004. Although the single year with most money was 2007, it did little to change the overall 3-year rolling average of being half now what it was 6 years ago. The 2010 moneys were at about the 1996 investment level. Which does not mean that infra-
structure money may not be coming in under other themes – like malaria, nutrition or tuberculosis (http://search.worldbank.org/projects?qterm=HIV, accessed on 20.05.10). They also lend, offer technical support, and do analytic work. For example, in light of the current economic crisis, the Bank has supported countries through technical assistance by assessing the fiscal implications of scaling up national AIDS programs. Their interest-free loan commitments continue to climb (+50% in the past five years), while their actual disbursements are falling (same level now as in 2006).
They have approved some 10 health-related projects in Africa until July 2012 worth approximately $313M. Health is the largest piece of the pie within the Bank and HIV/AIDS accounts for the largest part of that, followed by TB.

**UNAIDS**

UNAIDS provides technical support to countries, assisting them with expertise and planning for national AIDS programs, to help ‘make the money work’ for the people on the ground. UNAIDS tracks, evaluates and projects the financial resource requirements at global, regional and country levels to generate reliable and timely information on the epidemic and the response. Based on these evaluations, UNAIDS produces guidelines and progress reports. Much of the international data we juggle is set and approved by UNAIDS. At the 2012 World AIDS Conference in Washington DC, USA, they set out more plans for “Getting to Zero” and other platitudes-ridden slogans and programs. They are making a good effort on tackling major social issues like homophobia, financial sustainability and gender equality. “Together we will end AIDS”, whose title is annoyingly cheerleader-ish, actually offers some really important information like the fact that low- and middle-income countries now invest some $8.6B in their HIV/AIDS response, an 11% increase over 2010, while donor countries stayed flat at $8.2B. Therefore, the current gap is ~$7B, set to be maintained through 2015. At the 2011 United Nations High Level Meeting on AIDS, countries adopted a Political Declaration on HIV/AIDS in which they agreed to increase investments for HIV to between $22–24 billion by 2015. A concerted effort by all countries is needed to scale up funding if this target is to be met. Another promising approach would be to expand innovative mechanisms like indirect taxation (airline tickets, mobile phone usage, exchange rate transactions) to support global health initiatives, including HIV. The larger community must continue to support and strengthen existing financial mechanisms, including the Global Fund and relevant UN organizations.

**The Bill and Melinda Gates Foundation**

The largest private philanthropic organization is located in Seattle, US, “focusing on improving people’s health and giving them the chance” to emerge from “hunger and extreme poverty.” They have approximately 980 employees with an endowment of $33.5 billion. They have committed $26.19 billion since inception and in 2010 committed grants to the tune of $2.6 billion in over 100 countries (the 2011 annual report is not ready as of 29 Aug 2012). Much of these moneys are for non-AIDS-specific works, including development (reducing poverty and hunger). In health (58% of the total spending), they fight and prevent enteric and diarrheal diseases, HIV/AIDS, malaria, pneumonia, TB, neglected and infectious diseases, working on integrated health solutions, improving delivery of existing tools and supporting research and development in new interventions like vaccines, drugs and diagnostics (http://www.gatesfoundation.org). Bill Gates made a video in 2011 decrying the slow rates of reducing costs of treatments, implementing prevention and finding a vaccine. He calls for having a heightened crisis mentality!

**Drugs available from whom and where**

**FDA's qualification of generics**

Generic drugs are important options that allow greater access to health care. They have the same high quality, strength, purity and stability as brand-name drugs. Generic manufacturing, packaging, and testing sites must pass the same quality standards as those of brand name drugs.
For PEPFAR use, all drugs need FDA approval. As of 29 August 2012, FDA had approved 152 generic drugs for use in the PEPFAR program that are approved in as short a time as six weeks. While quality, strength, purity and stability are guaranteed, administration, delivery and correct use is another issue. For example, a drug approved in May 2010 was a fixed-dose combination of d4T and 3TC. And there the rub. Generics companies (in the case of FDA for PEPFAR, to date there are thirteen Indian generics companies, 1 South African company, two from China and two from the US) copy what is easiest and cheap, not necessarily the most innovative, or optimal treatments only. We must continue to try to remind the generics companies that what is best for the patient will continue selling for years, while (hopefully) a less-than-optimal combination like 3TC+d4T has a limited life-time, and can do a lot of harm via side effects along the way. Although the WHO pulled d4T from its list of recommended products in 2009, the switch to more effective treatments like TDF has not happened due to pricing.

Lopinavir/r is the first PI approved for generic licensing although there are eight approved PIs on the market in the Global North. Aurobindo got approval for a 25 mg version of ritonavir in early 2009, what could be a very interesting option in boosting in the future. Matrix got an FDA approval of a ritonavir 50 mg version (with lopinavir) on the same day. Matrix and Emcure both have approval for atazanavir (2010). Atazanavir + ritonavir together in one capsule by Mylan (2011). There are a handful of generics companies with an abacavir approval. As HLA testing for abacavir HSR is not easily available in the Global South, it is very important to train both the medical profession as well as users on diagnosis of HSR and what to do if it occurs, and the importance of never re-starting it once HSR is suspected, things that from an international regulatory agency would be hard to monitor. And although REMS programs from FDA or EMA would accept information on side effects from the Global South (which has up to 6 times the amount of people on drug), they probably contribute little to the overall numbers and therefore safety of these drugs.

In 2012 (until 29 August), FDA has issued no warning letters to any generics company that manufactures HIV products.

In 2012, FDA inspectors along with EMA will perform manufacturer-related inspections. Enforcement actions from suspension to closures can be considered.

### WHO-approved generics

#### Prequalification and quality assurance of antiretroviral products – a fundamental human right


Invitations to manufacturers to submit an expression of interest (EOI) for product evaluation are issued not only for HIV/AIDS-related care and treatment products, but also for anti-malarial medicines, anti-tuberculosis medicines, influenza-specific antiviral medicines and reproductive health products.

On the WHO List of Prequalified Medicinal Products is an extended list of 294 products (http://apps.who.int/prequal/query/ProductRegistry.aspx, accessed 20 Aug
Prequalification may be better described as pre-, on-going, and post-qualification, as they do inspections at all these time points. On this list is a new combination of tenofovir, lamivudine, atazanavir and ritonavir, from an Indian generics company. Neither Brazil nor Thailand have pre-approved drugs on either list (FDA or WHO) because although they both have and produce generic HIV drugs, they do so only for domestic use. On the list are many drugs for OIs (acyclovir, ceftriaxone, ciprofloxacin, amongst others). WHO also approves medicines quality control laboratories (QCLs): 25 QCLs are currently prequalified all around the world.

Total antiretroviral therapy in low- and middle-income countries by region, December 2011

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated number of people receiving ART</th>
<th>Estimated number of people needing ART</th>
<th>ART coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>5,064,000</td>
<td>10,400,000</td>
<td>49%</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>521,000</td>
<td>820,000</td>
<td>63%</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>922,000</td>
<td>2,300,000</td>
<td>39%</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>129,000</td>
<td>570,000</td>
<td>23%</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>14,900</td>
<td>150,000</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td>6,650,000</td>
<td>14,200,000</td>
<td>47%</td>
</tr>
</tbody>
</table>


A chasm

Improved treatment in line with scientific evidence and recognized international standards of care

Médecins Sans Frontières (MSF, Doctors without Borders) serves approximately 170,000 of the ~8 million people today on ARVs, and because they are on the front lines in clinics and health centers in more than 70 countries, their advocacy is not of the ivory tower type. Due to the implementation of ART, they have seen first hand the reduction in mortality for both adults and children, the lowering of incidence of TB as well as the importance of supporting HIV prevention by lowering incidence. They believe that not continuing to invest today in improved treatment and protocols will cost lives down the road, increase a double standard in HIV care and lead to increased costs. They were the first to talk about the risk that donors may not continue to support or try to delay the implementation of proven and recommended medical strategies for the sake of short-term savings. They recommend:

- Supporting initiation of ART at a CD4 T cell threshold of 350/µl to reduce the incidence of TB and other OIs and improve survival rates, reducing the need for costly and complex acute care.
- Implementing a tenofovir-based first-line regimen will allow patients to stay on their first regimen as long as possible with fewer side effects and delay the need for more costly second-line regimens.
- Providing access to viral load testing to support adherence and detect treatment failure earlier, thereby preventing resistance and needless switching to expensive sub-optimal second-line treatment.
- Supporting innovation that can lead to further improvement and simplification of HIV treatment in resource-poor settings.
According to MSF, most people with HIV/AIDS in need of treatment in the world will die within three years if they do not gain access to treatment now. MSF/UNAIDS recently released a report called “Speed Scale-Up” that measures treatment strategies, tools and policies in 23 countries. The full report can be accessed at http://www.msfaccess.org/about-us/media-room/press-releases/first-ever-study-hiv-treatment-policies-23-countries.

How to ensure that prices of drugs and diagnostics remain reasonable?
The international community needs to support policies that will enable funds to stretch as far as possible to meet needs and contain costs in the short- and long-term by, amongst other measures, ensuring a competitive supply for drugs. In accordance with the Doha Declaration on TRIPS and Public Health, governments can authorize governmental use or compulsory licenses to ensure generic production of patented products (as in Brazil and Thailand).

Companies and governments can support the Medicines Patent Pool for antiretroviral medicines at www.medicinespatentpool.org. This mechanism brings together patents held by different owners and makes them available to others for generic production and further development. Gilead was the first company to sign on, in July 2011, following the US NIH. They are negotiating with F. Hoffmann-La Roche, Sequoia Pharmaceuticals, and Viiv Healthcare. BI and BMS have started to negotiate. This Pool could save lower income countries more than $1 billion a year in drug costs. Shamefully, J&J (all the Tibotec/Janssen drugs) has clearly replied with a no.

Prices of first-line regimens in low-income countries
The decline in drug prices through 2008 can be attributed to the scaling up of treatment programs, increased competition between a growing number of products pre-qualified by WHO, new pricing policies by pharmaceutical companies and successful negotiations between the William J. Clinton Foundation (CHAI) and major generic manufacturers. The median price paid for tenofovir+3TC+efavirenz (pre-qualified by WHO) in low-income countries in August 2012 was $145 per person per year for the fixed-dose combination, somewhat of a plateau over the last two or three years. Some specific combinations, like those with d4T ( stavudine) and ddI (didanosine) are cheaper, and studies continue to be carried out with lower doses, etc, yet the long-term side effects outweigh any limited short-term good, and programs should move to tenofovir-containing regimens as soon as possible.

Second-line regimens
Second-line regimens are still significantly more expensive than first-line regimens in low- and middle-income countries. In 2012, the median cost of a regimen of AZT/3TC+atazanavir/r, is $340 in low-income countries and significantly higher in middle-income countries. Prices paid for second-line regimens can vary significantly between countries.

In the UK, a recent study showed that first-line treatments can last 8 years or longer (UK Chic 2010). If ARV access in the developing world started in earnest in 2002 (without all the management and strategic tools of retention and adherence used in the North, like viral load measurements), we are beyond the 8-year mark. What to do with the approximately 1 million people who probably need to move to a new regimen? And of the regimens that fail, NNRTIs fail at a rate almost three times higher than the rate of PIs. Most people in resource-limited settings are on an NNRTI containing regimen (nevirapine or efavirenz). MSF estimates that regimen failure is “largely under-diagnosed” due to limited lab facilities for viral load testing, which can only lead to resistance and harder-to-construct post-first-line regimens.
How to expand treatment to more people plus switch those currently failing to a more expensive second-line regimen, all within a framework of cutting back on donor spending? As the absolute numbers of people who need access to second-line regimens continue to grow, addressing the high cost of second-line regimens will become increasingly important to ensure the cost-effective use of available resources. A third-line treatment can be up to 8 times as expensive as a second-line treatment. Obviously, management, retention and adherence issues need to be fully incorporated into care in order to keep everyone on treatments and help them not need to advance to more complicated and expensive regimens.

Future Funding
As funding stalls, major funders – US, UK, Netherlands, France, Germany, Norway and Sweden – may be becoming fatigued. In 2001 at the UNGCP meeting, recipient countries were asked to dedicate 15% of their national budgets to health, agreed to in theory by the Abuja Declaration. Only one African country has reached that target. Overall, 26 countries have increased the proportion of government expenditures allocated to health and 11 have reduced it since 2001. In the other 9, there is no obvious trend up or down. Current donor spending varies dramatically, from $115 per person in one country, to less than $5 per person in 12 others. On a more positive note, as mentioned earlier, in 2011, for the first time ever, recipient nations are now spending more on their national health budgets than donors.

New strategies have to be developed – small taxes on currency transactions (Oxfam’s Robin Hood tax), an airline ticket tax, a Global Health charge on alcohol and tobacco consumption (Hill 2012), etc. Product(Red) is a fund-raising mechanism tied to the Global Fund that coordinates profits from sales from businesses, and has recently reached the $190 million mark.

It is perhaps more important than ever that we all contribute, whether economically or advocacy-based, to getting to the goal needed to optimally treat everyone.

Europe gets involved
The European Union can impact access to medicines for developing countries through its policies, legislation and bilateral and regional trade agreements. The EU can adopt appropriate measures to improve access to existing medical tools (medicines, diagnostics, vaccines) as well as stimulate the research and development of better tools for people in resource-starved countries. The Working Group on Innovation, Access to Medicines and Poverty-Related Diseases will create a meaningful dialogue between Members of the European Parliament, the European Commission, and civil society. The European Parliament recently voted down a measure called ACTA that could have restricted access to affordable generic medicines.

How do we get there? From rhetoric to reality
Successes in controlling the epidemic can be attributed to a comprehensive response and commitment from all sectors of society, according to on-the-ground experts in sub-Saharan Africa. Buy-in from the highest political offices is important in creating polices that place HIV on the national agenda. For instance, in Rwanda, all government departments were mandated to carry HIV messages over a long period, which helped stabilize spread of the disease. The Rwandan Minister of Health reminds us to include youth in the messaging.

Although extensively reviewing the latest International AIDS Conference is impossible here, there was an effort to demonstrate the importance of including patients and their broader communities in the delivery of services (www.aids2012.org), aka locally-mobilized resources, which has to include building civil society capacity to
monitor government spending as well as simply for any significant long-term community-driven transformation. While the disease is declining in many parts of the world, the opposite is true in Eastern Europe, where there is a higher incidence driven by a take-no-prisoners attitude in intravenous drug use policy. Ukraine gives a positive spin on how to do it with combination prevention and substitution therapies. Educating political leadership in these countries (including Russia) is important since so few resources are allocated to fighting HIV.

This is not one epidemic with one simple answer. At the 2012 International AIDS Conference, commercial sex workers were missing, and if they are not at the table, they cannot be part of the discussion in either prevention or treatment of HIV for sex workers.

Perhaps a simple list would be helpful for “getting there”:

- Cascading implementation structures from national to grassroots level
- Ensuring increasing national government budget allocation to HIV responses while donors support ongoing gaps (ie, country ownership)
- Mobilising all sectors of society to play their part in HIV
- Integrating principles and of good governance from the outset to ensure accountability at all levels.

The unconscionable health gap: a global plan for justice

In the Lancet, Lawrence Gostin outlined a plan for health access for all (Gostin 2010). Despite robust international norms, health disparities render a person’s likelihood of survival drastically different depending on where she or he is born. International health assistance has quadrupled over two decades rising to $21.8 billion in 2007 (Ravishankar 2009). This level of funding might seem impressive but sits modestly beside the annual $1.5 trillion spent globally on military expenditures (2.43% of global gross domestic product), and $300 billion in agricultural subsidies. Foreign aid simply is not predictable and scalable to needs and often reflects donors’ geostrategic interests rather than the key determinants of health. Developed countries recognize the health gap, but are resistant to taking bold remedial action.

If the health gap is unfair and unacceptable, how can the international community be galvanized to make a genuine difference? A global plan for justice would be a voluntary compact between states and their partners. It would simply encourage the WHO to exercise its constitutional powers and leadership.

A global plan for justice would set achievable funding targets for a global health fund to be distributed according to need (Ooms 2008). Although WHO would negotiate the funding levels, developed countries could donate, for example, 0.25% of gross national income per annum, in addition to current foreign assistance.

A global plan for justice would guarantee a universal package of essential services, comprising core components like essential vaccines and medicines, basic survival needs, and adaption to climate change.

The international community must do more than lament ongoing, unconscionable health inequalities. It must act boldly and with a shared voice, such as through a global plan for justice. If the world does not act, the avoidable suffering and early death among the world’s most vulnerable people will continue unabated—a breach of social justice that is no longer ethically acceptable (Gostin 2010).

The amount of people who need access to ART in the next few years will continue. Because of this, we need to keep up the pressure on all actors – donor organisations as well as individual nations, manufacturers, health care workers and affected communities of all sizes – to do their part in order to provide the most current and useful prevention and treatment strategies to the adequate and most at-risk populations.
In order to achieve this, we can not sit idly by and hope for the best – we must continue to push that boulder up the hill for as long as it takes so everyone who needs it has access to treatment and care as early and for as long as necessary.

*Because global access is such a moving target, most references are web-based.*

**References**


**Links**


http://www.globalfund.org/en/applicantsimplemeters/resources/?lang=en


www.msfaccess.org/main/access-patents/european-parliament-working-group/about-working-group/


http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanCommission/ucm294120.htm

http://www.fda.gov/ICECI/Inspections/ForeignInspections/default.htm


http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm


http://utw.msfaccess.org/background

http://bi.theglobalfund.org/analytics/saw.dll?Dashboard&scid=7&J901Mhef4


http://www.avac.org/ht/a/GetImageAction/i/42801
7. Management of Side Effects

CHRISTIANE SCHIEFERSTEIN-KNAUER, THOMAS BUHK

Patients on ART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. Adherence problems, regimen changes or even withdrawal from therapy are often the result of drug toxicity (Al-Dakkak 2012). In the past, often 25% of patients stopped therapy within the first year on ART because of side effects (d’Arminio Monforte 2000, Yuan 2006). Between 2003 and 2007, the rate was still about 20% (Cicconi 2010). Only over the last five years tolerability of ART has been improved, thanks to new drugs. Treatment cessation due to side effects has become less frequent (Carr 2009).

Factors for poor or non-adherence include poverty, intravenous drug abuse, young age, Afro-American origin, hepatitis coinfection and regular alcohol consumption (Robison 2008, Hendershot 2009). The patient should be counseled in detail on the potential side effects, so that he or she is in a position to recognize them and to contact their physician quickly. This can save lives or prevent the irreversible damage of some side effects, such as polyneuropathy. Being prepared for the occurrence of possible problems and providing potential solutions improves both the acceptance of treatment and adherence. This information needs to be presented by the provider to the patient in a user-friendly and accessible manner – the extensive package inserts tend to frighten and confuse patients. It must be stressed that the majority of patients are able to tolerate ART well, even for years. Nevertheless, the regular monitoring of treatment by an HIV clinician, even in asymptomatic patients, is recommended via quarterly visits, and even more frequently at the beginning of any new regimen when visit schedules may be weekly. Standard evaluations include a thorough history (including allergies and other side effects), a physical examination and measurement of vital signs and body weight. Routine investigations include a full blood count, liver, pancreas and renal function tests, electrolytes (plus phosphate in patients on tenofovir) as well as fasting cholesterol, triglycerides and glucose levels. A urine dipstick can detect proteinuria in patients on tenofovir.

It is often difficult to distinguish between symptoms related to HIV infection and those caused by ART. An accurate history considering the intensity, variation and reproducibility of complaints is mandatory.

Gastrointestinal side effects

Gastrointestinal (GI) problems are the most common side effects even if they have fortunately become less frequent, as older NRTIs like AZT, ddI or d4T are no longer part of current recommendations for ART (Robison 2008, Chubineh 2008). GI side effects appear more frequently during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting, heartburn, abdominal pain, gas in the abdomen or intestines and constipation. Diarrhea occurs frequently with all PIs, with integrase inhibitors raltegravir and elvitegravir, and more rarely with 3TC. In addition to the often considerable impact on everyday life, gastrointestinal side effects can lead to dehydration, malnutrition with accompanying weight loss, and low plasma drug levels with the risk of treatment failure and development of resistant viral strains.

In most cases, symptoms occur early on in therapy. Patients should be informed that these side effects usually resolve after some weeks (4–6) of treatment. If gastrointestinal side effects appear for the first time after longer periods on ART, other causes such as gastritis and infectious diarrhea need to be considered.
Nausea and vomiting

If administration on an empty stomach leads to nausea and vomiting, most drugs can be taken together with meals. Only the NNRTI efavirenz has to be administered on an empty stomach; small quantities of low-fat salty crackers may lessen nausea. Ginger, peppermint or chamomile teas or sweets may also be helpful, as well as more frequent but smaller meals. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided.

If treatment is necessary, metoclopramide has been proven to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron can also be taken. Antiemetic drugs can not only be administered if the patient is feeling ill, but taken regularly prophylactically, ideally 30 to 45 minutes before taking ART. If taken on a regular basis, attention should be paid to side effects such as dyskinesia. After a few weeks, doses of antiemetics can be slowly reduced. If nausea persists for long time, a gastroscopy should be performed. If the patient suffers from nausea for more than two months, a change of treatment should be considered – otherwise adherence problems will certainly occur.

Diarrhea

In patients with acute or severe diarrhea, the priority is to treat dehydration and loss of electrolytes. Other causes such as GI infection or lactose intolerance should be excluded. Difficult-to-digest foodstuffs (particularly those high in fat or glucose) should be avoided and those that are easy to digest (e.g., potatoes, rice, noodles) eaten instead. It makes sense to remember approved “homespun” remedies (see Table 1). If significant dehydration and loss of electrolytes occur, coca-cola and salty crackers, sports drinks, herbal teas or electrolyte solutions may be helpful. Oral rehydration solution can easily be made from the juice of 5 oranges, 800 ml of boiled water or tea (cooled to room temperature), a teaspoon of iodized salt and two tablespoons of sugar.

Oat bran tablets have been proven to be useful and cheap for PI-associated diarrhea. They can be taken together with antiretroviral therapy (daily dose 1500 mg). Pancrelipase, a synthetic pancreatic enzyme, has also been shown to be effective for PI-associated diarrhea. PI-associated diarrhea can also be alleviated by calcium (Turner 2004), taken as calcium carbonate, at a dose of 500 mg BID. However, as calcium binds with many other agents, it should be taken 2 hours apart from HIV medication. Oral supplements of glutamine (10–30 g/day) or alanyl-glutamine (up to 44 g/day) alleviate diarrhea and can also boost levels of antiretroviral drugs in the blood (Bushen 2004, Heiser 2004). Glutamine can be purchased in drugstores or ordered online. The probiotics Saccharomyces boulardii and Lactobacillus acidophilus are used in infectious diarrhea and for the prevention of antibiotic-associated diarrhea. They can sometimes ameliorate medication-associated diarrhea. Alternatively, psyllium may be effective. It should not be taken together with loperamide or opium tincture, or at the same time as HIV medication. Charcoal tablets might be helpful. The cornerstone of allopathic symptomatic treatment is loperamide which inhibits bowel movement (initially 2–4 mg, followed by 2 mg, up to a maximum of 16 mg daily). If loperamide is not effective, opium tincture is an alternative (initially 5 drops, maximum 15 to 20 drops), and attention should be paid to the risk of intestinal obstruction, especially if overdosed. In some cases, a combination of different antidiarrheal drugs may be appropriate.
Table 1: “Approved” homespun remedies

<table>
<thead>
<tr>
<th>remedy</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectin</td>
<td>In apples (raw and pared), bananas (purée), carrots (purée, cooked, soup), St. John’s bread (oatmeal gruel or rice gruel with St. John’s flour). Pectin is a dietary fiber, which is not digested, it binds water and toxic agents and lessens the diarrhea.</td>
</tr>
<tr>
<td>Gruel</td>
<td>Soupy oatmeal or rice</td>
</tr>
<tr>
<td>Tanning agents</td>
<td>Black or green tea, dried blueberries (tea, powder), dark chocolate</td>
</tr>
</tbody>
</table>

**Hepatotoxicity**

ART has led to a substantial reduction in the number of deaths related to AIDS. However, this has been accompanied by an increase in liver-related morbidity and mortality which now is the most common non-AIDS-related cause of deaths among HIV-infected patients (Price 2010, Joshi 2011).

Elevated liver enzymes are common with ART, and severe hepatotoxicity occurs in up to 10% of patients (Price 2010). Liver failure is rare (Nunez 2005). Hepatotoxicity occurs more often in patients with pre-existing liver dysfunction (Soriano 2008).

Severe, sometimes fatal liver damage has been associated with nevirapine, ritonavir and tipranavir, with several fatalities linked to nevirapine and tipranavir (Bjornsson 2006, Rachlis 2007, Chan-Tack 2008). Case reports also exist about liver failure occurring on darunavir, indinavir, lopinavir, ritonavir, tipranavir, atazanavir, efavirenz, nelfinavir and different NRTIs (Carr 2001, Clark 2002, Nunez 2010). Liver enzyme elevation and severe hepatotoxicity has also been reported for maraviroc and raltegravir.

Risk factors for severe hepatotoxicity are elevated liver enzymes before initiating treatment, chronic hepatitis B or C, concomitant hepatotoxic medication, PI therapy, older age, higher BMI, female gender, thrombocytopenia, high alcohol intake, high viral load or renal dysfunction (Sulkowski 2002, Servoss 2006, Nunez 2010). Patients with pre-existing liver disease should use these drugs only along with strict monitoring. Four possible mechanism of hepatotoxicity are: hypersensitivity reaction, mitochondrial toxicity/steatohepatitis, direct drug toxicity/drug metabolism or immune reconstitution syndrome. These hepatotoxic reactions occur at different time points for different drug classes.

Hypersensitivity reactions are typical for NNRTIs, are not not dose-related and symptoms resolve usually after stopping the drug (Joshi 2011). They occur within the first 4 to 12 weeks. There are black box warnings for hypersensitivity for nevirapine, rilpivirine (Cohen 2011, Molina 2011), the nuke abacavir as well as the CCR5 inhibitor maraviroc. NNRTIs can also cause direct drug toxicity which appears within the first couple of months (Price 2010).

Nucleoside analogs lead to hepatic steatosis, which is probably caused by mitochondrial toxicity and usually occurs after more than 6 months on treatment. PIs and boosted atazanavir, indinavir and tipranavir can lead to hepatotoxicity at any stage during the course of treatment – once again, patients with chronic viral hepatitis are particularly at risk (Sulkowski 2004). One possible cause is immune reconstitution syndrome while on ART, with increased cytolysis activity against hepatitis virus infected liver cells usually within the first two months on ART accompanied by a decline in HIV RNA and a rise in CD4 T cell count (Price 2010).
NNRTIs

Liver toxicity occurs more commonly on nevirapine than on other antiretroviral drugs. Clinically asymptomatic and symptomatic liver toxicity, including rapidly occurring fatal liver failure have been observed (Bjornsson 2006). Serious and fatal liver toxicity has been reported even during post-exposure prophylaxis (PEP), but not after single-dose nevirapine (McKoy 2009). Therefore the use of nevirapine in occupational or non-occupational PEP is contraindicated. Symptomatic hepatotoxicity seems to depend on different risk factors, such as female gender, a body mass index lower than 18.5 (Sanne 2005) or chronic hepatitis C (Torti 2007). A higher risk of serious liver toxicity was also observed in patients with higher CD4 T cell counts prior to initiation of therapy. A retrospective analysis of the Boehringer Ingelheim database showed a higher risk for females with CD4 T cell counts >250 cells/µl and males >400/µl. Although these findings have not been confirmed by other studies (Manfredi 2006, Peters 2010), the Indications and Usage section of the Viramune® label advises against starting nevirapine treatment above these CD4 T cell counts unless the benefits clearly outweigh the risks. The increased risk seems to be particular to ART-naïve patients. Virologically suppressed patients switching to nevirapine seem not to have a significantly higher risk (Mallolas 2006, De Lazarri 2008). These findings were confirmed by an evaluation of seven observational clinical cohorts. Initiating nevirapine in antiretroviral-experienced patients with high CD4 cell counts was well tolerated provided there is no detectable viremia (Kesselring 2009). For pregnant women, data are inconsistent. One study showed a significant association between CD4 T cell count and hepatotoxicity with nevirapine (Jamisse 2007) whereas another study did not (Ouyang 2010). However, pregnancy itself is significantly associated with increased hepatotoxicity (Ouyang 2009).

NNRTIs should be used with caution in patients with HCV coinfection. They should be avoided in patients with liver cirrhosis Child–Pugh class B or C (Nunez 2010). Liver toxicity occurs usually early during ART (within 18 weeks of starting) and may progress to liver failure despite laboratory monitoring, which is not characteristic of other antiretrovirals. If liver enzymes increase to >3.5 times the upper limit of normal (ULN) during treatment, nevirapine should be stopped immediately. If liver enzymes return to baseline and if the patient has had no clinical signs or symptoms of hepatitis, rash, flu-like symptoms, fever or other findings suggestive of organ dysfunction, it may, on a case-by-case basis, be possible to reintroduce NVP. However, frequent monitoring is mandatory in such cases. If liver function abnormalities recur, nevirapine should be permanently discontinued. If clinical hepatitis (anorexia, nausea, jaundice, etc) occurs, nevirapine must be stopped immediately and never re-administered.

In patients treated with efavirenz or rilpivirine, minor enzyme elevations are generally safe and usually resolve so that a treatment change may not be necessary (Gutierrez 2008, Kontorinis 2003, Cohen 2011, Molina 2011). This also applies to tenofovir (Lattuada 2008).

Protease inhibitors

Atazanavir and indinavir inhibit the hepatic enzyme UDP glucuronosyltransferase, increasing the level of bilirubin in up to 50% of patients (Torti 2009). UGT1A1*28 variant allele seems to be a predictor of severe hyperbilirubinemia (Turatti 2012). Hyperbilirubinemia is not usually associated with signs or symptoms of hepatocellular injury. It clinically resembles Gilbert’s syndrome. The levels of bilirubin return to normal following discontinuation of the drug. If bilirubin is only mildly elevated (3–5 times ULN) and the serum liver enzyme levels are normal, treatment change is
not mandatory. If the bilirubin is constantly markedly elevated, medication should be discontinued: no one knows about the long-term consequences of hyperbilirubinemia (Sulkowski 2004). Pre-existing liver fibrosis or cirrhosis seem to not increase the risk of severe transaminase elevations substantially with atazanavir/r in coinfected patients (HIV plus hepatitis) (Pineda 2008). In patients with end-stage liver disease, unboosted atazanavir did not worsen liver disease; in fact, atazanavir allowed patients to maintain or gain immunovirological eligibility for orthopic liver transplantation (Guaraldi 2009).

Tipranavir/r is associated with a risk of transaminase elevations. In the RESIST trials, grade 3 or 4 transaminase elevations were significantly more common in tipranavir/r than in all other boosted PIs (Hicks 2006). From June 2005 to March 2007, twelve cases of liver-associated deaths were identified (Chan-Tack 2008). Tipranavir/r should not be administered to patients with hepatic impairment Child-Pugh Class B or C. Extreme caution should be exercised when administering it to patients with mild hepatic impairment or patients with chronic hepatitis, as treatment-experienced patients with chronic hepatitis B or C coinflection or elevated transaminases are at approximately a 2-fold elevated risk for developing grade 3 or 4 transaminase elevations or hepatic decompensation. Frequent monitoring is mandatory in such cases. Besides serological tests for viral hepatitis, an abdominal ultrasound should be performed in order to recognize structural liver dysfunction early, e.g., non-alcoholic steatohepatitis or liver cirrhosis, before initiating ART. Liver function should be monitored biweekly at the start of treatment with nevirapine and PIs and even more frequently in patients with pre-existing liver disease. Monthly tests are generally sufficient for all other drugs. If liver enzymes (ALT, AST) are moderately elevated (<3.5 times ULN) in the absence of clinical symptoms, treatment can be continued under close monitoring. If liver enzymes are elevated to more than 3.5 times ULN, additional diagnostic tests should be performed, including an abdominal ultrasound. In cases of coinfecion with hepatitis B or C, treatment of these conditions should be considered. With other pre-existing liver conditions, it may be useful to determine drug plasma levels. Discontinuation of treatment may not be necessary except in the case of nevirapine (see above).

If liver enzymes are elevated in a later phase of therapy (after more than 6 months after initiation), a thorough investigation including serology for viral hepatitis, CMV, and EBV, as well as an abdominal ultrasound, should be performed. Lactic acidosis, hypersensitivity reactions to abacavir and other hepatotoxic drugs should also be considered. A liver biopsy can reveal macro- and microvesicular steatosis and mitochondrial alterations in NRTI-induced steatosis and is therefore helpful to identify a nucleoside-induced hepatopathy and to distinguish it from other causes of liver injury. In patients with HCV coinfection, hepatitis C should, if possible, be treated before the initiation of ART (see chapter on Hepatitis C). In HBV coinfection, the ART regimen should include FTC or 3TC with tenofovir. Patients with pre-existing liver dysfunction should undergo drug plasma level monitoring, especially during treatment with PIs. Doses can be adjusted according to the plasma levels to help keep the patient on therapy.

Renal problems

Renal problems occur in particular with tenofovir as well as with atazanavir and the nowadays rarely used indinavir. Indinavir and atazanavir cause nephrothiasis through excretion of unchanged drug in the urine (see Chapter HIV and Kidney).
**Tenofovir**

Tenofovir is a potentially nephrotoxic drug. Although experience over several years shows that severe renal toxicity occurs rarely, tenofovir has an effect on renal function. One study showed that elevations in serum creatinine occurred in 2.2% of patients (Nelson 2007). In ART-naïve patients initiating ART, tenofovir was associated with a greater decline in renal function and a higher risk of proximal tubular dysfunction: 4.8% of patients on tenofovir had a more than 50% decline of GFR compared to 2.9% without tenofovir (Horberg 2010). A meta-analysis of 17 studies confirmed an association with a statistically significant loss of renal function with tenofovir, although the clinical magnitude of this effect was modest (Cooper 2010). An evaluation of more than 10,000 patients has shown that tenofovir exposure is independently associated with increased risk for non-reversible renal toxicity (Scherzer 2012).

Severe cases have been reported with acute renal failure, proximal tubulopathy with Fanconi’s syndrome and nephrogenic diabetes insipidus and rarely hypophosphatemic osteomalacia (Rollot 2003, Saumoy 2004). Renal toxicity occurs after some months, rarely at the beginning of therapy. Risk factors include a relatively high TDF exposure due to pre-existing renal impairment, low body weight (Nishijima 2012) or co-administration of nephrotoxic drugs (Nelson 2007).

PIs can interact with the renal transport of organic anions, leading to proximal tubular intracellular accumulation of tenofovir (Izzedine 2004 + 2007, Rollot 2003). The combination of ATV/r plus tenofovir caused greater GFR decreases compared with EFV (Albini 2012). This was confirmed by another study showing that tenofovir with a boosted protease inhibitor leads to a greater initial decline in eGFR than tenofovir with efavirenz; this decline may be worse with ATV/r than with LPV/r (Young 2012).

Furthermore, extensive pre-treatment with nucleoside reverse transcriptase inhibitors seems to be another risk factor (Saumoy 2004). However, even in patients without any predisposing factors, nephrotoxicity may occur (Barrios 2004). In case of renal dysfunction, especially in patients with low body weight, tenofovir should be avoided, or the dosing interval should be adjusted. The manufacturer recommends administering TDF every 48h in patients with creatinine clearance of between 30 and 49 ml/min. In case of severe renal dysfunction (creatinine clearance <30 ml/min) it should not be administered. Normal creatinine levels may be misleading especially in subjects with low body weight, which is why creatinine clearance should be measured before initiating tenofovir treatment. Renal function tests including creatinine, urea, creatinine clearance, proteinuria, glycosuria, blood and urine phosphate should be monitored every other week.

The majority of the incident renal dysfunction in tenofovir patients is related to pre-existing renal disorders (Brennan 2011). Therefore it is not recommended for use in patients with pre-existing renal insufficiency. It should also be avoided with concomitant or recent use of nephrotoxic agents such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2. Usually, abnormalities resolve upon discontinuation of the drug (Izzedine 2004, Roling 2006).

**Neurological side effects**

The most important neurological side effects are peripheral polyneuropathy caused by NRTIs and CNS side effects caused by efavirenz (see chapter, *Neuromuscular Disorders*).
Peripheral polyneuropathy

Peripheral polyneuropathy (PNP) is mainly caused by NRTIs that are no longer prescribed as first- or second-line drugs in most Western Countries, although still frequently used in Africa or Asia, such as ddI, d4T or AZT. Because of their continued use in resource-limited areas, we will review the symptoms and possibilities for palliation. PNP usually presents with a distal symmetrical distribution and sensorimotor paralysis. Patients complain of paresthesia and pain (“tingling”) in hands and feet and perioral dysesthesia. The symptoms often begin gradually after several months of therapy. HIV infection itself can lead to PNP, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients must be informed that they should consult their treating physician as soon as possible if these complaints develop. Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus, malnutrition, or treatment with other neurotoxic drugs, e.g., INH, should be addressed as well. In any case, the nucleoside analogs ddI and d4T have been dropped from first-line therapy recommendations (ddC is no longer manufactured). If possible they should be avoided in salvage therapy as well. Symptoms frequently improve within the first two months following discontinuation of the drugs responsible, but may initially increase in intensity and are not always fully reversible. Because treatment is difficult, and there is no specific therapy, it is extremely important that peripheral polyneuropathy is recognized early by the doctor, resulting in a rapid change of treatment. The causative agent needs to be stopped.

An easy test, in practice, is to test vibration with a tuning fork. A 64-Hz tuning fork (Rydel-Seiffer) is applied to the appropriate bony surface (e.g., distal hallux, medial malleolus or lateral malleolus) bilaterally. The patient is asked to report the perception of both the start of the vibration sensation and the cessation of vibration on dampening. As the intensity of the vibration starts to diminish the two triangles move closer together again. The intensity at which the patient no longer detects the vibration is read as the number adjacent to the intersection. It can thus be quantified and compared to the results of other tests. Through this simple method first signs of polyneuropathy can be recognized easily.

Apart from symptomatic treatment with metamizole, acetaminophen (paracetamol), carbamazepine, amitriptyline, gabapentine and opioids, methods such as acupuncture or transcutaneous nerve stimulation have been tried with varying success. Vitamin B supplementation can help to improve peripheral polyneuropathy faster. Tight shoes or long periods of standing or walking should be avoided; cold showers may relieve pain before going to bed.

CNS side effects

In up to 40% of patients, treatment with efavirenz may lead to CNS side effects such as dizziness, insomnia, nightmares, mood fluctuations, depression, depersonalization, paranoid delusions, confusion and suicidal ideation. These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in approximately 3% of patients. There is an association between high plasma levels of efavirenz and the occurrence of CNS symptoms (Marzolini 2001). Genetic predisposition also seems to play a role. Different variations described in the enzyme system CYP2B6 may be responsible for the elimination of efavirenz (Haas 2004). Certain genetic variations more frequent in Afro-Americans than in Europeans raise the levels of efavirenz (Wyen 2007). High plasma levels can also be caused by medication interactions, so a thorough drug history
should be taken; perceptions of drug tolerance by the patients can play an important role. It has been shown that efavirenz changes the sleeping pattern (Moyle 2006). Patients should be informed thoroughly about the nature of these side effects and that they are usually expected to resolve after a relatively short period of time. Driving cars or operating machinery can be impaired in the first weeks. Treatment with efavirenz should not be started before exams or other important events.

If the CNS side effects persist for more than two to four weeks, it is reasonable to prescribe 200 mg pills, so that the dose can be divided into a 400 mg night dose and a 200 mg morning dose. With this schedule, we observed a reduction in unpleasant CNS side effects in 50% of patients in our center. The daily dose should not be reduced from 600 mg to 400 mg because of the higher risk of therapy failure and development of drug resistance.

Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares, but both drugs should be restricted to severe cases, because of their side effects and addictive potency (lorazepam). If the side effects persist even after splitting the dosage as described above for more than six weeks, efavirenz should be replaced.

CNS side effects are possible with etravirine and rilpivirine, too (Madrua 2007, Cohen 2011, Molina 2011), although they are less intensive and less frequent. Depression, insomnia and even psychosis rarely occur or get worse on 3TC or abacavir therapy. If the patient complains of CNS-related side effects, 3TC or abacavir may be considered as a possible cause (Foster 2004).

HIV infection itself may cause neurocognitive impairment, for which the earliest possible start of ART is a good preventative measure (Fessel 2009).

**Allergic Reactions**

Allergic reactions are frequent during HIV therapy. They occur with all NNRTIs, as well as with the nucleoside analog abacavir and the PI’s fosamprenavir, tipranavir, atazanavir and darunavir. Because fosamprenavir, tipranavir and darunavir are sulfonamides, they should be given with caution to patients with sulfonamide allergies. When there are limited alternative treatment options, desensitization may permit continued use of fosamprenavir or darunavir in patients with a history of allergy (Marcos Bravo 2009). Atazanavir-associated macular or maculopapular rash is reported in about 6% of patients and is usually mild, so that treatment withdrawal is not necessary (Ouagari 2006).

**NNRTIs**

Nevirapine may cause a rash in 15 to 30% of patients, leading to discontinuation in about 5%. The rash is seen less frequently during efavirenz, etravirine and rilpivirine therapy, where only rarely do patients discontinue the drug (Carr 2001, Cohen 2011, Molina 2011). With etravirine, fatal cases of toxic epidermal necrolysis have been reported as well as hypersensitivity reactions sometimes accompanied by hepatic failure (Borrás-Blasco 2008). It should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop.

The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include myalgia (sometimes severe), fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. Women are more often and more severely affected (Bersoff-Matcha 2001). If symptoms occur later than 8 weeks after initiation of
therapy, other drugs should be suspected. Severe reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis (Lyell’s syndrome) or anicteric hepatitis are rare. Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases >5 times the upper limit of normal) or fever >39°C. Approximately 50% of NNRTI allergies resolve without discontinuation of therapy. Antihistamines may be helpful. Prophylactic treatment with glucocorticosteroids or antihistamines has no protective effect; rashes were even more common in some studies (Montaner 2003, The Grupo Estudio 2004). Following a severe allergic reaction, the drug responsible for the reaction should never be given again.

Abacavir hypersensitivity

Abacavir causes a hypersensitivity reaction (HSR), which may be life-threatening if not recognized in time. It occurs in approximately 4–8% of Caucasian patients (Hughes 2008). A higher rate is noted in patients on a once-daily regime, in ART-naïve patients, in patients with a nevirapine allergy, and in acute HIV infection. In over 90% of cases, the HSR occurs after a median of 8 days, and within the first 6 weeks. Hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele, which has a prevalence of approximately 6% in Caucasians, and a very low prevalence in black population (Orkin 2010). The prospective PREDICT study involving 1956 patients from 19 countries showed that HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir (Mallal 2008). HLA-B*5701 screening should be incorporated into routine care for patients who may require abacavir (Phillips 2009). It can prevent significant HSR-related costs and is likely to lead to overall net savings (Wolf 2010). Nevertheless, HLA-B*5701-negative patients should be informed about HSR, as it can rarely present also in these patients. The rash associated with the abacavir HSR is often discrete, in contrast to the skin reactions caused by nevirapine or efavirenz; in 30% of patients it may not occur at all. 80% of patients have fever. In addition to general malaise (which grows worse day to day), other frequent symptoms include gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain. Respiratory symptoms, such as dyspnea, cough and sore throat, are rare. Changes in the blood count, elevation of liver transaminases, alkaline phosphatase, creatinine and LDH may accompany the HSR. There is usually no eosinophilia. One case of Stevens Johnson Syndrome has been described (Bossi 2002).

The simultaneous start of abacavir with NNRTIs is unfavorable because of the difficulties of differentiating between allergic reactions to NNRTIs and HSR. If abacavir is part of the initial therapy and flu-like symptoms occur, it is difficult to distinguish between immune reconstitution syndrome (IRIS) and HSR; HSR is diagnosed clinically. The differential diagnosis from an intercurrent infection is often difficult. Criteria in favor of HSR include the development of symptoms within the first 6 weeks of treatment, deterioration with each dose taken and the presence of gastrointestinal side effects. If abacavir is discontinued in time, the HSR is completely reversible within a few days. HSR may be fatal if not diagnosed. Following discontinuation of abacavir, further supportive treatment includes intravenous hydration and possibly steroids.

If the suspicion of HSR is only vague, and abacavir is not stopped, the patient should be seen or spoken to daily, to be able to react immediately in case of clinical worsening. Once the diagnosis of HSR has been established and abacavir stopped, rechallenge with abacavir can be fatal and is strictly contraindicated. If there is only a vague suspicion of HSR and abacavir stopped, rechallenge under in-patient condi-
tions is possible. Whenever treatment is interrupted, it needs to be noted that the HSR can occur for the first time after restarting treatment, even without a prior HSR. Treatment with abacavir requires detailed counseling on the possible occurrence and symptoms of the HSR. Patients should know whom to contact in case of possible HSR. It is important, however, to emphasize to patients that unnecessary discontinuation must also be avoided. Due to the implementation of routine HLA-B*5701 screening the diagnosis of HSR is becoming increasingly rare.

**Avascular necrosis**

The incidence of asymptomatic avascular necrosis is approximately 4.4% in HIV-positive patients, significantly more frequent than in the general population (Lawson-Ayayin 2005, Cazanave 2008). The postulated association with PIs has not been confirmed (Loiseau-Peres 2002). Risk factors for avascular necrosis are alcohol over-use, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis. Virological (viral load) or immunological parameters are not associated with a risk of developing avascular necrosis (Mondy 2003). The most common site of the necrosis is the femoral head and, less frequently, the head of the humerus. Initially, patients complain of pain when bearing weight on the affected joint, with symptoms worsening over the following days and weeks. The initial stages may be asymptomatic, but are followed by severe bone pain and reduced mobility. Necrosis of the femoral head produces pain in the hip or groin, which may radiate to the knee.

All patients on ART, especially those with additional risk factors like steroids should be monitored closely when hip pain occurs for the first time. Even in subjects with moderate bone or joint pain, an MRI should be performed early on, as this is more sensitive than conventional radiography. Early diagnosis and treatment can spare patients pain, loss of mobility and surgical intervention.

If the diagnosis is confirmed, patients should be referred to an orthopedic surgeon as soon as possible. Different treatment strategies are available for reducing bone and joint damage as well as pain, depending on the stage of disease, localization and grade of severity. In the early stages, reduced weight bearing with crutches is often sufficient. Surgical core decompression is an option: several holes are drilled in the femoral neck or head, causing new blood vessels to develop and thereby reducing the pressure within the bone. In the more advanced stages, the chances of success decrease with the size of the necrosis. The alternative, osteotomy, has the disadvantage of reducing the mobility of patients over long periods of time. In severe cases, a total endoprosthesys (TEP) is usually necessary.

Further risk factors need to be identified and eliminated. If possible, steroids should be discontinued. Sufficient data are lacking as to whether treatment modification on non-PI therapy is successful (Mondy 2003). Physiotherapy is recommended. Non-steroidal anti-inflammatory drugs (e.g., ibuprofen) are the treatment of choice for analgesia.

**Osteopenia and osteomalacia**

HIV-infected individuals have, according to nadir CD4 level, a lower bone density than uninfected individuals (Loiseau-Peres 2002, Fessel 2011). Bone density is determined by the measurement of X-ray absorption (e.g., DEXA scan). Results are given as the number of standard deviations (the T-score) from the mean value in young, healthy individuals. Values between -1 and -2.5 standard deviations (SD) are referred to as osteopenia, values above -2.5 SD as osteoporosis. Osteomalacia is the softening of the bones. Osteopenia and osteomalacia may occur in combination. In addi-
tion to HIV infection, other factors such as malnutrition, diminished fat tissues, steroid treatment, hypogonadism, immobilization and treatment with PIs and (N)NRTIs, seem to play a role in the pathogenesis of this disorder (Herzman 2009). One study showed a loss of bone mineral density after antiretroviral therapy initiation, independent of which antiretroviral regimen was given (Brown 2009). For the association between tenofovir and bone metabolism, see chapter Rheumatic Disorders and Bone Disorders.

Osteopenia and osteoporosis are often asymptomatic. Osteoporosis occurs mainly in the vertebrae, lower arms and hips. A bone fracture in a HIV patient should always make one suspect osteopenia or osteoporosis.

The following tests should be performed in all patients with AIDS: a lumbar spine X-ray in the standard anteroposterior and lateral views, bone density measurement (DEXA scan) of the lumbar spine and hip; and laboratory blood tests, including calcium, phosphate and alkaline phosphatase. Osteopenia should be treated with 1000 I.E. vitamin D daily and a calcium-rich diet or calcium tablets at a dose of 1200 mg/day. Patients should be advised to exercise and offered methods on how to give up alcohol and nicotine. In cases of osteoporosis, bisphosphonates (e.g., alendronate at 70 mg QW) should be added (McComsey 2007, Huang 2009). The tablets should be taken on an empty stomach 30 minutes before breakfast, and an upright position should be maintained for at least 30 minutes. No calcium should be taken on that day. Antiretroviral therapy should not be taken together with calcium. Because testosterone suppresses osteoclasts, hypogonadism should be treated. Alcohol and smoking should be avoided; regular exercise is an essential part of the therapy.

**Enfuvirtide (T-20)**

The most common side effect of T-20 is an injection site reaction (ISR) with erythema, induration, nodules, pruritus, ecchymosis, pain and discomfort. Almost every patient is affected, most of them, however, only mildly. ISR rarely limits treatment, and only 3–7% of patients discontinue therapy (Lazzarin 2003). The practitioner and the patient have to get used to the injection technique and the management of ISRs. Good injection technique (see Table 2) may be most effective in minimizing the incidence and severity, as well as the incidence of associated events, including infections. The appropriate management of ISR can lessen the reaction (Clotet 2004). Desensitization therapy is available for the skin rash that occurs rarely with T-20 (Shahar 2005). Patients traveling to foreign countries should be prepared for questions about their injection material. Taking along a medical certificate stating that the patient is on injection therapy can help to avoid unpleasant situations.

**Table 2: Suggestions for prevention and management of injection site reactions (ISR) and other injection-related adverse events (Clotet 2004)**

<table>
<thead>
<tr>
<th>Good injection technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ensure solution is at room temperature</td>
</tr>
<tr>
<td>• Avoid muscle by bevelling needle at 45–90 degrees, depending on body habitus</td>
</tr>
<tr>
<td>• Inject slowly</td>
</tr>
<tr>
<td>• Maintain sterile technique (wash hands, use gloves, clean injection area and vial caps with alcohol swabs, never touch needle)</td>
</tr>
<tr>
<td>• Feel for hard, subcutaneous bumps, avoid injecting into sites of previous ISR</td>
</tr>
<tr>
<td>• Avoid indurated or erythematous areas</td>
</tr>
<tr>
<td>• Avoid injections on the belt line</td>
</tr>
<tr>
<td>• Rotate sites (abdomen, thighs, arms) and never inject two consecutive doses into the same place</td>
</tr>
<tr>
<td>• Gentle manual massage after every injection</td>
</tr>
</tbody>
</table>
### Interventions for ISR

1. **Injection pain**
   - Topical anesthetic (e.g., lidocaine gel)
   - Oral analgesics pre-injection (e.g., ibuprofen or metamizole)
   - Numb area with ice or a cool pack before injecting

2. **Management of pruritus**
   - Oral antihistamines
   - Emollient creams or lotions (non-alcohol based and fragrance-free)

### Changes in blood count

HIV infection itself may cause pancytopenia. A very low CD4 T cell count may therefore be rarely due to a severe leukopenia. In this case, the percentage of the CD4 T cells and the CD4/CD8 ratio is normal.

Some antiretroviral drugs (especially AZT) are myelosuppressive, especially with respect to red cells, and lead to anemia (de Jesus 2004). Most commonly affected are patients with advanced HIV infection and pre-existing myelosuppression, on chemotherapy or co-medication with other myelotoxic drugs such as cotrimoxazole, pyrimethamine, amphotericin B, ribavirin, and interferon, or with other antiretroviral drugs.

5 to 10% of patients taking AZT develop anemia – usually during the first 3 months of therapy, but sometimes even after years on treatment (Carr 2001). AZT should be discontinued in severe cases, and a blood transfusion may be necessary. MCV is always elevated, even in patients on AZT without anemia, and is therefore a measure of adherence. It sometimes makes sense to change from Combivir® to the single drugs Retrovir® and Epivir® in anemic patients, because of the lower AZT dose in Retrovir® (250 mg) compared to Combivir® (300 mg). Because there are many alternatives to this third-line myelotoxic drug we see no reason to give high cost medications like erythropoietin.

Due to drug-induced neutropenia, it is possible that despite viral suppression the CD4 T cells remain low after an initial rise. In these cases treatment should be changed to less myelotoxic antiretroviral drugs and AZT should be avoided. Leukopenia may also occur on abacavir, tenofovir or indinavir. A low CD4 T cell count is also seen on combination of tenofovir and ddI.

For thrombocytopenia see also chapter *HIV-associated Thrombocytopenia*.

### Increased bleeding episodes

HIV-infected patients with hemophilia A or B, after some weeks of treatment with PIs, may have increased episodes of spontaneous bleeding into joints and soft tissues. Rarely, intracranial and gastrointestinal bleeding has occurred. The etiology is unclear (Review: Wilde 2000).

During clinical trials with tipranavir/r, the manufacturer received 14 reports of intracranial hemorrhage, among them 8 fatal cases, in 13 out of 6840 HIV-1 infected individuals. Most of them occurred more than one year after initiating therapy. So far, there have been no more spontaneous reports of intracranial hemorrhage on marketed tipranavir. Many of the patients affected had other risk factors for intracranial hemorrhage such as CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse, or were receiving anticoagulant or antiplatelet agents. Tipranavir was observed *in vitro* to inhibit human platelet aggre-
gation (Graff 2007). No pattern of abnormal hematologic or coagulation parameters was observed. Therefore, routine measurement of coagulation parameters is not indicated. Tipranavir/r should be avoided if possible in patients with the above mentioned risk factors. This applies also for patients on antiplatelet agents or anticoagulants. Patients should be informed about the possible risk of intracranial hemorrhage.

Lactic acidosis

Lactic acidosis is a rare but life-threatening complication due to mitochondrial toxicity. It occurs most frequently on treatment with d4T and ddI, and less so in patients on AZT, abacavir and 3TC (Garrabou 2009). Risk factors are obesity, female sex, pregnancy and therapy with ribavirin or hydroxyurea, a diminished creatinine clearance and a low CD4 T cell nadir (Bonnet 2003, Butt 2003, Wohl 2006). Cases of severe lactic acidosis can occur without prior symptomatic hyperlactatemia. Lactate levels do not need to be monitored routinely, as increases are not predictive and may lead to unnecessary changes in treatment (Brinkman 2001, Vrouenraets 2002). In contrast, lactate levels should be tested immediately in symptomatic patients complaining of fatigue, sudden weight loss, abdominal disturbances, nausea, vomiting or sudden dyspnea, in pregnant women on NRTI treatment and in patients on NRTIs post-lactic acidosis (Carr 2003).

For clinical symptoms, pathogenesis, and treatment please see chapter on Mitochondrial Toxicity.

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8. Lipodystrophy Syndrome

GEORG BEHRENS, REINHOLD E.SCHMIDT

Background

The HIV lipodystrophy syndrome including metabolic complications and altered fat distribution is a possible side effect of HIV therapy. Fortunately, modern therapy regimens are much less likely to lead to fat tissue abnormalities. The metabolic abnormalities may harbor a significant risk of developing cardiovascular disease. In addition, several studies report a reduced quality of life in patients with body habitus changes leading to a reduced treatment adherence. Despite the impact of lipodystrophy syndrome on HIV management, little is known about the pathogenesis, its prevention, diagnosis and treatment. Current data indicate a rather multifactorial pathogenesis where HIV infection, ART, and patient-related factors are all major contributors. The lack of a clear and easy definition reflects the clinical heterogeneity, limits a clear diagnosis and impairs the comparison of results among clinical studies. Therapeutic and prevention strategies have so far been of only limited clinical success, where avoiding the use of thymidine analogues appears to be most effective in avoiding peripheral fat loss. General recommendations include dietary changes and lifestyle modifications, altering antiretroviral therapy (replacing protease inhibitors with NNRTIs or replacing d4T and AZT with abacavir or tenofovir), and finally, the use of metabolically active drugs. Here we summarize the pathogenesis, diagnosis and treatment options of the HIV lipodystrophy syndrome.

Clinical manifestation

Lipodystrophy was originally described as a condition characterized by regional or generalized loss of subcutaneous fat. The non-HIV-associated forms, such as congenital or familial partial lipodystrophy, have a very low prevalence. Generally, these forms are associated with complex metabolic abnormalities and are difficult to treat. The term “lipodystrophy syndrome” was introduced to describe a complex medical condition including an apparent abnormal fat redistribution and metabolic disturbances in HIV patients receiving protease inhibitor therapy (Carr 1998). Now, years after its first description, there is still no consensus on a case definition for lipodystrophy syndrome in HIV. Thus, the diagnosis of lipodystrophy in clinical practice often relies on a more individual interpretation than on an evaluated classification. Finally, changes in fat distribution have to be considered as being part of a rather dynamic process. In most cases, peripheral lipoatrophy is clinically diagnosed when significant fat loss of about 30% has already occurred.

HIV-associated lipodystrophy includes both clinical and metabolic alterations. The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), limbs, and buttocks. Prospective studies in patients on thymidine analogues have demonstrated an initial increase in limb fat during the first months of therapy, followed by a progressive decline over the ensuing years (Mallon 2003), which is mostly persistent (Grunfeld 2010). Peripheral fat loss can be accompanied by an accumulation of visceral fat, which can cause mild gastrointestinal symptoms. Initially truncal fat increases on therapy and then remains stable (Mallon 2003). Visceral obesity, as a singular feature of abnormal fat redistribution, appears to occur in only a minority of patients. Fat accumulation may also be found as dorsocervical fat pads (buffalo hump) or within the muscle and the liver. Female HIV-positive patients sometimes complain about painful breast enlargement, attributed
to the lipodystrophy syndrome. Whether gynecomastia in male patients is a component of the syndrome remains unclear. There is now accumulating evidence that the major clinical components – lipoatrophy, central adiposity and the combination of both – result from different pathogenetic developmental processes.

The prevalence of a clinically evident lipodystrophy syndrome was estimated to be between 30 and 50% based on cross-sectional studies before 2005. A prospective study over an 18-month period after initiation of therapy revealed a prevalence of 17% but current HIV therapy combinations can be expected to lead to a lower incidence. More recent studies estimated the annual incidence rates of detectable but clinically inapparent peripheral fat loss (~20%) at about 5–10% in patients receiving a nuke-backbone with tenofovir, abacavir, 3TC or FTC. Lipodystrophy, and in particular lipoatrophy, has been observed most frequently in patients receiving a combination regimen of nucleoside analogues (particularly thymidine analogues) and protease inhibitors, although almost all antiretroviral drug combinations can be associated with fat redistribution. The risk of the syndrome increases with the duration of treatment, the age of the patient and the level of immunodeficiency. Children can be affected, like adults, with clinical fat redistribution shortly after initiation or change of ART. The evolution of the individual clinical components of the lipodystrophy syndrome is variable. The nucleoside analogue linked most strongly to lipoatrophy is d4T, particularly when used in combination with ddI. Tenofovir combined with 3TC and efavirenz is associated with less loss of limb fat than d4T in a similar combination in therapy-naïve HIV patients (Gallant 2004).

Frequently, complex metabolic alterations are associated with these body shape alterations. These include peripheral and hepatic insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, increased free fatty acids (FFA), and decreased high-density lipoprotein (HDL). Often these metabolic abnormalities appear or deteriorate before the manifestation of fat redistribution. The prevalence of insulin resistance and glucose intolerance has been reported in the literature at 20 to 50% depending on the study design and measurement methods and it increases with age (Hasse 2011). Frank diabetes is less frequent with a prevalence of between 1 and 6%. The incidence rate were highest at the time when PIs were introduced around 2000 but remain elevated as compared to seronegative control groups (Capeau 2012). Lipodystrophic patients present with the highest rates of metabolic disturbances.

Hyperlipidemias are a frequently observed side effect of antiretroviral therapy, especially in combinations that include PIs. Newer drugs such as maraviroc or raltegravir, second-generation NNRTIs such as rilpivirine and investigational intergrase inhibitors elvitegravir and dolutegravir seem to cause only minor disturbances in lipid metabolism (DeJesus 2010, Sax 2012). Given that many HIV-infected patients present with already decreased HDL levels, these are not further reduced by antiretroviral drugs, but usually improve to some degree, particularly when NNRTIs such as nevirapine are used. Hypertriglyceridemia, especially in patients with evidence of body fat abnormalities, is the leading lipid abnormality either alone or in combination with hypercholesterolemia. Several weeks after initiation or change of HIV therapy, lipid levels usually reach a plateau and remain stable. Part of this increase can be considered as reconstitution of health, as some patients return to the lipid levels they had before seroconversion. All protease inhibitors can potentially lead to hyperlipidemia, although to different extents. For example, atazanavir and darunavir appear to be less frequently associated with dyslipidemia and insulin resistance. In contrast, ritonavir often leads to hypertriglyceridemia correlating to the drug levels. Lopinavir leads to an approximate 18% mean increase in total cholesterol and 40% mean increase in triglycerides in patients on first line therapy.
The therapy-induced dyslipidemias are characterized by increased low-density lipoproteins (LDL) and triglyceride-rich very low density lipoproteins (VLDL). Detailed characterization revealed an increase of apolipoprotein B, CIII and E. Raised levels of lipoprotein(a) have been described in protease inhibitor recipients. Mild hypercholesterolemia can occur during therapy with efavirenz but is not typical with nevirapine. D4T-based ART is associated with early and statistically significant increases in total triglycerides and cholesterol or NRTIs. Several studies suggest that tenofovir exerts a moderate lipid-lowering effect on both total and LDL cholesterol as well as HDL cholesterol (Randell 2010). It is important to note that HIV infection itself is associated with disturbed lipid metabolism. During disease progression, total cholesterol, LDL, and HDL levels decline and the total triglyceride level rises. The latter is presumably caused by increased cytokine concentrations (TNFα, IFNγ) and an enhanced lipogenesis in addition to impaired postprandial triglyceride clearance.

**ART, lipodystrophy syndrome and cardiovascular risk**

The fat redistribution and disturbances in glucose and fat metabolism resemble a clinical situation that is known as the “metabolic syndrome” in HIV-negative patients. This condition includes symptoms such as central adipositas, insulin resistance and hyperinsulinemia, hyperlipidemia (high LDL, Lp(a) hypertriglyceridemia and low HDL) and hypercoagulopathy. Given the well-established cardiovascular risk resulting from this metabolic syndrome, there is growing concern about a potential therapy-related increased risk of myocardial infarction in HIV-positive patients. These fears are further sustained by reports of arterial hypertension on ART, a high rate of smoking among HIV patients and increased levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with lipodystrophy. Although many of the mainly retrospective studies dealing with this issue are inconclusive, data from a large international study (the D:A:D study) provide evidence for an increased relative risk of myocardial infarction during the first 7 years of ART (Friis-Møller 2003, El-Sadr 2006). The incidence of myocardial infarction increased from 1.39/1,000 patient years in those not exposed to ART, to 2.53/1,000 patient years in those exposed for < 1 year, to 6.07/1,000 patient years in those exposed for ≥6 years (RR compared to no exposure: 4.38, p = 0.0001). After adjustment for other potential risk factors, there was a 1.17-fold increased risk of myocardial infarction per additional year of combined ART exposure. It is, however, of note that older age, male gender, smoking, diabetes mellitus, and pre-existing coronary artery disease were still associated with a higher risk of sustaining cardiovascular events than ART in this study. Analysis of this cohort later provided evidence that PIs (particularly indinavir and lopinavir, but not atazanavir), abacavir and triglycerides contribute to this increased risk (Friis-Møller 2007, D:A:D Study Group 2008, Worm 2010, Worm 2011; d’Arminio Monforte 2012). Several other cohort studies, although not all (Lang 2011, Behrens 2011), confirmed the association of abacavir use and myocardial infarction (Behrens 2010). According to a meta-analysis (Cruciani 2011) considering prospective, controlled studies about the use of abacavir, the rate of myocardial infarction in these mostly young patients with a rather low cardiovascular risk profile was not significantly different to control regimens. Currently, it seems reasonable to consider alternatives for abacavir only in patients with a high cardiovascular risk (Framingham risk score >20%).

Although the CHD risk profile in D:A:D patients worsened over time, the risk of myocardial infarction decreased over time after controlling for these changes. Several other studies used ultrasonography to measure the thickness of the carotid intima media or endothelial function to predict the cardiovascular risk. Some of these inves-
tigations found abnormal test results (e.g., reduced flow-mediated dilation) that correlated either with the use of PIs or the presence of dyslipidemia (Currier 2005). Interestingly, HIV infection may lead to endothelial dysfunction and an unfavorable pro-atherogenic profile (Grunfeld 2009). While there is some indication of an increased rate of coronary artery disease with ART, particularly in combinations containing abacavir (D:A:D 2008), the benefit of suppressed viral replication and improved immune function resulting in reduced morbidity and mortality, clearly argues for the use of antiretroviral drugs according to current international guidelines. It seems obvious however, that pre-existing cardiovascular risk factors in individual patients need to be considered more carefully before starting or switching ART.

Recommendations such as the National Cholesterol Education Program (NECP) have been proposed for non-HIV-infected patients with similar risk profiles. These guidelines are being considered for HIV patients as well (Schambelan 2002, Grinspoon 2005). According to these recommendations, the overall cardiovascular risk in HIV-infected patients can be determined from specific risk factors by using the Framingham equation. Prediction of coronary heart disease using this equation, however, may have some limitations. A 10-year CHD risk estimation at any time point is determined by the individual’s past and expected future lipid levels (best assessed as area under the curve). Hyperlipidemia in many treated HIV-infected patients, however, does not follow the 10-year time course seen in the uninfected population due to therapy changes that may lower total cholesterol, increase HDL, and improve atherogenic risk (Behrens 2005). Thus, the validity of this calculation for long-term cardiovascular risk assessment in young patients with changing lipid levels and medication regimens requires further studies, but it seems helpful to identify patients with increased myocardial risk.

Clearly, more clinical studies are necessary to assess whether these recommendations are also applicable in the presence of HIV and to determine the clinical value of lipid lowering drug therapy in these patients. Most importantly, the information about drug interactions of lipid lowering and antiretroviral drugs is still incomplete. The accumulation of pre-existing and drug-related risk factors will get more clinical attention, because, by improving the HIV-associated morbidity and mortality, ART consequently increases an additional relevant cardiovascular risk factor: the age of patients who are effectively treated with antiretroviral drugs.

Pathogenesis

For a better understanding of the pathogenesis of complex metabolic abnormalities, it is useful to separate individual aspects of the lipodystrophy syndrome: adipocytes/fat redistribution, lipid metabolism, and carbohydrate metabolism. This is because it is very likely that the lipodystrophy syndrome is not a stereotypic syndrome but rather an amalgam of miscellaneous clinical features, with perhaps multifactorial causes. Studies published in recent years provide evidence for two fundamental assumptions: firstly, lipoatrophy and lipaccumulation result from divergent or only partially overlapping pathogenetic reasons. Secondly, NRTIs, NNRTIs, PIs, and even drugs within each class contribute to the lipodystrophy syndrome and its individual features by different possibly overlapping mechanisms.

NRTIs and lipodystrophy

The patterns of fat redistribution in patients who are only taking NRTIs are unlike those observed in patients on PI therapy. Peripheral fat loss is the major symptom observed in NRTI therapy (particularly d4T and AZT), although a few clinical studies
have described a minimal intra-abdominal fat increase in these patients, which is clearly less than on PIs. In ACTG 5142, in which patients receiving efavirenz (+2 NRTIs) or lopinavir (+2 NRTIs) were compared, a 20% percent reduction in peripheral fat tissue was significantly more frequently found in patients receiving d4T or AZT (Haubrich 2009). Given that, commonly, only a mild increase in triglycerides has been observed, exclusive NRTI therapy seems to be of minor impact on lipid metabolism, but is also not a preferred choice of therapy. Postprandially elevated FFA in patients with lipodystrophy, together with in vitro experiments, have led to the hypothesis that NRTIs could impair fatty acid binding proteins (FABP) that are responsible for cellular fat uptake and intracellular fat transport.

It is well established that long-term NRTI therapy can cause mitochondrial toxicity. The clinical manifestation of this presents in symptoms such as hepatic steatosis, severe hyperlactatemia, and polyneuropathy. As an explanation for these symptoms, the “pol-γ hypothesis” has been proposed, which was later extended to reveal the lipoatrophy observed under NRTIs (Brinkman 1999). To maintain an adequate bioenergetic level for accurate cell function, all metabolically active cells depend on a persistent polymerase γ-mediated mitochondrial (mt) DNA synthesis. Mitochondria require a constant supply of nucleosides for this process. The mitochondrial DNA polymerase γ retains both DNA- as well as RNA-dependent DNA polymerase activity. The latter is perhaps responsible for the HIV reverse transcriptase activity and therefore its susceptibility for interactions with NRTIs. Experimental data reveals that, for NRTI uptake into mitochondria, the subsequent phosphorylation and then incorporation into the DNA, certain pharmacodynamic requirements need to be fulfilled. These requirements, including thymidine kinase activity and deoxynucleotide transport specificity of the mitochondrial membrane, are apparently different for AZT and d4T, which partially explains the prevailing association between lipoatrophy and d4T therapy. The postulated mechanisms of NRTI-induced mitochondrial dysfunction consist of competitive inhibition, incorporation into the mtDNA resulting in mtDNA depletion, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and induction of apoptosis. Depletion of mtDNA and structural changes in the mitochondria, resulting in increased rates of apoptosis in subcutaneous adipocytes, have been confirmed in other studies. Despite the experimental link between mitochondrial toxicity and fat tissue as one potential target organ, the degree to which mitochondrial damage contributes to fat distribution abnormalities and its specificity remains unknown. Most likely, additional factor may be relevant given that mtDNA loss and mitochondrial dysfunction has been found in fat tissue of therapy-naïve patients (Garrabou 2011). Also, mt DNA measurement in PBMCs from the blood may be of little relevance for toxicity in fat tissue. In contrast, mitochondrial damage is widely believed to be responsible for other NRTI-related side effects, such as myopathy, hyperlactatemia, microvesicular steatosis, and steatohepatitis with lactic acidosis.

Protease inhibitors and lipodystrophy

PIs account for the majority of metabolic abnormalities associated with the lipodystrophy syndrome. Numerous studies report increases in the levels of total triglycerides and triglyceride-rich lipoproteins (VLDL) accompanied by raised LDL levels after initiation of PI therapy (Walli 1998, Behrens 1999). Conversely, these parameters improve substantially in most studies after discontinuation of the PI or on switching to abacavir or nevirapine. The hyperlipidemic changes are frequently associated with hyperinsulinemia and/or insulin resistance.

It has been proposed, based on in vitro experiments, that PIs such as saquinavir, indi-
navir, and ritonavir are able to inhibit proteasomal degradation of apolipoprotein B leading to intracellular stockpiling of this lipoprotein and excessive release in response to FFA (Liang 2001). Using stable isotopes in vivo, other authors demonstrate a dramatic increase in FFA turnover together with increased lipolysis and decreased clearance of triglyceride-rich VLDL and chylomicrons (Shekar 2002). These conditions point towards an impaired postprandial insulin-mediated lipid metabolism, since insulin, on the one hand, normally inhibits lipolysis and, on the other hand, increases uptake of FFA, triglyceride synthesis, and fat oxidation in favor of glucose oxidation.

It remains unclear whether impaired insulin action eventually leads to dyslipidemia, or whether hyperlipidemia is responsible for reduced insulin function and insulin resistance in the periphery. Presumably, both mechanisms are important given that some PIs (e.g., indinavir) have been shown to induce insulin resistance without changes occurring in lipid metabolism after short-term administration (Noor 2001, Noor 2002), whereas other PIs (e.g., ritonavir) have been demonstrated to cause mainly hypertriglyceridemia due to increased hepatic synthesis without major changes occurring in glucose metabolism (Purnell 2000).

It is reasonable to speculate that lipid abnormalities and, in particular increased FFA levels, contribute substantially to the peripheral and central insulin resistance of skeletal muscles and the liver, presumably due to the increased storage of lipids in these organs (Gan 2002). Given this hypothesis, the visceral adiposity could reflect the adaptation of the body in response to raised FFA concentrations and an attempt to minimize the lipotoxic damage to other organs.

Several in vitro experiments have indicated that almost all PIs can potentially lead to insulin resistance in adipocytes. Short-term administration of indinavir caused an acute and reversible state of peripheral insulin resistance in healthy volunteers, which was determined in an euglycemic-hyperinsulinemic clamp. These effects are most likely caused by the inhibition of glucose transport mediated by GLUT-4, the predominant transporter involved in insulin-stimulated cellular glucose uptake in humans (Murata 2002). A common structural component found in most PIs has been proposed to cause GLUT-4 inhibition. In some patients with lipodystrophy, additional impairment of glucose phosphorylation may contribute to insulin resistance (Behrens 2002). This is presumably due to an impaired insulin-mediated suppression of lipolysis and subsequently increased FFA levels (Behrens 2002, van der Valk 2001) and accumulation of intramyocellular lipids. Peripheral insulin resistance may also account for an increase in the resting energy expenditure in HIV lipodystrophy and a blunted insulin-mediated thermogenesis.

Indinavir may also induce insulin resistance by inhibiting the translocation, processing or phosphorylation of the sterol regulatory element-binding protein 1c (SREBP-1c). Either directly or via the peroxisome proliferator activated receptor γ (PPARγ), SREBP-1 regulates FFA uptake and synthesis, adipocyte differentiation and maturation, and glucose uptake by adipocytes. Similarly, the function of these factors has been proposed to be disturbed in inherited forms of lipodystrophy. Finally, hypoadiponectinemia, as found in patients with abnormal fat distribution, may contribute to insulin resistance (Addy 2003). Genetically, host factors interfering with drug metabolism (Domingo 2011) and additional predisposing factors in mechanistically plausible and other genes (Montes 2010, Pinti 2010, Wangsomboonsiri 2010) in addition to hormones and HIV proteins (De Luca 2012, Díaz-Delfín 2012, Egana-Gorrorno 2012, Gasparatto 2012) appear to contribute.
Diagnosis

Both the lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences leads to a continuing discussion about appropriate guidelines for the assessment and management of HIV lipodystrophy syndrome and its metabolic abnormalities. Outside clinical studies, the diagnosis relies principally on the occurrence of apparent clinical signs and the patient reporting them. A standardized data collection form may assist in diagnosis (Grinspoon 2005). This appears sufficient for the routine clinical assessment, especially when the body habitus changes develop rather rapidly and severely. For clinical investigations however, especially in epidemiological and interventional studies, more reliable measurements are required. A recent multicenter study to develop an objective and broadly applicable case definition proposes a model including age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum HDL cholesterol, trunk-to-peripheral-fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. Using these parameters, the diagnosis of lipodystrophy had a 79% sensitivity and 80% specificity (Carr 2003). Although this model is largely for research and contains detailed body composition data, alternative models and scoring systems, incorporating only clinical and metabolic data, also gave reasonable results (for more information, see http://www.med.unsw.edu.au/nchecr).

Despite individual limitations, several techniques are suitable for measuring regional fat distribution. These include dual energy x-ray absorptiometry (DEXA), computer tomography (CT), magnetic resonance imaging (MRI) and sonography. Anthropometric measurements are safe, portable, cheap and much easier to perform than imaging techniques. Waist circumference or sagittal diameter are more sensitive and specific measures than waist-to-hip ratio. Repeated measurements of skin fold thickness can be useful for individual long-term monitoring but need to be performed by an experienced person.

The main imaging techniques (MRI, CT, DEXA) differentiate tissues on the basis of density. Single-slice measurements of the abdomen and extremities (subcutaneous adipose tissue = SAT, visceral adipose tissue = VAT) and more complex three-dimensional reconstructions have been used to calculate regional or total body fat. Limitations of these methods include most notably their expense, availability and radiation exposure (CT). Consequently, CT and MRI should only be considered in routine clinical practice for selected patients (e.g., extended dorso-cervical fat pads, differential diagnosis of non-benign processes and infections).

DEXA is appropriate for examining appendicular fat, comprised almost entirely of SAT, and has been successfully employed in epidemiological studies. However, SAT and VAT cannot be distinguished by DEXA, which therefore limits the evaluation of changes in truncal fat. Application of sonography to measure specific adipose compartments, including those in the face, requires experienced investigators and has been minimally applied in HIV infection so far. Bioelectrical impedance analysis estimates the whole body composition and cannot be recommended for measurement of abnormal fat distribution.

Patients should routinely be questioned and examined for cardiovascular risk factors, such as smoking, hypertension, adiposity, type 2 diabetes, and family history. For an accurate assessment of blood lipid levels, it is recommended to obtain blood after a fasting of at least 8 hours. Total cholesterol and triglycerides together with LDL and HDL cholesterol should be obtained prior to the initiation of, or switch to, any new antiretroviral therapy and repeated 3 to 6 months later. Fasting glucose should be assessed with at least a similar frequency. The oral glucose tolerance test (OGTT) is a reliable and accurate instrument for evaluating insulin resistance and glucose
intolerance. An OGTT may be indicated in patients with suspected insulin resistance such as those with adipositas (BMI > 27 kg/m²), a history of gestational diabetes and a fasting glucose level of 110 to 126 mg/dl (impaired fasting glucose). The diagnosis of diabetes is based on fasting glucose levels > 126 mg/dl, glucose levels of > 200 mg/dl independent of fasting status, or a 2-hour OGTT glucose level above 200 mg/dl. Screening of HbA1c appears to be less reliable as in sero-negative patients (Kim 2009, Eckhardt 2011). Additional factors that could lead to or assist in the development of hyperlipidemia and/or insulin resistance always need to be considered (e.g., alcohol consumption, thyroid dysfunction, liver and kidney disease, hypogonadism, concurrent medication such as steroids, β-receptor blockers, thiazides, etc.).

**Therapy**

So far, most attempts to improve or even reverse the abnormal fat distribution by modification of the antiretroviral treatment have shown only modest clinical success. In particular, peripheral fat loss appears to be resistant to most therapeutic interventions. The metabolic components of the syndrome may be easier to improve (Table 1). Thus, preventing lipoatrophy by avoiding thymidine analogues (AZT, d4T) is the main goal (Behrens 2008). For more detailed recommendations for improving fat redistribution and treating dyslipidemia, please see the guidelines of the European AIDS Clinical Society (www.europeanaidsclinicalsociety.org). These guidelines emphasize that all traditional cardiovascular risk factors, such as arterial hypertension, hyperlipidemia and type 2 diabetes should be assessed and considered for intervention.

**Lifestyle changes**

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia. Use of NCEP guidelines may reduce total cholesterol and triglycerides by 11 and 21%, respectively. Whenever possible, dietary restriction of total fat to 25–35% of the total caloric intake should be a part of any treatment in conjunction with lipid-lowering drugs. Consultation with professional and experienced dieticians should be considered for HIV-infected patients and their partners. Patients with excessive hypertriglyceridemia (>1,000 mg/dl) may benefit from a very low fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis. Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution (reduction in truncal fat and intramyocellular fat) and should be considered in all HIV-infected patients (Driscoll 2004a). All patients should be advised and supported to give up smoking in order to reduce cardiovascular risk. Cessation of smoking is more likely to reduce cardiovascular risk than any choice or change of ART or use of any lipid-lowering drug (Petoumenos 2010).

**Table 1: Therapeutic options for HIV-associated lipodystrophy and related metabolic complications**

<table>
<thead>
<tr>
<th>Lifestyle changes</th>
<th>Reduce saturated fat and cholesterol intake, increase physical activity, stop smoking</th>
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<tbody>
<tr>
<td>Change antiretroviral therapy: replacement of PI, d4T (Zerit®) or AZT (Retrovir™)</td>
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<tr>
<td>Statins: Atorvastatin (Sortis®), Pravastatin (Pravasin®), Fluvastatin (Lescol®)</td>
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<tr>
<td>Fibrates: Gemfibrozil (Gevilon®) or Bezafibrat (Cedur®)</td>
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<td>Metformin (Glucophage®)</td>
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<td>Thiazolidinediones: pioglitazone (Actos®)</td>
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<tr>
<td>Recombinant human growth hormones (e.g., Serostim®) or analogues (e.g. Tesamorelin®)</td>
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<tr>
<td>Surgical intervention</td>
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Specific interventions

Given the extensive indications that PIs are the culprits that substantially contribute to metabolic side effects, numerous attempts have been made to substitute the PI component of a regimen with nevirapine, efavirenz, or abacavir. Similarly, given the close association of d4T-based therapy with lipoatrophy, replacement of this thymidine nucleoside analogue by, for example, abacavir or tenofovir has been evaluated in several studies. Indeed, these “switch studies” have demonstrated substantial improvement, although not normalization, of serum lipids (total and LDL cholesterol, triglycerides) and/or insulin resistance in many patients. In patients with hyperlipidemia, substitution of PIs with alternative PIs that have less metabolic side effects (e.g., atazanavir) has also been proven to be a successful strategy (Mallolas 2009, Moebius 2005). Protease inhibitor cessation has not been shown to improve lipoatrophy. However, stopping administration of the thymidine nucleoside analogue d4T or AZT usually leads to a slow recovery (over months and years) measured by DEXA and moderate clinical increase in limb fat (Moyle 2006, Tebas 2009). Under restricted inclusion criteria and study conditions, most patients maintain complete viral suppression after changes to the ART regimen, but not all of these studies included control groups with unchanged antiretroviral therapy. Recently, a pilot study evaluating the effect of uridine (Nucleomax®) on lipoatrophy in HIV-infected patients continuing their ART regimen described a significant increase in subcutaneous fat after only three months, but this effect was not confirmed in a larger randomized trial (McComsey 2010).

The most advantageous changes of metabolic parameters have been observed by replacement of the PI with nevirapine or abacavir. This option is, however, not always suitable, and the clinical benefit of effective viral suppression and improved immune function needs to be considered in view of drug history, current viral load, and resistance mutations. When options are limited, antiretroviral drugs that may lead to elevation of lipid levels should not be withheld for fear of further exacerbating lipid disorders. Lipid-lowering agents should be considered for the treatment of severe hypertriglyceridemia, elevated LDL or a combination of both. The clinical benefit, however, of lipid lowering or insulin-sensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated. In light of the potentially increased cardiovascular risk to recipients of antiretroviral therapy, the AIDS Clinical Trials Group (ACTG) published recommendations based on the National Cholesterol Education Program (NCEP) for primary and secondary prevention of coronary artery disease in seronegative patients. In addition, more detailed recommendations by the European AIDS Clinical Society have been published to provide guidelines for physicians actively involved in HIV care that will be regularly updated (www.europeanaidsclinicalsociety.org). However, these recommendations should be considered as being rather preliminary, given the so far limited numbers, size and duration of the clinical studies they are based on. It appears reasonable to measure fasting lipid levels annually before and 3–6 months after ART is initiated or changed. Whenever possible, the ART least likely to worsen lipid levels should be selected for patients with dyslipidemia. The decision on lipid-lowering therapy can be based on estimating the 10-year risk for myocardial infarction according to the Framingham equation (http://hin.nhlbi.nih.gov/atpiii/calculator.asp). In case of a more than 20% risk, dietary interventions and change of antiviral therapy should be considered. In patients with frank diabetes or coronary heart disease (CHD), lipid lowering drugs are recommended. The EACS guidelines (2011) recommend to target total cholesterol levels of < 190 mg/dl (<5 mmol/l) and for patients with type 2 diabetes and CHD levels < 155 mg/dl
(<4 mmol/l). For LDL-cholesterol levels one should aim for levels < 115 mg/dl (<3 mmol/l), and if possible, in patients with type 2 diabetes or CHD, levels < 80 mg/dl (<2mmol/l).

HMG-CoA reductase inhibitors have been successfully used in combination with dietary changes in HIV-positive patients with increased total and LDL cholesterol. These drugs may decrease total and LDL cholesterol by about 25% (Grinspoon 2005).

Many of the statins (as well as itraconazole, erythromycin, diltiazem, etc.) share common metabolism pathways with PIs via the cytochrome P450 3A4 system, thereby potentially leading to additional side effects due to increased plasma levels of statins which can then cause liver and muscle toxicity. They can be combined with ezetimibe in order to improve their lipid lowering effect (Negredo 2006). Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis®), fluvastatin (Lescol®), and pravastatin (Pravasin®), carefully administered at increasing doses, are the preferred agents for a carefully monitored therapy in HIV-infected patients on ART. Lovastatin (Mevinacor®) and simvastatin (Zocor®) should be avoided due to their potential interaction with PIs.

Fibric acid analogues such as gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels by up to 50% (Rao 2004, Miller 2002) and should be considered in patients with severe hypertriglyceridemia (>1000 mg/dl). Fibric acid analogues retain a supportive effect on lipoprotein lipase activity and can thereby lower LDL levels. Despite their potentially synergistic effect, co-administration of fibric acid analogues and statins in patients on ART should only be used carefully in selected individuals, since both can cause rhabdomyolysis. Niacin acid has been shown to only minimally improve the hyperlipidemia induced by ART. It does, however, increase peripheral insulin resistance (Gerber 2004). Extended-release niacin (Niaspan®) has been shown to have beneficial effects mainly on triglycerides and was well tolerated at a dose of 2,000 mg daily in a study with 33 individuals (Dube 2005). Similarly, polyunsaturated fatty acids could be beneficial in patients with hypertriglyceridemia (De Truchis 2007). Finally, it should be stressed that the long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes, especially in HIV-positive patients with moderate or severe hypertriglyceridemia, are unknown.

Metformin has been evaluated for the treatment of lipodystrophy syndrome. Some studies have revealed a positive effect on the parameters of insulin resistance and the potential reduction of intra-abdominal (and subcutaneous) fat, although not clinically obvious. Together with exercise training, metformin has been described to reverse the muscular adiposity in HIV-infected patients (Driscoll 2004b). Metformin, like all biguanides, can theoretically precipitate lactic acidosis and should thus be used with caution. Use of metformin should be avoided in patients with creatinine levels above 1.5 mg/dl, increased aminotransferase levels, or hyperlactatemia. Thiazolidinediones, such as rosiglitazone (Avandia®) or pioglitazone (Actos®), exhibit the potency to improve insulin sensitivity via stimulation of the PPARγ and other mechanisms. However, both drugs have been associated with significant side effects and can currently not be recommended for HIV-infected patients. Rosiglitazone has been successfully used to treat abnormal fat distribution in genetic lipodystrophies. Three published studies on HIV patients, however, revealed no or only minimal improvement in abnormal fat distribution. But, insulin sensitivity was increased at the expense of increased total cholesterol and triglycerides (Carr 2004, Hadigan 2004, Sutinen 2003, Cavalcanti 2007, Sheth 2010). Thus, rosiglitazone cannot be recommended for general treatment of lipoatrophy in HIV (Grinspoon 2005). It also reduces the bioavailability of nevirapine, although not of efavirenz and lopinavir (Oette 2005). A randomized double-blind placebo-controlled trial
ANRS 113) revealed a significant increase in subcutaneous fat 48 weeks after treatment with pioglitazone 30 mg once daily without demonstrating negative effects on lipid parameters (Slama 2008). The peripheral fat increase was most pronounced in patients, which stopped thymidine analogue therapy (Tungsiripat 2010), but because of side effects pioglitazone cannot be recommended to treat HIV-associated lipoatrophy.

Recombinant growth hormone (Serostim®) at doses of 4–6 mg/d sc over 8–12 weeks has been demonstrated in small studies to be a successful intervention for reducing visceral fat accumulation, but it also reduces subcutaneous fat (Kotler 2004). Unfortunately, these improvements have been shown to consistently reverse after the discontinuation of growth hormone therapy. Studies with lower maintenance doses have not been performed yet. The possible side effects associated with growth hormone therapy include arthralgia, peripheral edema, insulin resistance and hyperglycemia. Alternatively, a stabilized analogue of the growth hormone-releasing factor (Tesamorelin®), administered subcutaneously, can lead to reduction in visceral fat accumulation with less side effects (Falutz 2007) and was recently approved by the FDA.

Surgical intervention (liposuction) for the treatment of local fat hypertrophy has been successfully performed, but appears to be associated with an increased risk of secondary infection (Guaraldi 2011), and recurrence of fat accumulation is possible. For the treatment of facial lipoatrophy, repeated subcutaneous injection of agents such as poly-L-lactic acid (Sculptra®, New-Fill®), a resorbable molecule that promotes collagen formation, has been effectively used in HIV patients (Valantin 2003, Lafaurie 2005, Guaraldi 2005, Mest 2004, Casavantes 2004, Behrens 2008). In 2004, Sculptra® was approved by the FDA as an injectable filler to correct facial fat loss in people with HIV. We recommend consultation with experienced specialists for surgical treatments and injection therapy. Further evaluation in long-term follow-up studies is necessary to fully assess the value of these methods.

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9. Mitochondrial Toxicity of NRTIs
NILS VENHOFF AND ULRICH A. WALKER

Introduction
Two years after the introduction of PIs into the armamentarium of ART, reports of HIV-infected individuals experiencing clinically relevant changes in body metabolism began to surface. These metabolic symptoms were initially summarized under the term “lipodystrophy” (Carr 1998). Nowadays this lipodystrophy syndrome is understood to be the result of overlapping yet distinct effects of the different drug components in ART. The main pathogenetic mechanism through which nucleoside analogs are thought to contribute to metabolic changes and organ toxicities is mitochondrial toxicity (Brinkman 1999).

Pathogenesis of mitochondrial toxicity
NRTIs are prodrugs (Kakuda 2000) – they require activation in the cell through phosphorylation before they are able to inhibit their target, HIV reverse transcriptase. In addition to impairing the HIV replication machinery, the NRTI-triphosphates also inhibit a human polymerase called gamma-polymerase, which is responsible for the replication of mitochondrial DNA (mtDNA), a small circular molecule normally present in multiple copies in each mitochondrion and in hundreds of copies in most human cells. Thus, the inhibition of gamma-polymerase by NRTIs leads to a decline in mtDNA content (Lewis 2003). The biological task of mtDNA is to encode for enzyme subunits of the respiratory chain, which is located in the inner mitochondrial membrane. Therefore, by causing mtDNA depletion, NRTIs also lead to a defect in the respiratory chain function.

An intact respiratory chain is the prerequisite for numerous metabolic pathways. The main task of the respiratory chain is to oxidatively synthesize ATP, our chemical currency of energy. In addition, the respiratory chain consumes NADH and FADH as end products of fatty acid oxidation. This explains the micro- or macrovesicular accumulation of intracellular triglycerides, which often accompanies mitochondrial toxicity. Last but not least, a normal respiratory function is also essential for the synthesis of DNA, because the de novo synthesis of pyrimidine nucleosides depends on an enzyme located in the inner mitochondrial membrane. This enzyme is called dihydroorotate dehydrogenase (DHODH) (Löffler 1997). The clinical implications of this are detailed below.

The onset of mitochondrial toxicity follows several principles (Walker 2002a):
1. Mitochondrial toxicity is concentration-dependent. High NRTI concentrations cause a more pronounced mtDNA depletion compared to low concentrations. The clinical dosing of some nucleoside analogs is close to the limit of tolerance with respect to mitochondrial toxicity.
2. Mitochondrial toxicity is time dependent and develops with prolonged NRTI exposure. Changes in mitochondrial metabolism are observed only if the amount of mtDNA depletion exceeds a certain threshold. As a consequence, long-term NRTI exposure may lead to mitochondrial effects despite relatively low NRTI concentrations and the onset of toxicity is typically not observed in the first few months of ART.
3. There are significant differences in the relative potencies of nucleoside and nucleotide analogs in their ability to interact with gamma-polymerase. The active NRTI metabolites of zalcitabine (ddC, HIVID®), didanosine (ddI, Videx®) and stavu-
dine (d4T, Zerit®) are much more potent inhibitors of gamma-polymerase than the other members of this drug class.

4. Zidovudine (AZT, Retrovir®) may be peculiar because its active triphosphate is only a weak inhibitor of gamma-polymerase. However, another mechanism can explain how zidovudine might cause mtDNA depletion independent from gamma-polymerase inhibition. AZT is an inhibitor of mitochondrial thymidine kinase type 2 (TK2), and, as such, interferes with the synthesis of natural pyrimidine nucleotides, thus potentially impairing the formation of mtDNA (McKee 2004). Indeed, inborn defects of TK2 are known to cause mtDNA depletion in human muscle tissue (Saada 2001). It has also been demonstrated that AZT can be non-enzymatically converted into d4T within the body, at least within some cells (Becher 2003, Bonora 2004).

5. Mitochondrial toxicity is tissue-specific. Tissue specificity is explained by the fact that the uptake of the NRTI pro-drugs into cells and their mitochondria as well as activation by phosphorylation may be different in different cell types. TDF for example is actively transported by means of carrier molecules into the renal proximal tubular epithelial cells. High intratubular TDF concentrations could then account for the renal toxicity of TDF.

6. There may be additive or synergistic mitochondrial toxicities if two or more NRTIs are used in combination.

7. Data suggest that mitochondrial transcription may also be impaired without mtDNA alterations (Galluzzi 2005, Mallon 2005). However, the mechanism and clinical significance of this are not yet understood. NRTI exposure has also been linked with an early and increased acquisition of somatic mutations in mtDNA, a process that has been associated with aging (Payne 2011).

**Clinical manifestations**

MtDNA depletion may manifest clinically in one or several target tissues (Fig. 1). In the liver, mitochondrial toxicity is associated with increased lipid deposits, resulting in micro or macrovesicular steatosis. Steatosis may be accompanied by elevated liver transaminases. Such steatohepatitis may progress to liver failure and lactic acidosis, a potentially fatal, but fortunately rare complication.

Although steatohepatitis and lactic acidosis were already described in the early 90s in patients receiving didanosine monotherapy (Lambert 1990), mitochondrial liver toxicity is now observed with all NRTIs that have a relatively strong potential to inhibit gamma-polymerase, especially with the so called “d-drugs” ddI, d4T (and formerly, ddC). Liver complications have also been described with AZT. It has been demonstrated in the hepatic tissue of HIV patients that each of the d-drugs leads to a time dependent mtDNA depletion. On electron microscopy, morphologically abnormal mitochondria were observed.

A typical complication of mitochondrial toxicity is an elevation in serum lactate. Such hyperlactatemia was more frequently described with prolonged d4T treatment (Carr 2000, Saint-Marc 1999), especially when combined with ddi. The toxicity of ddi is also increased through interactions with ribavirin and hydroxyurea. The significance of asymptomatic hyperlactatemia is unclear. When elevated lactate levels are associated with symptoms, these are often non-specific such as nausea, right upper quadrant abdominal tenderness or myalgia. In the majority of cases, levels of bicarbonate and the anion gap (Na⁺ – [HCO₃⁻ + Cl⁻]) are normal, although liver transaminases are mildly increased in the majority of cases (Lonergan 2000). Therefore, the diagnosis relies on the logistically more cumbersome direct determination of serum lactate. In order to avoid artifacts, venous blood must be drawn without the use of a tourniquet from resting patients. The blood needs to be col-
lected in fluoride tubes and transported to the laboratory on ice for immediate analysis. Non-mitochondrial causes must also be considered in the differential diagnosis of lactic acidosis (Table 1) and underlying organ toxicities should be looked for. The incidence of lactic acidosis is low; it was estimated at 1 per 1000 patient years in NRTI exposed patients (Imhof 2005). In South Africa, much higher incidence rates (10.6 cases per 1,000 patient years) have been reported (Bolhaar 2007).

Mitochondrial myopathy in antiretrovirally treated HIV patients was first described with high dose AZT (Arnaudo 1991). Skeletal muscle weakness may manifest under dynamic or static exercise. The serum CK is often normal or only minimally elevated. Muscle histology helps to distinguish this form of NRTI toxicity from HIV myopathy, which may occur simultaneously. On histochemical examination, the muscle fibers of the former are frequently negative for cytochrome c-oxidase and carry ultrastructurally abnormal mitochondria, whereas those of the latter are typically infiltrated by CD8-positive T lymphocytes. Exercise testing may detect a low lactate threshold and a reduced lactate clearance, but in clinical practice these changes are difficult to distinguish from lack of aerobic exercise (detraining).

In a murine model of cardiomyopathy, nine weeks of oral AZT and ddC induced mitochondrial lesions with mtDNA depletion, diminished respiratory chain function and ultrastructural abnormalities of mitochondria (Balcarek 2010). Prolonged treatment with d-drugs can also lead to a predominantly symmetrical, sensory and distal polyneuropathy of the lower extremities (Moyle 1998, Simpson 1995). An elevated serum lactate level can help distinguish this axonal neuropathy from its HIV-associated phenocopy, although in most cases the lactate level is normal. The differential diagnosis may also take into account the fact that the mitochondrial polyneuropathy mostly occurs weeks or months after initiation of the d-drugs. In contrast, the HIV-associated polyneuropathy generally does not worsen and may indeed improve with prolonged antiretroviral treatment. In mice AZT and ddC induce a mitochondrial neurotoxicity with ddC predominantly affecting the peripheral and AZT mainly the central nervous system (Venhoff 2010). This is consistent with findings in patients (Tardieu 2005, Moyle 1998). Although the toxic effects of AZT on the central nervous system have not been studied well in humans, they are plausible because AZT penetrates well into the CNS.
Table 1: Causes of hyperlactatemia/lactic acidosis.

<table>
<thead>
<tr>
<th>Type A lactic acidosis</th>
<th>Type B lactic acidosis</th>
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<tr>
<td>(Tissue hypoxia)</td>
<td>(Other mechanisms)</td>
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<tr>
<td>Shock</td>
<td>Thiamine deficiency</td>
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<tr>
<td>Carbon monoxide poisoning</td>
<td>Alkalosis (pH &gt;7.6)</td>
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<tr>
<td>Heart failure</td>
<td>Epilepsy</td>
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<tr>
<td></td>
<td>Adrenalin (iatrogenic, endogenous)</td>
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<td></td>
<td>Liver failure</td>
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<td></td>
<td>Neoplasm (lymphoma, solid tumors)</td>
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<tr>
<td></td>
<td>Intoxication (nitroprusside, methanol, methylene glycol, salicylates)</td>
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<tr>
<td></td>
<td>Fructose</td>
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<tr>
<td></td>
<td>Rare enzyme deficiencies</td>
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<tr>
<td></td>
<td>mtDNA mutations</td>
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<td></td>
<td>mtDNA depletion</td>
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In its more narrow sense, the term lipodystrophy denotes a change in the distribution of body fat. Some individuals affected with lipodystrophy may experience abnormal fat accumulation in some body areas (most commonly in the abdomen or in the dorsocervical region), whereas others may develop fat wasting (Bichat’s fat pad in the cheeks, temporal fat, or subcutaneous fat of the extremities). Both fat accumulation and fat loss may occur simultaneously in the same individuals. Fat wasting (also called lipoatrophy) is partially reversible and generally observed not earlier than one year after the initiation of antiretroviral therapy. In the affected subcutaneous tissue, ultrastructural abnormalities of mitochondria and reduced mtDNA levels have been identified, in particular in subjects treated with d4T (Walker 2002b). In vitro and in vivo analyses of fat cells have also demonstrated diminished intracellular lipids, reduced expression of adipogenic transcription factors (PPAR-gamma and SREBP-1), and increased apoptotic indices. NRTI treatment may also impair some endocrine functions of adipocytes. For example, NRTIs may impair the secretion of adiponectin and through this mechanism may promote insulin resistance. D4T has been identified as a particular risk factor, but other NRTIs such as zidovudine may also contribute. When d4T is replaced by another NRTI, mtDNA levels and apoptotic indices improve (McComsey 2005), along with an objectively measurable, albeit small increase of subcutaneous adipose tissue (McComsey 2004). In contrast, switching away from protease inhibitors did not ameliorate lipoatrophy or adipocyte apoptosis. Taken together, the available data indicate a predominant effect of mitochondrial toxicity in the pathogenesis of lipoatrophy. Some studies have suggested an effect of NRTIs on the mtDNA levels in blood (Coté 2003, Miro 2003). The functional consequence of mitochondrial toxicity on lymphocytes is still unknown. In this context, it is important to note that a delayed loss of CD4 and CD8 lymphocytes was observed when ddI plasma levels were increased by co-medication with TDF or when ddI was given to subjects with low body weight (Negredo 2004). Recent in vitro investigations with exposure of mitotically stimulated T lymphocytes to only slightly supratherapeutic concentrations of ddI also detected a substantial mtDNA depletion with a subsequent late onset decline of lymphocyte proliferation and increased apoptosis (Setzer 2005a, Setzer 2005b). Thus, mitochondrial toxicity is the most likely explanation for the late onset decline of lymphocytes observed with ddI. DdI, d4T and AZT induce mitochondrial toxicity in human B lymphocytes and impair the immunoglobulin synthesis (Setzer 2012). This may explain the observation that the incidence of pneumococcal infections in HIV
patients remains considerably elevated after initiation of ART. Taken together, the data suggest that the mitochondrial toxicity of some NRTIs may suppress normal T and B lymphocyte function.

Furthermore an elevation of serum urate was observed on therapy with dideoxynucleosides (ddI and d4T). Impaired ATP production as a result of mitochondrial toxicity may increase urate production in the purine nucleotide cycle (Walker 2006b). After long and controversial discussions, several studies now provide evidence that TDF does cause mitochondrial damage to the kidney. TDF is a nucleotide analog reverse transcriptase inhibitor (Viread®) that has been associated with cases of renal dysfunction, Fanconi’s syndrome and cases of osteomalacia in animals (Tenofovir review team 2001) and patients (Gupta 2008, Wanner 2009). Patients treated with TDF often present with elevated serum alkaline phosphatase and hypophosphatemia due to a diminished renal phosphate resorption (Kinai 2005). Also, osteomalacia was observed in patients treated with TDF, especially when combined with lopinavir/r (Parsonage 2005, Wanner 2009). TDF is taken up into the proximal renal tubules by human renal organic anion transporters (hOATs) 1 and 3. Despite the fact that TDF only has a low potency to impair the polymerase gamma, the hOATs may generate high intratubular tenofovir concentrations that then interfere with the replication of mtDNA (Cote 2006). Decreased mtDNA levels have been found in renal biopsies from patients exposed to TDF+ddI (Cote 2006, Perazella 2010). In an animal model, TDF induced an organ-specific nephrotoxicity with mtDNA depletion and tubular dysfunction of mtDNA-encoded respiratory chain subunits (Lebrecht 2009). It is therefore not recommended to use TDF in patients with established renal dysfunction.

The use of AZT to avoid vertical HIV transmission diminishes mtDNA levels in the placenta, as well as in the peripheral cord blood of perinatally exposed newborns (Divi 2004, Shiramizu 2003, Gingelmaier 2009). AZT was found to be incorporated into mtDNA in pregnant monkeys treated with AZT plus 3TC prior to delivery and mtDNA depletion was found in skeletal muscle, heart and brain (Gerschenson 2004) in which perinatally acquired lesions were shown to persist for months after cessation of NRTI exposure in some models.

Mitochondrial symptoms and abnormal cerebral imaging were found at increased frequency in infants perinatally exposed to NRTIs (Blanche 1999, Tardieu 2005). Hyperlactatemia is not infrequently observed and may persist for several months after delivery (Noguera 2003). Other clinical trials in contrast did not detect an increased perinatal risk in association with perinatal AZT prophylaxis although key parameters of mitochondrial dysfunction were not assessed. Long-term follow-up data are urgently needed (Venhoff 2006). The available information however does not justify deviating from the currently recommended strategy to use AZT to prevent vertical HIV transmission as part of combination therapy for the mother.

**Monitoring**

There is currently no method to reliably predict the mitochondrial risk of an individual patient. Routine screening of asymptomatic NRTI-treated subjects with lactate levels is not warranted, since elevated lactate levels in asymptomatic subjects are not predictive of clinical mitochondrial toxicity (McComsey 2004). Quantification of mtDNA levels in PBMCs is not reliable. The $[^{13}C]$methionine breath test can be used to analyze the oxidative capacity of liver mitochondria, but results may be confounded by several factors other than HIV or ART (Sternfeld 2009). Quantifying mtDNA within affected tissues is likely to be more sensitive; however this form of monitoring is invasive and not evaluated with regard to clinical endpoints.
Once symptoms are established, histological examination of a biopsy may contribute to the correct diagnosis. The following findings in tissue biopsies point towards a mitochondrial etiology: ultrastructural abnormalities of mitochondria, diminished histochemical activities of cytochrome c oxidase, the detection of intracellular and more specifically microvesicular steatosis, and the so-called ragged-red fibers.

**Treatment & prophylaxis of mitochondrial toxicity**

**Drug interactions**

Drug interactions may precipitate mitochondrial symptoms and must be taken into account. The mitochondrial toxicity of ddI for example is augmented through drug interactions with ribavirin, hydroxyurea and allopurinol (Ray 2004). When ddI is combined with TDF, the dose of ddI must be reduced to 250 mg once daily. The thymidine analog brivudine is a herpes virostatic that may sensitize for NRTI-related mitochondrial toxicity because one of its metabolites is an inhibitor of DHODH (see below). Brivudine should therefore not be combined with antiretroviral pyrimidine analogues.

**Mitochondrial toxins**

An impairment of mitochondrial metabolism may also result from ibuprofen, valproic acid and acetylsalicylic acid as these agents impair the mitochondrial utilization of fatty acids. Numerous cases have been described in which a life-threatening lactic acidosis was triggered by valproic acid both in HIV-infected patients and in patients with inherited mutations of mtDNA. Acetylsalicylic acid may damage mitochondria and such damage to liver organelles may result in Reye’s syndrome. Amiodarone and tamoxifen also inhibit the mitochondrial synthesis of ATP. Acetaminophen and other drugs impair the antioxidative defense (glutathione) of mitochondria, allowing for their free radical-mediated damage. Aminoglycoside antibiotics and chloramphenicol not only inhibit the protein synthesis of bacteria, but in certain circumstances may also impair the peptide transcription of mitochondria as our bacteria-like endosymbionts. Adefovir and cidofovir are also inhibitors of gamma-polymerase. Alcohol is a mitochondrial toxic and should be avoided. Lastly, TDF nephrotoxicity may be precipitated by coadministration with lopinavir/r (Wanner 2009). Lopinavir/r increases tenofovir serum levels and may also inhibit MDR4, with both mechanisms then contributing to intratubular tenofovir accumulation.

The most important clinical intervention is probably the discontinuation of the NRTI responsible for the mitochondrial toxicity. Several studies have demonstrated that switching from stavudine (Zerit®) to a less toxic alternative led to an objective and progressive improvement in lipoatrophy (Martin 2004, McComsey 2004, Moyle 2004). In contrast, a switch from protease inhibitors to NRTIs was not associated with an improvement of lipoatrophy. These findings stress the importance of mitochondrial toxicity in the pathogenesis of fat abnormalities.

**Uridine**

As outlined above, any respiratory chain impairment also results in the inhibition of DHODH, an essential enzyme for the synthesis of uridine and its derived pyrimidines (Fig. 2). This decrease in intracellular pyrimidine pools leads to a relative excess of the exogenous pyrimidine nucleoside analogs, with which they compete at
gamma-polymerase. A vicious circle is closed and contributes to mtDNA depletion. By supplementing uridine either prophylactically or therapeutically, this depletion may be interrupted, resulting in increased mtDNA levels (Setzer 2008). Indeed, uridine abolishes all the effects of mtDNA depletion in hepatocytes and normalizes lactate production, cell proliferation, the rate of cell death and intracellular steatosis in vitro (Walker 2003). In d4T-exposed adipocytes uridine was able to normalize mitochondrial function and lipid metabolism (Walker 2006a). New data indicate that uridine is also able to prevent ddC-induced hepatotoxicity (Lebrecht 2007), and AZT-induced myopathy (Lebrecht 2008), cardiomyopathy and neuropathy (Venhoff 2010) in mice.

The oral substitution of uridine as a pyrimidine precursor is well tolerated by humans, even at high doses (Kelsen 1997, van Groeningen 1986). Mitocnol®, a food supplement, was shown to have a more than 8-fold uridine bioavailability over conventional uridine (Venhoff 2005, Weinberg 2011).

Two randomized placebo-controlled double-blind trials utilizing mitocnol in patients with lipoatrophy on continued therapy with d4T or AZT have yielded conflicting results (Sutinen 2007, McComsey 2010).

Mitochondrial steatohepatitis is antagonized by mitocnol in animal models, as well as in HIV-positive patients (Walker 2004, Banasch 2006, Lebrecht 2007). In AZT-induced myopathy in mice, mitocnol attenuated mtDNA depletion and muscle atrophy (Lebrecht 2008). Mitochondrial cardiomyopathy and neuropathy was successfully prevented by mitocnol in an animal model (Balcarek 2010, Venhoff 2010). Mitocnol® is well tolerated and adverse events have not been observed so far. There are no known negative interactions of uridine with antiretroviral treatment (Koch 2003, McComsey 2007, Sommadossi 1988, Sutinen 2007, Venhoff 2008).

Hyperlactatemia

With symptomatic hyperlactatemia and with lactic acidosis, NRTIs should be immediately discontinued (Brinkman 2000).
With respect to mtDNA depletion, vitamin supplements were not found to be effective either \textit{in vitro} or in clinical studies (Venhoff 2002, Walker 1995). In animals and humans mitocnol improves hyperlactatemia (Lebrecht 2007, Sutinen 2007). NRTI re-exposure may be possible after normalization of lactate (Lonergan 2003). The supportive treatment of hyperlactatemia and lactic acidosis is summarized in Table 2.

Table 2: Supportive treatment of lactate elevation in HIV-infected patients (non-pregnant adults)

<table>
<thead>
<tr>
<th>Lactate 2-5 mmol/L + symptoms</th>
<th>Lactate &gt;5 mmol/L or lactic acidosis</th>
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<tbody>
<tr>
<td>Discontinue mitochondrial toxins</td>
<td>Discontinue NRTIs and all mitochondrial toxins</td>
</tr>
<tr>
<td>Consider vitamins and</td>
<td>Intensive care</td>
</tr>
<tr>
<td>Mitocnol® (NucleomaxX®, 36g TID on 3 consecutive days/month)</td>
<td>Maintain hemoglobin &gt;100 g/L</td>
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<td></td>
<td>Avoid vasoconstrictive agents</td>
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<td></td>
<td>Oxygen</td>
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<tr>
<td></td>
<td>Correct hypoglycemia</td>
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<tr>
<td></td>
<td>Bicarbonate controversial – 50-100 mmol if pH &lt;7.1</td>
</tr>
<tr>
<td></td>
<td>Coenzyme Q10 (100 mg TID)</td>
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<tr>
<td></td>
<td>Vitamin C (1 g TID)</td>
</tr>
<tr>
<td></td>
<td>Thiamine (Vit. B1, 100 mg TID)</td>
</tr>
<tr>
<td></td>
<td>Riboflavin (Vit. B2, 100 mg QD)</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine (Vit. B6, 60 mg QD)</td>
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<tr>
<td></td>
<td>L-acetyl carnitine (1 g TID)</td>
</tr>
<tr>
<td></td>
<td>Mitocnol® (NucleomaxX®, 36 g TID until lactate &lt;5 mmol/L)</td>
</tr>
</tbody>
</table>

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The goal of antiretroviral therapy is to achieve maximum suppression of viral replication. Viral blips while on suppressive ART are relatively common and are mostly due to random biological and statistical fluctuations. However, patients with repeated episodes of detectable viremia – suggesting ongoing viral replication rather than viral release from latent reservoirs due to immune activation – are at increased risk for development of drug resistance. The level of viral load while on therapy is the best predictor of subsequent virological failure which starts to increase at viral load levels between 100 and 300 copies/ml (Nettles 2005, Delaguerre 2009, Garcia-Gasco 2008). The highest probability of drug resistance to any drug class is between 1000 and 10,000 copies/ml (Prosperi 2011).

The rapid development of resistant variants is due to the high turnover of HIV – in an untreated HIV-infected patient approximately 10 million new viral particles are produced every day (Perelson 1996) – and the exceptionally high error rate of HIV reverse transcriptase. This leads to a high mutation rate and constant production of new viral strains, even in the absence of treatment. In the presence of antiretroviral drugs, the development of HIV-1 resistance depends on the selection of resistance-associated mutations (RAMs). If a virus has acquired one or more RAMs leading to reduced drug sensitivity, the mutant virus attains a replication advantage in comparison to wild-type virus when exposed to drugs (Drake 1993). The development of resistant viral strains is one of the main reasons for virological failure of antiretroviral therapy. However, with the strategic use of the newer drug classes, effective regimens are available even in salvage situations.

The discussion about genotypic resistance and viral tropism in this chapter focuses on the methods of resistance and tropism testing, on mutation patterns emerging on ART, and their interpretations and clinical relevance. Most data are derived from patients with subtype B viruses, representing the main subtype in North America, Australia and Europe, but only about 12% of the global HIV-1-positive population. During recent years, non-B subtype viruses have been investigated, some with different resistance pathways and patterns (Snoeck 2006).

Assays for resistance testing

There are two established assays for measuring resistance or sensitivity of HIV to specific antiretroviral drugs – the genotypic and the phenotypic resistance tests (Wilson 2003). Conventional (population-based) genotypic tests can only detect viral mutants when these comprise at least 20% of the total virus population. For the detection of minority variants ultrasensitive methods (allele-specific real-time PCR, single genome sequencing) are used.

Conventional genotypic assays accredited by the FDA are
- HIV-1 TruGene® (Siemens Healthcare Diagnostics)
- ViroSeq® (Abbott Molecular/Applera Corp. of Applied Biosystems and Celera).

The clinical relevance of minority populations remains a controversial issue although there is evidence for minor variants with NNRTI mutations (Li 2011). Ultrasensitive sequencing systems such as GS FLX (Roche/454 Life Sciences), HiScanSQ (Illumina) and SOLiD (Life Technologies) are currently used for research purposes. With the availability of smaller devices such as GS Junior (Roche/454 Life Sciences), Ion Torrent PGM (Life Technologies) or MiSeq (Illumina) this next-generation technology
becomes interesting for routine diagnostics. However, utilization and interpretation of test results must be resolved prior to routine application. Furthermore, most devices and reagent kits are not yet certified.

**Phenotypic resistance tests** include:

- PhenoSense® HIV (Monogram Biosciences)
- PhenoTecTM (InPheno)
- Phenoscript™ (EuroFins/VIRalliance)
- Antivirogram® (developed by Virco Lab) is no longer available for routine clinical use, only for research and drug discovery.

The cost of genotyping ranges from 260 to 400 €, depending on the assay and laboratory used. It is approximately twice that much for phenotyping. The drawback of both methods is that a minimum amount of virus is necessary in order to perform the test. Depending on the method and on the laboratory 100–1,000 copies/ml are required for detection of resistance. Tables 1 and 2 show the advantages and disadvantages of phenotypic and genotypic resistance analyses.

**Basic principles of phenotyping**

Phenotypic resistance tests involve direct quantification of drug sensitivity. Viral replication is measured in cell culture under the selective pressure of increasing concentrations of antiretroviral drugs and is compared to viral replication of wild-type virus. Drug concentrations are expressed as IC\textsubscript{50} values (50% inhibitory concentration), the concentration of drug required to inhibit viral replication in cell cultures by 50%. The sensitivity of the virus is expressed as the IC\textsubscript{50} divided by the IC\textsubscript{50} of a wild-type reference virus (fold-change (FC) also reported as resistance factor) and compared to the so-called cut-off value. The cut-off value indicates by how much the IC\textsubscript{50} of an HIV isolate can be increased in comparison to that of the wild-type and still be classified as sensitive. The determination of the cut-off is crucial for the interpretation of the results.

Table 1: Advantages and disadvantages of phenotypic resistance analysis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct measure of drug susceptibility</td>
<td>Only detection of viral mutants comprising ≥ 20–30% of the total virus population</td>
</tr>
<tr>
<td>Measure of drug susceptibility feasible irrespective of the presence of unknown resistance mutations</td>
<td>Clinical cut-offs not available for all drugs</td>
</tr>
<tr>
<td>Measure of drug susceptibility feasible irrespective of the complexity of resistance patterns and the presence of re-sensitizing mutations</td>
<td>Expensive (reimbursement by health insurance often not guaranteed)</td>
</tr>
<tr>
<td></td>
<td>Time-consuming (several weeks)</td>
</tr>
<tr>
<td></td>
<td>HIV-1 subtyping not possible</td>
</tr>
<tr>
<td></td>
<td>Interactions between antiviral drugs are not reflected in the test results</td>
</tr>
<tr>
<td></td>
<td>Test results are not affected by amino acid exchanges, which are only an intermediate step to resistance</td>
</tr>
</tbody>
</table>

**Cut-offs: technical, biological and clinical**

Three different cut-offs are currently being used. The technical cut-off is a measure of the methodological variability of the assay. The biological cut-off involves the inter-individual variability of wild-type virus isolates from ART-naïve HIV-positive patients.
If the IC$_{50}$ is below the biological cut-off, virological success is very likely. However, an IC$_{50}$ above the biological cut-off does not allow prediction of the virologic response to a drug. In contrast, the clinical cut-off indicates up to what levels of IC$_{50}$ virologic effectiveness can still be expected. Complete resistance to a drug (i.e., to protease inhibitors) generally evolves gradually with the acquisition of several amino acid changes.

In general, lower and upper clinical cut-offs are defined. The lower clinical cut-off is the fold-change in IC$_{50}$ (FC) which indicates slightly reduced virological response. An FC above the upper clinical cut-off indicates resistance, and an FC between the two cut-offs indicates partial resistance. Due to limited clinical experience cut-off data is often lacking for recently approved drugs. In these cases, interpretations are based on biological cut-offs.

In the phenotypic analysis, mutations that do not confer resistance by themselves but provide evidence for transmitted, emerging or reverting resistance have no influence on the measure of resistance.

**Basic principles of genotyping**

The HIV genome consists of 2 RNA (ribonucleic acid) strands containing the genetic information of the virus. Within the nucleotide sequence of the HIV genome, a group of three nucleotides, called a codon, code for a particular amino acid in the protein sequence. Resistance mutations are described using a number for each gene, showing the position of the relevant codon, and two letters, the letter preceding the number corresponding to the amino acid specified by the codon at this position in the wild-type virus, while the letter after the number describes the amino acid that is produced from the mutated codon.

A change in the nucleotide sequence of a codon is called a mutation. ‘Silent’ mutations code for the same amino acid. ‘Lethal’ mutations cause a defective protein structure leading to a stop of the viral replication cycle. Only those mutations that code for a different amino acid that leads to a change in the protein structure are clinically relevant. This affects protein function and can contribute to the development of resistance to antiretroviral agents. M184V indicates a mutation in codon 184 of the reverse transcriptase gene leading to a valine for methionine substitution in the reverse transcriptase enzyme and rendering the virus resistant to 3TC and FTC.

<table>
<thead>
<tr>
<th>Genotypic resistance analysis</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Indirect measurement of resistance</td>
</tr>
<tr>
<td>• Quickly performed (results within days)</td>
<td>• Only detection of viral mutants comprising ≥20-30% of the total virus population</td>
</tr>
<tr>
<td>• Widely used (no specific safety requirements for laboratory)</td>
<td>• Complex resistance patterns are often difficult to interpret</td>
</tr>
<tr>
<td>• Listing of all changes in the nucleotide sequence</td>
<td>• Unknown mutations are not considered for interpretation</td>
</tr>
<tr>
<td>• Detection of any mutation – with either evidence of resistance, emerging resistance or reverting resistance</td>
<td>• Interpretation systems must be updated regularly</td>
</tr>
<tr>
<td>• HIV-1 subtyping possible</td>
<td>• In general reimbursement by health insurance (i.e., sequencing of the protease and the RT genes)</td>
</tr>
</tbody>
</table>
Genotypic assays are based on the analysis of mutations associated with resistance. These are determined by the direct sequencing of the amplified HIV genome or by specific hybridization techniques with wild-type or mutant oligonucleotides. For therapeutic decision making, sequencing of the **pol** region, which encodes for the viral enzymes protease, reverse transcriptase and integrase, and sequencing of the **env** region, which encodes for the glycoproteins of the viral envelope, gp41 and gp120, are of relevance. Other gene regions, in particular RNase H and gag, are reported to be associated with phenotypic drug resistance. However, sequencing of these regions has only been performed in the context of research and is not part of routine diagnostics.

The interpretation of genotypic resistance patterns is based on the correlation between genotype, phenotype and clinical response. There is data available from *in vitro* studies, clinical studies, clinical observations and duplicate testing, in which genotypically localized mutations have been investigated for phenotypic resistance.

**Rules-based interpretation systems**

For the phenotypic interpretation of genotypic mutation patterns rules-based interpretation systems are commonly available. Expert panels, e.g., from ANRS, HIV-GRADE, the Rega Institute or Stanford University, have developed algorithms based on the literature and clinical outcomes (Obermeier 2012). Table 3 shows an overview of widely used interpretation systems.

Several commercial providers of resistance assays have integrated interpretation guidelines into their systems.

**Data-based interpretation systems and virtual phenotype**

Contrary to the knowledge-based interpretation algorithms developed by experts, data-based interpretation systems like geno2pheno or vircoType™ HIV-1 are mathematical approaches to predicting (“virtual”) phenotype from genotypic information. The virtual phenotype is characterized by the fact that phenotypic information is derived from genotype without performing a phenotypic resistance test in the laboratory. Phenotypic estimates derive from large databases of paired genotypic and phenotypic information.

<table>
<thead>
<tr>
<th>Interpretation system</th>
<th>Interpretation</th>
<th>Available free of charge</th>
<th>Internet address: http://</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-GRADE (07/2011), Germany</td>
<td>Rules-based</td>
<td>Yes</td>
<td><a href="http://www.hiv-grade.de">www.hiv-grade.de</a></td>
</tr>
<tr>
<td>Rega V8.0.2 (HIV-1&amp;2) (06/2009), Belgium</td>
<td>Rules-based</td>
<td>Yes</td>
<td>rega-web.med.kuleuven.be/ software/rega_algorithm</td>
</tr>
<tr>
<td>ANRS (HIV1&amp;2) V21 (10/2011), France</td>
<td>Rules-based</td>
<td>Yes</td>
<td>hivfrenchresistance.org/</td>
</tr>
<tr>
<td>EuResist</td>
<td>Data-based</td>
<td>Yes</td>
<td>euresist.org</td>
</tr>
<tr>
<td>EuResist Network GEIE</td>
<td>Data-based</td>
<td>No</td>
<td><a href="http://www.monogrambio.com/">www.monogrambio.com/</a></td>
</tr>
<tr>
<td>MGRM GeneSeq® (Monogram Bioscience)</td>
<td>Rules- and databased</td>
<td>No</td>
<td>200HIVProducts.aspx</td>
</tr>
<tr>
<td>geno2pheno, Germany</td>
<td>Data-based</td>
<td>Yes</td>
<td><a href="http://www.geno2pheno.org/">www.geno2pheno.org/</a></td>
</tr>
<tr>
<td>Virco®Type HIV-1 (Janssen Diagnostics, formerly Virco)</td>
<td>Data-based (virtual phenotype)</td>
<td>No</td>
<td><a href="http://www.janssendiagntistics.com/hiv-resistance/vircotype-hiv-1">www.janssendiagntistics.com/hiv-resistance/vircotype-hiv-1</a></td>
</tr>
</tbody>
</table>
The interpretation system geno2pheno, available free of charge, uses machine learning techniques such as decision trees and support vector machines (Beerenwinkel 2003).

The vircoType™ interpretation is based on a multiple linear regression model, which is applied to a database consisting of more than 61,000 (as of October 2011) matched genotype/phenotype pairs: For every drug the fold-change in IC$_{50}$ is a function of all mutations of the patient’s virus that contribute to specific drug resistance. To account for synergistic and antagonistic effects between mutations, specific pairs of mutations are included in the model. According to their relevance, drug-specific weight factors are attributed to individual mutations or pairs of mutations. Weight factors are positive for mutations or pairs that contribute to resistance, negative for mutations or pairs with a resensitizing effect.

**Methods of tropism testing**

To enter the target cell, HIV binds to the CD4 receptor and so-called chemokine co-receptors, of which the most important are CCR5 and CXCR4. Dependent on the use of co-receptors ("tropism") the virus is classified as CCR5-("R5"-)tropic or CXCR4-("X4"-)tropic. Viral strains using both co-receptors are called dual-tropic. Since tropism tests cannot distinguish between dual-tropic viral isolates and a mixture of R5- and X4-tropic viral isolates, the term dual/mixed (D/M) tropic is used.

Analogous to resistance testing, tropism testing can be performed genotypically or phenotypically. In the European guidelines concerning the use of tropism testing, both the enhanced sensitivity Trofile assay and V3 loop population sequencing were recommended (Vandekerckhove 2011). However, the choice of the test should be based on local capacity, logistics, cost and turnaround time. The preferred method of analysis for patients with viral load levels <1000 copies/ml is the V3 loop population sequencing of viral RNA or proviral DNA in case of very low or undetectable plasma viremia.

**Phenotypic tropism testing**

Due to its use in clinical trials, Trofile™ is the best-known phenotypic tropism test. The original standard test had a sensitivity limit of 5 to 10%. With the enhanced sensitivity Trofile™ assay (ESTA) minor viral populations can be detected that comprise less than 1% of the total virus population. Another phenotypic test is Phenoscript® ENV (EuroFins/VIRalliance). An 85% agreement between both assays has been reported (Skrabal 2007).

**Genotypic tropism testing**

For genotypic tropism analysis, the V3 domain of the gp120 gene – which is crucial for co-receptor binding and encodes for the viral tropism – is sequenced. Web-based bioinformatic tools are used to predict viral tropism from the respective nucleotide sequence. These tools use methods like the charge rule, support vector machines or decision trees (Skrabal 2007, Garrido 2008, Obermeier 2008). Tropism prediction tools for genotypic sequences can be found at:

- geno2pheno [http://coreceptor.bioinf.mpi-sb.mpg.de/cgi-bin/coreceptor.pl](http://coreceptor.bioinf.mpi-sb.mpg.de/cgi-bin/coreceptor.pl)

The interpretation with the co-receptor tool of geno2pheno is widely used and shows good concordance with ESTA (Prosperi 2010). In contrast to phenotypic analysis, genotypic analysis cannot distinguish between X4-tropic and dual-tropic or mixed populations. The result of the geno2pheno co-receptor tool is the so-called false pos-
itive rate (FPR), which is the probability of classifying an R5-virus falsely as X4. A false positive rate of 0.1% means that X4-tropism is very likely, whereas a FPR of 90% means that X4-tropism is very unlikely because an X4-prediction would be false with a 90% probability.

The current FPR cut-offs recommended in national and international guidelines range between <5–10% for X4 prediction and ≥10–20% for R5 prediction. For tropism testing from proviral DNA, which is used in case of undetectable viral load or low level viremia, the same FPR cut-offs can be used. The European guidelines recommend triplicate PCR amplification and sequencing (which is expensive and labor-intensive). The corresponding FPR when using the geno2pheno co-receptor interpretation tool should be 10% to discriminate between R5- and X4-tropic virus. In case of single testing the FPR should be increased to 20% (Vandekerckhove 2011). The German guidelines do not recommend multiple testing. For R5 prediction an FPR of ≥15% is recommended, for X4 prediction an FPR of ≤5% is recommended.

For indeterminate results between 5 and 15% the use of CCR5 antagonists should be carefully weighed against other therapeutic options (Walter 2012). As for genotypic resistance testing, a distinction is made between standard population sequencing (detecting X4-tropic virus variants if they comprise at least 20% of the total virus population) and ultrasensitive methods (such as ultra-deep sequencing (UDS) with detection limits of a few percent or less).

In a study using maraviroc+atazanavir/r in ART-naïve patients, ESTA was used for tropism testing. All samples were analyzed using population sequencing and UDS, each with a FPR of 5.75%. Using ESTA, R5-tropic virus was found in 123 samples (69%); D/M-tropic virus was detected in 39 samples (22%). In 16 samples, tropism testing failed. Using population sequencing, R5-tropic virus was found in 82% of samples, X4-tropic virus in 15%. In 3% of samples genotyping was not successful. The concordance for R5-tropic virus between population sequencing and UDS was 95%. Of samples classified as R5-tropic by population sequencing, only 3% (3 of 114) harbored X4-tropic virus of more than 2%. For all failing ESTA measurements viral tropism was determined with population sequencing (Portsmouth 2010a).

The advantages of genotypic tropism testing are its wide availability and the rapid results. Analyses that have correlated genotypic and phenotypic tropism results with virologic response showed that the two methods can be considered equivalent (Braun 2009, Harrigan 2009).

Table 4: Advantages (+) and disadvantages (−) of genotypic and phenotypic tropism testing, (examples using geno2pheno and Trofile™)

<table>
<thead>
<tr>
<th>Phenotypic tropism test ESTA™</th>
<th>Genotypic tropism test geno2pheno</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phenotypic analysis using the complete gp160</td>
<td>• Genotypic analysis based on V3 sequence</td>
</tr>
<tr>
<td>• Result derives from cell culture</td>
<td>• Prediction of tropism using bioinformatics tools</td>
</tr>
<tr>
<td>+ Validated by clinical data</td>
<td>+ Validated by clinical data</td>
</tr>
<tr>
<td>+ Differentiation of R5-, X4- and D/M (dual/mixed)-tropic HIV</td>
<td>+ Result based on the exclusion of X4-tropic virus</td>
</tr>
<tr>
<td>− Commercial test / expensive</td>
<td>+ Feasible in molecular biology laboratories</td>
</tr>
<tr>
<td>− Result within about ≥3-4 weeks</td>
<td>+ Widely available / less expensive</td>
</tr>
<tr>
<td>− Required viral load of ≥500 – 1,000 copies/ml when using RNA</td>
<td>+ Result within about 5 days</td>
</tr>
<tr>
<td>+ Feasible in case of low/undetectable plasma viral load when using proviral DNA</td>
<td>− Required viral load of ≥500 – 1000 copies/ml when using RNA</td>
</tr>
<tr>
<td>+ Genotyping of proviral DNA in case of low or undetectable viral load</td>
<td></td>
</tr>
</tbody>
</table>
Another advantage of genotypic tropism testing is its feasibility in samples with undetectable plasma viral load. Genotyping of proviral DNA is of clinical importance in successfully treated patients requiring a treatment change due to side effects. According to the results of parallel measurements, X4 tropism tends to be detected slightly more often in cell-associated proviral DNA than in plasma RNA (Verhofstede 2009). By sequencing proviral DNA, good concordance has been shown between Trofile™ results and the genotypic tropism predictions (Obermeier 2008). In the meantime, Trofile™ has also become available for the testing of proviral DNA.

Mechanisms of resistance

NRTIs are prodrugs that only become effective after being intracellularly converted to triphosphates. Nucleotide analogs require only two instead of three phosphorylation steps. Phosphorylated NRTIs compete with naturally occurring dNTPs (deoxynucleotide triphosphates). The incorporation of a phosphorylated NRTI into the proviral DNA blocks elongation of the DNA, resulting in interruption of the chain. There are two main biochemical mechanisms that lead to NRTI resistance (De Mendoza 2002):

Sterical inhibition is caused by mutations enabling reverse transcriptase to recognize structural differences between NRTIs and dNTPs. Incorporation of NRTIs is then prevented in favor of dNTPs, e.g., in the presence of mutations M184V, Q151M, L74V, or K65R (Naeger 2001, Clavel 2004).

Phosphorolysis via ATP (adenosine triphosphate) or pyrophosphate leads to the excision of the NRTIs already incorporated into the growing DNA chain. This is the case with M41L, D67N, K70R, L210W, T215Y and K219Q (Meyer 2000). Phosphorolysis leads to cross-resistance between NRTIs, the degree of which may differ between agents (AZT, d4T > abacavir > ddI > 3TC). Contrary to the excision mutations, K65R leads to a decreased excision of all NRTIs when compared to wild-type, resulting in a greater stability once incorporated. For K65R, the combined effect of its opposing mechanisms (decreased incorporation and decreased excision) results in a decreased susceptibility to NRTIs but an increased susceptibility to AZT (White 2005).

NNRTIs also inhibit the viral enzyme reverse transcriptase (RT). NNRTIs are small molecules that bind to the hydrophobic pocket close to the catalytic domain of the RT. Mutations at the NNRTI binding site reduce the affinity of the NNRTIs to the RT and thus lead to a loss of antiviral activity due to NNRTI treatment failure. Whereas a single mutation can confer resistance to first generation NNRTIs, resistance patterns are more complex for second generation NNRTIs (Vingerhoets 2008, Molina 2008).

PIs hinder the cleavage of viral precursor gag-pol-polyprotein by the HIV protease, thereby producing immature, non-infectious viral particles. PI resistance usually develops slowly, as several mutations must first accumulate. This is also referred to as the genetic barrier. For PIs, a distinction is made between major (or primary) and minor (or secondary) mutations.

Table 5: PI-specific resistance mutations

<table>
<thead>
<tr>
<th>Major mutations</th>
<th>Minor mutations (a selection)</th>
</tr>
</thead>
</table>

(HIV Drug Resistance Database, Sequence Analyses Program, version 6.2.0; The table was updated on 2012-06-13; http://hivdb.stanford.edu/pages/documentPage/PI_mutationClassification.html)
Major mutations are responsible for phenotypic resistance. They are selected early in the process of resistance to a drug and/or are located within the active site of the target enzyme, the HIV protease. They reduce the ability of the protease inhibitor to bind to the enzyme. Major or primary mutations may also lead to reduced activity of the protease.

Minor mutations (often referred to as secondary mutations) are located outside the active site and usually occur after major mutations. Minor mutations are commonly found at polymorphic sites of non-B subtypes. Minor mutations compensate for the reduction in viral fitness caused by major mutations (Nijhuis 1999, Johnson 2007b). Mutations at positions 20, 36, 63, and 77 are polymorphisms which are observed without specific selective drug pressure particularly in non-B subtypes. Their contribution to resistance is minor and depends on the presence of other mutations.

Entry inhibitors prevent HIV from entering target cells. The first step in cell entry occurs when the HIV envelope glycoprotein gp120 binds to the CD4 receptor leading to conformational changes in gp120 and enabling the binding of the V3 loop of gp120 to the chemokine co-receptors, CCR5 or CXCR4, of the target cell. Interactions between the two heptad repeat regions HR1 and HR2 within the transmembrane glycoprotein subunit gp41 lead to a conformational change in gp41 and enable fusion of the viral and cellular membranes.

CCR5 antagonists bind to the CCR5 co-receptor and thereby impede interaction with the viral surface protein gp120 necessary for entry into the target cell. The fusion inhibitor T-20, a synthetic peptide consisting of 36 amino acids, mimics the C-terminal HR2 domain of gp41 and competitively binds to HR1. Thus, interactions between HR1 and HR2 are blocked and the conformational change of gp41 that is necessary for fusion of virions to host cells is inhibited. A single amino acid substitution in HR1 can reduce the efficacy of T-20.

Integrase inhibitors prevent insertion of HIV DNA into the human DNA genome. The primary role of viral integrase is to catalyze the insertion of the viral cDNA into the genome of infected cells. Integrase inhibitors like raltegravir or elvitegravir block the strand transfer step. They bind to the catalytic pocket of the integrase and are transported as a component of the DNA/integrase pre-integration complex into the cell nucleus where strand transfer activity of integrase is inhibited. The selection of key mutations in the integrase gene confers resistance to integrase inhibitors. Strand transfer as well as the preceding step of 3’ processing (cleavage of the terminal dinucleotides from both 3’ ends of viral cDNA to which integrase binds) can be affected by these mutations. Different resistance pathways have been observed. The accumulation of additional mutations leads to a further decrease in susceptibility (Fransen 2008, Miller 2008).

Transmission of resistant HIV strains

The prevalence of mutations already present in treatment-naïve patients differs in demographic regions. Prevalence of more than 20% has been observed in large US cities with significant populations of homosexual men and a long history of access to antiretroviral treatment. Data on the incidence and prevalence of primary drug resistance published before 2007 should be interpreted with caution, since a consensus definition of transmitted genotypic drug resistance had not been established at that time. In 2007, an international research group agreed upon criteria defining mutations indicative for transmitted drug resistance. The corresponding list of mutations was again updated in 2009 (Bennett 2009). This standardization allows for comparisons of epidemiological data across geographic regions and periods of time.
In the German seroconverter study of the Robert Koch Institute, the prevalence of resistance mutations was 12.2% between 1996 and 2009. Although the proportion of isolates with primary resistance remained stable during the observation period, the proportion of NRTI-resistant virus populations decreased (to 6.2%), while there was a trend toward more NNRTI resistance (2.4%) (Bartmeyer 2010, Meixenberger 2011). Dual- or triple-class resistance was rare with 1.5% and 0.3%, respectively. In chronically-infected patients of the German RESINA study, the proportion with primary resistance was 9.2% between 2001 and 2009 (Oette 2012). 

European-wide data from the years 2006–2007 derive from SPREAD (Strategy to Control Spread of HIV Drug Resistance), a program established to monitor primary resistance in newly infected patients and ART-naïve patients. 9.7% of newly diagnosed HIV+ patients were infected with virus harboring at least one resistance mutation. The proportion of isolates with NRTI, NNRTI and PI resistance was 5.7%, 3.9% and 1.7%, respectively. Two class resistance was present in less than one percent (Frentz 2011). 

Ultraspesitive methods such as allele-specific real-time PCR (AS-PCR) or ultra-deep sequencing detect resistance mutations more often than conventional sequencing methods. In a Swiss study, M184V and/or K103N quasi-species were detected as minor variants in 18% (13/74) of patients with primary HIV infection and documented wild-type virus (Metzner 2007a). In a study from Atlanta focusing on L90M, M41L, K70R, K103N, Y181C, M184V, T215F and T215Y, resistance mutations were detected in 39/256 acutely or chronically infected patients (16%) (Johnson 2007a). In a British study investigating 165 anonymized samples from the years 2003–2006, drug resistance was detected in 13% of samples when using the standard assay compared to 19% when using an assay more sensitive for K103N, Y181C or M184V. In particular, the proportion of M184V isolates increased from 0.6% to 8%. The prevalence of drug resistance was almost the same for treatment-naïve patients with either primary or chronic HIV infection (19% and 20%) confirming data showing that primary resistance can persist for a long time (Buckton 2010, Pao 2004). In a Spanish study a (partial) reversion of transmitted drug resistance was observed in only 3 of 10 seroconverters after a median time of 41 months (De Mendoza 2005b). Contrary to K103N or M184V, K65R is a rare primary mutation. K65R was observed in only 4/194 patients (2%) as a minority variant at initiation of treatment (Metzner 2007b). 

Transmitted resistance mutations can limit further treatment options and reduce treatment response rates (Little 2002, Wittkop 2010). This was also confirmed by a meta-analysis for minor NNRTI-resistant virus variants (10 studies, 985 patients) (Li 2011). However, with special regard to existing resistance, treatment success is often possible (Oette 2006, Reuter 2008). 

Table 6: Prevalence of resistance prior to initiation of therapy (a selection)

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Period</th>
<th>Patient population</th>
<th>N</th>
<th>Primary resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartmeyer 2010</td>
<td>Germany</td>
<td>1996–2007</td>
<td>Seroconverters</td>
<td>1298</td>
<td>12.4%</td>
</tr>
<tr>
<td>De Mendoza 2005</td>
<td>Spain</td>
<td>1997–2004</td>
<td>Seroconverters</td>
<td>198</td>
<td>12.1%</td>
</tr>
<tr>
<td>Recordon 2007</td>
<td>France</td>
<td>1996–2005</td>
<td>Seroconverters</td>
<td>194</td>
<td>15.7%</td>
</tr>
<tr>
<td>Jain 2010</td>
<td>San Francisco</td>
<td>2002–2009</td>
<td>Seroconverters</td>
<td>372</td>
<td>16.0%</td>
</tr>
<tr>
<td>Frentz 2011</td>
<td>Europe</td>
<td>2006–2007</td>
<td>Newly diagnosed</td>
<td>1630</td>
<td>9.7%</td>
</tr>
<tr>
<td>Jayaraman 2006</td>
<td>Canada</td>
<td>1999–2003</td>
<td>Newly diagnosed</td>
<td>768</td>
<td>10.2%</td>
</tr>
<tr>
<td>Nkengafac 2007</td>
<td>Cameroon</td>
<td>2005–2006</td>
<td>Newly diagnosed</td>
<td>180</td>
<td>7.8%</td>
</tr>
<tr>
<td>Oette 2012</td>
<td>Germany</td>
<td>2001–2009</td>
<td>Chronically infected</td>
<td>2078</td>
<td>9.2%</td>
</tr>
<tr>
<td>Cane 2005</td>
<td>Great Britain</td>
<td>1996–2005</td>
<td>Chronically infected</td>
<td>2357</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

* (18.2% in subtype B, 8.3% in non-B)
In early 2005, one patient from New York caused a sensation: he was infected with a multidrug resistant virus with a replication capacity comparable to that of wild-type virus. As a consequence, his remaining treatment options were very limited. Even though the transmission of multidrug resistant virus and rapid clinical progression are rare events, this case report demonstrates the possible clinical consequences of primary drug resistance (Markowitz 2005). In 2010 the transmission of a virus resistant to integrase inhibitors was reported for the first time. The virus also harbored NRTI, NNRTI and PI resistance mutations. Therefore the author recommended sequencing the integrase gene in cases of transmitted multidrug resistance (Young 2010).

Clinical studies

The clinical importance of resistance testing before making changes to therapy has been demonstrated in several prospective, controlled studies using genotypic tests such as VIRADAPT, CPCRA 046 or Havana (Durant 1999, Baxter 2000, Tural 2002) as well as in studies using phenotypic tests like VIRA 3001 (Cohen 2002). Patients whose physicians had access to information about existing mutations before the therapy was changed usually had more significant decreases in their viral loads than patients in whom ART was changed without knowledge of the resistance profile. With regard to the increased number of NRTIs, NNRTIs or PIs with different resistance profiles, the clinical relevance of resistance testing might be even greater today. For ethical reasons, studies that prospectively examine the benefits of resistance analysis, i.e., for regimens including new drug classes such as integrase inhibitors or CCR5 antagonists, are no longer justifiable.

A resistance test before ART initiation is part of routine diagnosis in regions where the transmission of resistant HIV viruses is seen. The impact of transmitted HIV resistance on the initial success of ART was investigated in a retrospective analysis of the Eurocoord-CHAIN project. Of 10,458 patients initiated on ART in 1998, blood samples from the period before therapy were retrospectively examined for resistance. The initial regimens’ activities were essential for durable therapeutic success. Patients who were treated with only partially active regimens had a 2.6-fold higher risk of treatment failure (Wittkop 2010).

Resistance testing at time of treatment initiation and at time of virological failure is an integral part of national and international guidelines for the management and treatment of HIV infection.

Interpretation of genotypic resistance profiles

The algorithms cited in the following chapter are only indicative. Treatment decisions should not be made based on these data alone. We recommend the use of a resistance interpretation system listed in Table 3.

NRTIs

For several NRTIs such as 3TC and for NNRTIs a high degree of resistance develops following just a single mutation. For this reason, such drugs should only be used as part of highly effective regimens. However, the 3TC-specific mutation, M184V, also reduces viral replication capacity (often referred to as reduced viral fitness) by 40–60% (Miller 2003, Deval 2004). After 52 weeks with 3TC monotherapy, the viral load remained 0.5 log below the initial levels despite early development of the M184V mutation (Eron 1995). When compared to treatment interruptions, continuous
monotherapy with 3TC delays virological and immunological deterioration (Castagna 2006). FTC has nearly the same genotypic and phenotypic resistance pattern as 3TC (Borroto-Esoda 2007). M184I is often detected before M184V, but is then quickly replaced by M184V (Schuurmann 1995). Depending on the co-medication, M184V is more common on 3TC than on FTC, especially in combination with tenofovir (Svicher 2010). However, in the HEAT study which compared TDF+FTC+lopinavir/r with ABC+3TC+lopinavir/r, M184V was more common on FTC (Smith 2008).

T69I is a rare mutation, observed in 0.5% of treated patients and 0.2% of ART-naive patients. This mutation causes high-level resistance to 3TC, FTC, and possibly also to tenofovir (Svicher 2010). Thymidine analog mutations, known as TAMs, include the mutations M41L, D67N, K70R, L210W, T215Y and K219Q, which were first observed on treatment with AZT (Larder 1989), but were also selected on d4T (Loveday 1999).

There are two mutation pathways: the so-called TAM-1 path with 41L, 210W and 215Y, and the TAM-2 path with D67N, K70R, T215F, and K219Q/E (Flandre 2004). Depending on the individual TAMs and their combination, AZT resistance factors and the degree of resistance vary largely. The variation of the corresponding d4T resistance factor is much smaller. However, for full resistance the resistance factor is much lower for d4T than for AZT. This demonstrates that resistance factors of different drugs cannot be compared. On AZT- and d4T-based regimens the TAM-1 pathway is more commonly observed (Cozzi-Lepri 2009).

The term NAMs (nucleoside analog mutations) is sometimes used instead of TAMs when these mutations are associated with cross-resistance to other nucleoside analogs (Harrigan 2000). In particular, the combination of certain TAMs can largely affect the effectiveness of abacavir, didanosine and tenofovir (Table 7). TAMs do not arise on ABC, ddI or TDF, but can be re-selected. The V75T mutation, which is associated with an approximately 5-fold increase in resistance to d4T and ddI, is only rarely observed (Lacey 1994).

Under failing therapy with ABC or ddI the mutation L74V/I usually occurs; the mutation K65R is less common (Miller 2000, Larder 2001). Y115F is a specific abacavir-associated resistance mutation, which also affects the susceptibility to TDF. Tenofovir primarily selects for the K65R mutation and leads to an (intermediate) resistance to tenofovir, abacavir, ddI, 3TC, FTC, and possibly d4T (Shafer 2002, Garcia-Lerma 2003). Although K65R may emerge on abacavir, K65R was rarely seen before the introduction of tenofovir. The reason is that with combination therapies containing AZT, the incidence of the K65R mutation is lower. Prior to tenofovir, abacavir was mainly used as part of the fixed-dose combination AZT+3TC+ABC (Trizivir®).

K65R seldom emerges in the presence of TAMs. Since K65R and TAMs represent two antagonistic resistance pathways (see Mechanisms of resistance), K65R is only rarely observed on the same genome together with TAMs, and almost never together with L74V (Wirden 2005). Corresponding to observations made in large clinical trials using tenofovir within divergent (PI- or NNRTI-containing) treatment regimens, the incidence of K65R stabilized at ≤5%. However, virological failure of other triple-nuke combinations such as ABC+3TC+TDF or TDF+3TC+ddI was often associated with the development of the K65R (Gallant 2003, Landman 2003). The main reason for the high failure rate seems to be the low genetic barrier of these regimens: the emergence of the K65R induces a loss of sensitivity to all three drugs. K65R increases sensitivity to AZT and induces a resensitization to AZT in the presence of (few) TAMs (White 2005, Underwood 2005). Vice-versa, TAMs reduce the K65R-associated resistance to TDF, ABC, and ddI (Parikh 2007).
As with M184V, the mutation K65R leads to a reduction in the viral replication capacity (RC), which is not the case with TAMs or the L74V/I. The median RCs for viruses with M184V/I (n=792), K65R (n=72) or L74V/I (n=15) alone were 68% (p<0.0001), 72% (p<0.0001) and 88% (p=0.16), respectively (McColl 2005). If both mutations K65R and M184V were present, an RC of only 29% was observed (White 2002, Deval 2004).

Less frequently than K65R, the mutation K70E or K70G was observed on failing therapy with tenofovir, particularly in NRTI-based regimens with ABC and 3TC (Delaugerre 2008). M70E and K65R may be observed simultaneously, but it is unlikely that these mutations emerge on the same genome (Lloyd 2005). There is one case report of the development of K70E and M184V during therapy with TDF and FTC, which were then replaced by K70G and M184V. Both mutations were located on the same genome and conferred phenotypic resistance to 3TC, FTC, ABC, ddI, and TDF, but not to AZT or d4T (Bradshaw 2007).

The 3TC-associated mutation, M184V, as well as the L74V mutation and the NNRTI-specific mutations, L100I and Y181C, may have an antagonistic effect on the further development of resistance (Vandamme 1999, Underwood 2005).

M184V induces re-sensitization to AZT and d4T, resulting in a reduction of IC50 by 50 and 30%, respectively. L74V/I with or without M184V leads to a reduction in IC50 of about 70%. However, re-sensitization is of clinical relevance only if there are no more than three other AZT- or d4T-associated mutations present (Underwood 2005).

The M184V mutation also increases sensitivity to tenofovir (Miller 2001, Miller 2004). In contrast, the presence of M184V plus multiple NAMs or mutations at positions 65, 74 or 115 increases resistance to ABC (Harrigan 2000, Shafer 2003).

So-called multidrug resistance (MDR) to all nucleoside analogs – except 3TC and probably FTC – is established if one of the following combinations occurs: T69SSX, i.e., the T69S mutation plus an insertion of 2 amino acids (SS, SG or SA) between positions 69 and 70, plus an AZT-associated mutation or Q151M, plus another MDR mutation (V75I, F77L or F116Y) (Shafer 1995, Masquelier 2001).

The MDR mutation Q151M is relatively uncommon, with a prevalence of less than 5%. Q151M alone leads to intermediate resistance to AZT, d4T, ddI and ABC and involves only a minor loss of tenofovir activity. Q151M combined with mutations at positions 75, 77, and 116 confers high-grade resistance to AZT, ddI, d4T and ABC and intermediate resistance to TDF (Shafer 2003). Instead, the T69SSX insertion induces an approximately 20-fold increase in the resistance to tenofovir (Miller 2001, Miller 2004).

The insertion T69SSX together with the mutation M184V, as well as the mutation Q151M together with M184V, leads to a 70% reduction in viral replication capacity (Miller 2003, White 2004).

In large patient cohorts, quantitative measurements of sensitivity have shown that up to 29% of NRTI-experienced patients have a hypersusceptibility to NNRTIs (i.e., a reduction in the inhibitory concentration by a factor of 0.3–0.6). A reduction in AZT or 3TC sensitivity correlates inversely with an increased NNRTI susceptibility (Shulman 2000). The reverse transcriptase mutations T215Y, H208Y and V118I seem predictive for EFV hypersusceptibility. This is also true for non-thymidine analog-associated NAMs like K65R, T69X, M184V and in particular for the combination K65R+M184V (Whitcomb 2000, Shulman 2004, Coakley 2005a). However, these results have not influenced treatment strategies.
NNRTIs

First generation NNRTIs (efavirenz, nevirapine)

NNRTI resistance mutations may occur individually or in combination. A single mutation can confer high-level resistance to one or more NNRTIs. The relatively frequent K103N mutation leads to a 20- to 50-fold increase in resistance to efavirenz and nevirapine (Petropolus 2000). Y181C/I causes a 30-fold increase in nevirapine resistance, and response to efavirenz is only temporary. G190A is associated with a high degree of nevirapine resistance and an intermediate resistance to efavirenz. G190S and Y188C/L/H are mutations that result in a high degree of resistance against both drugs (Shafer 2003, De Mendoza 2002). Mutations like L101P can confer high-level resistance to first generation NNRTIs. V106A confers a more than 30-fold resistance to nevirapine. In contrast to subtype B virus, V106M more frequently emerges in subtype C virus; V106M confers resistance against both drugs (Grossman 2004). Continued use of first generation NNRTIs is not recommended in the presence of mutations, because further mutations may be selected, which may influence the effectiveness of second generation NNRTIs.

Second generation NNRTIs

Etravirine (ETR) is effective against variants with single NNRTI mutations like K103N, Y188L and/or G190A (Andries 2004). Compared to earlier NNRTIs, etravirine has a higher genetic barrier, probably due to flexible binding to the reverse transcriptase site. High-level resistance is usually seen with more than two mutations (Mills 2007, Katlama 2007, Vingerhoets 2007). In a selection experiment, the dominant viral population harbored, after several in vitro passages, the mutations V179F (a new variant at this position) and Y181C. Other mutations that have been selected in vitro are L100I, E138K, Y188H, G190E, M230L, and V179I (Brilliant 2004, Vingerhoets 2005). The frequently occurring mutation K103N does not affect the effectiveness of etravirine (Vingerhoets 2006).

In the DUET studies, 17 ETR RAMS were identified: V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/F/T, Y181C/I/V, G190A/S and M230L. Based on these mutations, an etravirine resistance score weighting the individual NNRTI mutations was developed. A weighting factor of 3 was attributed to Y181I/V, followed by a weighting factor of 2.5 for L100I, K101P, Y181C, and M230L. The mutations E138A, V106I, G190S, and V179F received a weighting factor of 1.5 and the other mutations were weighted with 1. Total scores of 0–2, 2.5–3.5 and ≥4 corresponded to 74%, 52% and 38% virological response rates in the DUET studies (Vingerhoets 2008).

In a panel of 4248 NNRTI-resistant clinical HIV-1 isolates, the mutations with the highest weight, Y181I and Y181V, had a low prevalence of 1.5% and 0.9%, respectively. The mutation Y181C, which is selected more frequently in patients taking nevirapine than efavirenz, had a prevalence of 32% (Vingerhoets 2008).

Monogram has developed a weighted sum score including 37 mutations with the following weighting factors. Mutations with the highest level of resistance, i.e., L100I, K101P and Y181C/I/V, received 4 points. E138A/G, V179E, G190Q, M230L and K238N received 3 points; 101E, V106A/I, E138K, V179L, Y188L and G190S received 2 points. V90I, A98G, K101H, K103R, V106M, E138Q, V179D/F/I/M/T, Y181F, V189I, G190A/E/T, H221Y, P225H, and K238T contributed with 1 point. A loss of efficacy is likely with a total score of 4 or higher (Haddad 2010).

The effectiveness of rilpivirine (RPV) does not seem to be impaired by single NNRTI resistance mutations such as K103N, V106A, G190S/A; in vitro the following mutations were selected: V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I,
Y181C/I, V189I, G190E, H221Y, F227C and M230I/L (Azijn 2009). In a clinical study involving treatment-naïve patients without any (known) NNRTI mutations most of the in vitro mutations were confirmed (K101E, K103N, E108I, E138K/R, Y181C and M230L) (Molina 2008).

In the Phase III studies ECHO und THRIVE, in which rilpivirine was tested against efavirenz, virological failure was more frequent on rilpivirine (10.5% versus 5.7%), i.e., in patients with viral load levels >100,000 copies/mL at baseline. The development of resistance mutations was more common in patients failing on rilpivirine than in patients failing on efavirenz (63% versus 54%). The most common mutations were E138K (45%), K101E (13%), H221Y (10%), V189I (8%), Y181C (8%) and V90I (8%). In 46%, 31% and 23% of resistant isolates respectively, 1, 2 or 3 NNRTI mutations were detected.

Overall, 15 RAMs were identified as being associated with a decreased susceptibility to RPV: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, M230I/L. These RPV RAMs were identified either (a) in vitro as HIV-1 SDMs conferring phenotypic resistance to RPV (K101P, Y181I, and Y181V with fold-changes (FCs) in IC50 of 51.7, 15.3, and 12.2, respectively); (b) at the time of virological failure in ECHO and THRIVE (K101E, E138K/G, Y181C, H221Y, V179L, F227C, and M230L); (c) in in vitro selection experiments in strains with decreased susceptibility to RPV (E138R and E138Q); and (d) in clinical isolates with an increased FC to RPV (E138A). Cross-resistance to etravirine was commonly observed among patients failing rilpivirine (>90%) (Rimsky 2012).

Besides NNRTI mutations, NRTI mutations were also more frequent among treatment failures on rilpivirine (68% versus 32%) – with primarily M184I on rilpivirine and M184V on efavirenz.

**Protease Inhibitors (PIs)**

The spectrum of PI mutations is very large. Although there is a moderate to high degree of cross-resistance between PIs, the primary mutations are relatively specific for the individual drugs. If treatment is changed early on to another PI combination, i.e., before the accumulation of multiple mutations, the subsequent regimen may be successful. Much data on primary mutations that are selected for early on in the presence of a PI are derived from earlier studies using unboosted PIs. In first-line therapy with ritonavir-boosted lopinavir, fosamprenavir, saquinavir, atazanavir or darunavir, the emergence of major PI mutations was rare (Eron 2006, Walmsley 2007, Clumeck 2007, Gathe 2008, Lataillade 2008, Molina 2008). The development of primary PI resistance in patients failing boosted PI therapy has been observed in few cases (Lanier 2003, Conradie 2004, Friend 2004, Coakley 2005b, Lataillade 2008).

**First generation PIs**

Nelfinavir (NFV) has a specific resistance profile, with the D30N primary mutation and further secondary mutations, resulting in a relatively low degree of cross-resistance to other PIs. Virological failure with nelfinavir can also be associated with the emergence of L90M (Clotet 2002). In subtype B viruses, treatment with nelfinavir generally leads to the emergence of D30N or M46I plus N88S. In subtype C, G and AE viruses, however, the mutations L90M and I84V occur more frequently (Snoeck 2006).

Unboosted saquinavir primarily selects for G48V which leads to a 10-fold decrease in the susceptibility to saquinavir. G48V in combination with L90M reduces susceptibility to an even higher degree (Jakobson 1995). In general, several mutations including I84V/A are required to affect efficacy of ritonavir-boosted saquinavir (Valer...
One study re-evaluated the genotypic interpretation of saquinavir resistance in a retrospective analysis of 138 PI-experienced patients. Here, the presence of 3 to 4 mutations out of L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73ST, 82A/F/S/T, I84V, and L90M was identified as being most strongly associated with reduced virological response (Marcelin 2007a). In contrast, the mutation L76V (observed on failing lopinavir or fosamprenavir) can lead to a clinically relevant re-sensitization for saquinavir (Wiesmann 2011).

**Fosamprenavir:** In patients with virological failure while on amprenavir, the following mutations have been selected: I54L/M, I50V or V32I plus I47V, often together with the mutation M46I (Maguire 2002).

The Zephir study evaluated virological response to treatment with ritonavir-boosted fosamprenavir in 121 treatment-experienced patients. With less than three mutations of L10I/F/R/V, L33F, M36I, M46I/L, I54L/M/T/V, I62V, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I84V and L90M, viral load was reduced by 2.4 logs 12 weeks after treatment initiation compared to only -0.1 log with 4 or more mutations. At least 80% of patients with a maximum of 3 mutations reached a viral load below 400 copies/ml, compared to 35–45% of patients with 4–7 mutations and only 10% of patients with at least 8 mutations (Pellegrin 2005). In a retrospective study in 73 patients receiving fosamprenavir/r, the mutations L10F/I/V, L33F, M36I, I54L/M/V/A/T/S, I62V, V82A/F/C/G, I84V and L90M were associated with reduced virological response. In a univariate analysis the most striking mutations were I54L/M/V/A/T/S, V82A/F/C/G, and L90M: in the case of two mutations, virological response was reduced, while three mutations conferred resistance. N88S/D was associated with an increased response (Masquelier 2008).

L76V rarely selected by fosamprenavir confers resistance also to lopinavir and darunavir (Wiesmann 2011, Delaugerre 2009).

**Lopinavir/r:** As with other boosted protease inhibitors major PI mutations occur very rarely on lopinavir-based first-line therapy. Few case reports of emerging lopinavir resistance have been published. In one patient, virological failure was associated with the occurrence of the V82A followed by the mutations V32I, M46M/I and I47A (Friend 2004). On failing monotherapy three viral isolates harbored L76V (Delaugerre 2009).

The response in patients who had been exposed to first generation PIs correlated with a number of any of the following mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M. Five mutations or less resulted in an increase in the IC50 by a median factor of 2.7; with 6–7 mutations this factor was 13.5, and with at least 8 mutations it was 44 (Kempf 2001). A different algorithm to predict lopinavir resistance also includes mutations at novel amino acid positions. Viruses with any 7 mutations out of L10F/I, K20I/M, M46I, L, I50V, I54A/M/S/T/V, L63T, V82A/F/S as well as G16E, V32I, L33F, E34Q, K43T, I47V, G48M/V, Q58E, G73T, T74S, and L89I/M display approximately a 10-fold increase in the IC50. Mutations at positions 50, 54 and 82 particularly affect the phenotypic resistance. On failing lopinavir, mainly mutations at positions 82, 54 and 46 emerge. Mutations such as L33F, I50V or V32I together with I47V/I are selected less frequently. New mutations at positions 84 or 90 were not observed (Parkin 2003, Mo 2005, Jimenez 2005).

The mutation I47A, which has rarely been observed since the availability of lopinavir, was identified to be associated with lopinavir resistance. I47A reduces the binding affinity to lopinavir and results in an 86- to >110-fold loss of sensitivity. In contrast, I47A leads to saquinavir hypersusceptibility due to an enhanced binding affinity to saquinavir (Kagan 2005).
The mutation L76V, selected for by lopinavir (Delaugerre 2009) and rarely by amprenavir or darunavir, can lead to resensitization to atazanavir, saquinavir and tipranavir – even in the presence of 5–10 PI mutations which normally confer broad PI cross-resistance (Mueller 2004, De Meyer 2008, Wiesmann 2011).

**Atazanavir** is an azapeptidomimetic PI. The resistance profile differs in part from that of other PIs. In patients in whom first-line treatment with atazanavir failed, the mutation I50L – often combined with A71V, K45R, and/or G73S – was primarily observed. On the one hand, I50L leads to a loss of sensitivity to atazanavir; on the other hand, I50L leads to an increased susceptibility to other PIs. Mutants harboring I50L plus A71V showed a 2- to 9-fold increased binding affinity to the HIV protease. Even in the presence of other major and minor PI-mutations I50L can increase susceptibility to other PIs (Colonno 2002, Weinheimer 2005). In PI-experienced patients, the I50L mutation was selected for in only one third of patients failing atazanavir (Colonno 2004).

The accumulation of PI mutations such as L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, L90M, and in particular, I84V, leads to a loss of sensitivity to atazanavir. In the expanded access program using unboosted atazanavir the number of the respective PI mutations correlated with the change in viral load. For unboosted atazanavir, the threshold for resistance is generally met if 3–4 PI mutations are present; for ritonavir-boosted atazanavir, the genetic barrier is higher (Colonno 2004, Gianotti 2005).

In the CASTLE study using ritonavir-boosted atazanavir in treatment-naïve patients, only two patients developed resistance to atazanavir. In one patient with a mutant viral population harboring M46M/I+N88N/S viral load could be re-suppressed without ART change. In the second patient, two-class resistance with PI mutations (V32I, M46I, and L90M) and RT mutations (K65K/R, K70K/E, and M184V) was observed. It is not clear whether minor resistance mutations were already present at baseline (Lataillade 2008).

The Reyaphar score can predict response to ritonavir-boosted atazanavir in pre-treated patients, including mutations at 12 positions (L10I/F/R/V, K20I/M/R, L24I, M46I/L, 154L/M/T/V, Q58E, L63P, A71I/L/V/T, G73A/C/F/T, V771, V82A/F/S/T, I84V and L90M). With less than 5 Reyaphar mutations, the average viral load reduction at 12 weeks was 1.4 logs, compared to only 0.5 log with more than 5 mutations (Pellegrin 2006).

**Second generation PIs**

**Tipranavir**, the first non-peptidic protease inhibitor, shows good efficacy against viruses with multiple PI mutations. Even with reduced susceptibility to darunavir, about half of the 586 isolates proved susceptible to tipranavir (De Meyer 2006). *In vitro*, L33F and I84V are the first mutations selected by tipranavir, but the loss in sensitivity is only two-fold. Selection experiments ended up with viral isolates harbouring 10 mutations (L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V, V82L, I84V) resulting in an 87-fold reduced sensitivity (Doyon 2005).

Due to these and other experiments some mutations were regarded as key mutations, so-called PRAMs (protease inhibitor-associated resistance mutations) which include the following mutations: L33I/V/F, V82A/F/L/T, I84V and L90M. Resistance analyses showed that reduced sensitivity should be expected with at least three PRAMs. However, a sufficient short term viral load reduction of 1.2 logs was seen after two weeks on treatment with boosted tipranavir plus an optimized backbone regimen in patients with at least three PRAMs, compared to only 0.2–0.4 log with amprenavir, saquinavir or lopinavir plus OBR (Cooper 2003, Johnson 2008, Mayers 2004).
In a re-analysis of the Phase II and III trials, some PRAMs were confirmed, but new resistance mutations were also identified (Kohlbrenner 2004). Resistance mutations in clinical isolates of tipranavir-experienced patients included L10F, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V (Croom 2005).

Hence the “unweighted” tipranavir mutation score was developed, involving 21 protease mutations at 16 positions (I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V) (Baxter 2006). This score was followed by a “weighted” tipranavir score based on clinical data of the RESIST trials (Scherer 2007). The respective model includes mutations of the unweighted score plus five mutations which were related to an increased tipranavir susceptibility. Weight factors were assigned to the mutations according to their contribution to resistance. The weights of the mutations add up to the weighted tipranavir score. The major mutations I47V, I54A/M/V, Q58E, T74P, V82L/T, and N83D contribute significantly to resistance and have a greater weight than minor mutations like I10V, M36I, N43T, and M46L. L24I, I50L/V, I54L and L76V are mutations conferring an increase in sensitivity and carry a negative weight. The mutations L33F as well as I13V and H69K, the most commonly observed in non-B subtypes, were removed from this score. Other national resistance algorithms differ particularly in the weighting of mutations (Table 9).

**Darunavir** has also shown good activity against a wide spectrum of PI-resistant viruses. *In vitro*, resistance to darunavir develops more slowly than seen with nelfinavir, amprenavir or lopinavir. After several passages *in vitro*, further mutations were selected in addition to R41T and K70E, leading to a reduced replication fitness. A mutant virus with a more than 10-fold loss in darunavir susceptibility showed a corresponding loss in saquinavir susceptibility, but not for the other PIs (atazanavir was not tested). This means that primary darunavir failure is not necessarily associated with complete cross-resistance to first generation PIs (De Meyer 2003+2005). In the POWER studies, the previous use of fosamprenavir, tipranavir and lopinavir had no impact on virological response rates to darunavir-based HAART. However, since darunavir is chemically similar to amprenavir, antiretroviral treatment with darunavir in patients with key amprenavir RAMs should be considered with caution (Delaugerre 2007).

Eleven mutations at 10 positions were associated with a diminished response to boosted darunavir: V11I, V32I, L33F, I47V, I50V/L, I54L/M, T74P, L76V, I84V and L89V. With three or more of these mutations, the response rate was reduced. Individual mutations appear to influence susceptibility to darunavir in varying degrees. I50V has the highest impact, followed by I54M, L76V and I84V; V32I, and L33F, and I47V have less influence. The weakest impact was associated with V11I, I54L, G73S and L89V. This weighting needs to be validated. New mutations that have occurred on treatment failure with darunavir are V32I, L33F, I47V, I54L, and L89V. The median increase in darunavir IC$_{50}$ was 8.14. Approximately 50% of these isolates were sensitive to tipranavir. The median change in the tipranavir IC$_{50}$ was 0.82. Conversely, over 50% of isolates with reduced tipranavir susceptibility were still sensitive to darunavir (De Meyer 2006, De Meyer 2008, Prezista US Product Information 2006, Johnson 2008). Based on an analysis of the POWER and DUET data, the mutation V82A is positively associated with response to DRV (De Meyer 2009).

A database analysis of 50,000 paired geno- and phenotypes showed that for darunavir-resistant samples (n=2141) between 2006 and 2009 the median for
darunavir resistance factor increased from 38 to 50, whereas the tipranavir resistance factor decreased from 7.6 to 4.3. During this period, an increase of darunavir-associated mutations was observed, probably due to the increased use of the agent: I50V rose from 11 to 15%, I54L from 17 to 33% and L76V from 5 to 9%, respectively. The three mutations E35N, I47A and V82L were associated with resistance to both drugs. L10F, V82F and G48M were associated with darunavir resistance; I54S, I84V and I84C were associated with tipranavir resistance. Due to these at least partially different mutation patterns the sequencing of both drugs may be feasible in specific situations (Stawiski 2010).

Fusion inhibitors

The gp41 genome consisting of 351 codons has positions of high variability and well-conserved regions. Polymorphic sites are observed in all regions of gp41. The heptad repeat 2 (HR2) region has the highest variability. Primary resistance to T-20, the only fusion inhibitor thus far approved, is a rare phenomenon (Wiese 2005). A loss of efficacy is generally accompanied by the appearance of mutations at the T-20 binding site which is the heptad repeat 1 (HR1) region of gp41. Especially affected are the HR1 positions 36 to 45, such as G36D/E/S, 38A/M/E, Q40H/K/P/R/T, N42T/D/S, N43D/K, or L45M/L.

The fold-change in IC50, which ranges from \( \leq 10 \) to several hundred, depends on the position of the mutation and the substitution of the amino acid. The decrease in susceptibility is greater for double mutations than for a single mutation. For double mutations like G36S+L44M, N42T+N43K, N42T+N43S or Q40H+L45M, a fold-change of >250 has been observed. Additional mutations in HR2 also contribute to T-20 resistance (Sista 2004, Mink 2005). In clinical isolates harbouring G36D as a single mutation, a 4- to 450-fold decrease in susceptibility was found. In the isolate showing a 450-fold decrease in susceptibility a heterozygote change at position 126 in HR2 was observed (N/K). Other mutations in the gp41 gene were found at positions 72, 90 and 113 (Sista 2004, Monachetti 2004, Loutfy 2004).

In one small study, 6 of 17 patients with virological failure additionally developed the mutation S138A in the HR2 region of gp41 – mostly combined with a mutation at position 43 in the HR1 region and a range of HR2 sequence changes at polymorphic sites (Xu 2004).

The replication capacity (RC) in the presence of HR1 mutations is markedly reduced when compared to wild-type virus with a relative order of RC wild-type > N42T > V38A > N42T, N43K \( \approx \) N42T, N43S > V38A, N42D \( \approx \) V38A, N42T. Viral fitness and T-20 susceptibility are inversely correlated \( (r=0.99, p<0.001) \) (Lu 2004).

CCR5 antagonists

CCR5 antagonists are to be used in patients with exclusively R5-tropic virus. In the presence of X4-or dual-tropic virus, their use is not recommended. In about 80% of treatment-naive patients and 50–60% of treatment-experienced patients R5-tropic virus is detected. The detection of solely X4-tropic virus is unlikely but possible (Demarest 2004, Brumme 2005, Moyle 2005, Wilkinson 2006, Hunt 2006, Coakley 2006, Melby 2006). The probability of X4-tropic virus populations is higher with reduced absolute and relative CD4 cell counts, both in treatment-naive and treatment-experienced patients (Brumme 2005, Hunt 2006). For treatment-naive patients with a CD4 cell count of less than 200/µl, in only 62% of cases an R5-tropic virus population was detected (Simon 2010).
There are two ways to build up resistance to CCR5 antagonists: a receptor switch from R5- to X4-tropic or dual-tropic viruses or the emergence of mutations that enable the virus to use the CCR5 molecules for entry into the cell in the presence of CCR5 antagonists.

In approximately one third of patients on a failing regimen with maraviroc, a shift from R5- to X4-tropic virus was reported (Heera 2008). In individual cases, a receptor-shift was observed in the control arm as well. Retrospective studies using more sensitive methods have shown that some patients harbored minor X4 variants already at baseline (Mori 2007, Lewis 2007).

On failing treatment with maraviroc or vicriviroc (no longer being investigated) different mutations in the V3 loop of the HIV-1 envelope protein gp120 are detected. Respective resistance patterns were not uniform and included mutations outside the V3 loop. The frequency and clinical relevance of these env mutations is still part of clinical research and resistance analysis is not yet routine. Some of the detected mutations were not associated with an increase in IC50. Instead, phenotypic resistance was characterized by dose-response curves that display a reduction in the maximal inhibition (Mori 2008, McNicholas 2009). Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptors for entry (Landovitz 2006, Westby 2007, Johnson 2008, Craig 2009). Cross-resistance between maraviroc and vicriviroc has been described after several in vitro passages, but cross-resistance to other CCR5 antagonists or complete class resistance including TBR-652 remains to be determined (Palleja 2010). R5-tropic virus with resistance to maraviroc may be suppressed by using monoclonal antibodies, such as PRO 140. In contrast to maraviroc or vicriviroc, PRO 140 binds extracellularly to the CCR5 co-receptor. Therefore, cross-resistance between PRO 140 and maraviroc is unlikely (Jacobson 2009).

**Integrase inhibitors (INIs)**

Sequence analysis of viruses from treatment-naïve patients showed that the integrase gene is very polymorphic, but most of the relevant positions for resistance, such as 148 and 155, are conserved (Hackett 2008). Resistance analysis is currently indicated only in the case of virologically failing therapy with an integrase inhibitor therapy.

**First generation INIs**

*Raltegravir (RAL):* In STARTMRK, a study comparing first-line therapy with RAL plus TDF+FTC with efavirenz plus TDF+FTC, 4 patients had virological failure accompanied by the emergence of RAL RAMs; 42 of 49 patients failed without evidence of resistance. The integrase inhibitor mutation profiles were Q148H+G140S1, Q148R+G140S, Y143Y/H+L74L/M+E92Q+T97T/A and Y143R (Rockstroh 2011). Three RAL resistance pathways have been observed. The key mutations are N155H, Q148K/R/H and less frequently Y143R/C. Mutations observed along with N155H were L74M, E92Q, T97A, V151I, G163R, G163K, or S230R. In the presence of Q148K/R/H the following mutations may occur: L74M, T97A, E138A, E138K, G140A, G140S and G163R, whereas mutations at positions 140 prevail. The mutations N155H and Q148K/R/H do not occur on the same viral genome; this also applies for E92Q and mutations at position 148. The accumulation of additional mutations after the emergence of the key mutations N155H or Q148K/R/H causes an increase in resistance and, depending on the pattern of mutations, also an increase in viral fitness. This is particularly true for the mutation Q148H (Goethals 2008, Hatano 2008). Virus variants harboring N155H plus secondary mutations are often replaced by variants
with higher replicative fitness harboring Q148H + G140S (Fransen 2008, Miller 2008). In order to preserve the efficacy of second generation integrase inhibitors (i.e., dolutegravir), raltegravir should be discontinued after a first key mutation has occurred. Viral populations harboring the mutation N155H can also be replaced by viral populations harboring Y143C/H/R (da Silva 2010). The key mutation Y143H/R/C can involve the mutations E92Q, T97A, V151I, G163R or S230R (Cooper 2007, Fransen 2008, Steigbigel 2008, Hazuda 2007).

Recently, a novel double mutant consisting of T97A + L74M, emerged on failing raltegravir-based therapy (Margot 2011, Molina 2011). It is important to ensure that raltegravir is not used as functional monotherapy in patients with existing resistance mutations. The genetic barrier of raltegravir is not as high as that of boosted PIs, which, unlike raltegravir, can be used as monotherapy in special cases (Gatell 2009).

Elvitegravir (EVP): Primary INI mutations occurring on failing therapy are T66I/A, E92Q/G, T97A, Y143R/H/C, S147G, Q148R/H/K and N155H. E92Q is often associated with the compensatory mutation L68V (Goodman 2008, Margot 2011). Another secondary mutation is H51Y (Margot 2012b). Although there is a high level of cross-resistance between RAL and EVG, the resistance patterns at time of virological failure differ in part. This has been shown in a Phase III trial (Study 183–0145) in pretreated patients. In case of insufficient viral suppression or confirmed viral rebound >400 copies/ml on EVG-based therapy, the most frequently detected mutations were T66I/A (12%) and E92Q (8%). In the raltegravir group, T66I/A did not emerge and E92Q was detected only in 1% (Molina 2011, Margot 2011). T66I confers phenotypic resistance to EVG but not to RAL (mean fold-changes for EVG and RAL: 6.6–15 and 0.5-1.4, respectively). In combination with E92Q, the FCs increase for both, EVG and RAL (mean FCs for EVG and RAL: 190 and 18, respectively). For E92Q alone, the mean FC was between 13.5 and 33 for EVG and between 2.6 and 6.0 for RAL (Kobayashi 2011, Van Wesenbeck 2011, Margot 2012a).

The effectiveness of elvitegravir after failing raltegravir-based therapy is very limited due to a high level of cross-resistance, i.e., with Q148H/R+G140S (McColl 2007, Goodman 2008, DeJesus 2007, Waters 2009, Margot 2011, Margot 2012a). However, the presence of a single RAL RAM, namely Y143R, may allow for subsequent therapy with elvitegravir. On the other hand, single EVG RAMs such as T66I/A or S147G may not reduce the antiviral activity of raltegravir (Molina 2011, Métifiot 2011).

Second generation INIs

The integrase inhibitor dolutegravir (DTG) has a higher genetic barrier than raltegravir and elvitegravir (Kobayashi 2011). FDA and EMA approval are expected in early 2013. In first-line use, dolutegravir (in combination with ABC/3TC or TDF/FTC) showed promising results concerning the development of new resistance mutations. In the dolutegravir arm of the SPRING-2 study no new NRTI or INI mutations emerged during the first 48 weeks (Raffi 2012). Depending on the resistance pattern, little or no cross-resistance to first generation integrase inhibitors was observed in vitro (Lalezari 2009, Sato 2009). In the Viking study, 27 patients with raltegravir-specific resistance mutations and a viral load >1,000 copies/ml were treated with dolutegravir 50 mg QD. At day 11, 21/27 patients had a viral load of <400 copies/ml or a viral load reduction of at least 0.7 log. Resistance mutations at positions 143 and 155 had no impact on the effectiveness, in contrast to mutations at position 148 in combination with two other secondary mutations. With a higher dose of dolutegravir (50 mg twice daily), the
resistance can be overcome at least temporarily (Eron 2011, Soriano 2011). Fold-changes in the IC50 above 2.5 were observed in vitro or ex vivo for the following mutations: I151L (FC 3.6), T66K+L74M (FC 3.5), Q148R (FC 1.6–3.1), E138K+ Q148R (FC 3.0–4.0), G140C+Q148R (FC 4.9), E138K+Q148K (FC 19), G140S+Q148H (FC 2.6–17.7), G140S+Q148H+T92A (FC 14.4), E138A+G140S+Y143H+Q148H (FC 27.1), G140S+Q148R (FC 8.3–9.1), G140S+Q148R+G163R (FC 13.4), T112A+G140S+Q148H+G163R (FC 21.4), Q148R/N155H (FC 10) (Canducci 2011, Kobayashi 2011).

Summary

Resistance and tropism tests belong to the standard diagnostic tools in the management of HIV infection. Primary resistant viral variants can be observed in about 10% of treatment-naïve patients in regions that have access to antiretroviral drugs. Resistance testing prior to initiating ART results in significantly better response rates. The emergence of viral mutants is one of the main causes of virological treatment failure. With the aid of HIV resistance tests, antiretroviral treatment strategies can be improved. Pharmacoeconomic studies have shown that genotypic resistance tests are cost-effective both in treatment-experienced and in ART-naïve patients (Weinstein 2001, Corzillius 2004, Sax 2005). HIV treatment guidelines recommend the use of resistance testing. Newer classes such as integrase inhibitors and CCR5 antagonists should be included in the evaluation of resistance – at least at time of treatment failure and when a treatment change is needed. However, genotyping including sequence analyses of the integrase or envelope genomes is only partially covered by public health insurance in several countries.

Both, genotypic and phenotypic resistance tests as well as genotypic and phenotypic tropism tests show good intra- and inter-assay reliability. The interpretation of genotypic resistance profiles has become very complex and requires constant updating of respective guidelines. The determination of the thresholds associated with clinically relevant phenotypic drug resistance is crucial for the effective use of (virtual) phenotypic testing.

As for of resistance testing, genotyping has become the preferred method of tropism testing in clinical practice. With the co-receptor tool of geno2pheno, viral tropism can be predicted.

Even though treatment failure requires the consideration of all causal factors, such as patient adherence, metabolism of drugs and drug levels, resistance testing and measurement of viral tropism are of great importance in antiretroviral therapy. Finally, it needs to be emphasized that even with the benefit of well-interpreted resistance and tropism tests only experienced HIV practitioners should start, stop or change antiretroviral therapy keeping in mind the clinical and the psychosocial situation of the patient.

Resistance tables

All tables are based on different rules-based interpretation systems, such as HIV-GRADE (http://www.hiv-grade.de), the ANRS-AC 11 Resistance Group (http://www.hivfrenchresistance.org/) and the Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2011) as well as the references mentioned in the text.

These tables are not exhaustive and should not replace resistance interpretation tools (see Table 3) and communication between the practitioner and the laboratory experts in resistance interpretation.
Table 7: Mutations on the reverse transcriptase gene leading to NRTI resistance

<table>
<thead>
<tr>
<th>RTI</th>
<th>Resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>T215 Y/F (esp. with other TAMs)</td>
</tr>
<tr>
<td></td>
<td>≥3 of the following: M41L, D67N, K70R, L210W, K219Q/E</td>
</tr>
<tr>
<td></td>
<td>Q151M (esp. with A62V/F77L/F116Y) or T69SSX (insertion)*</td>
</tr>
<tr>
<td></td>
<td>(Potential resensitizing effect associated with K65R, L74V, Y181C and M184V)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>V75M/S/A/T</td>
</tr>
<tr>
<td></td>
<td>T215Y/F (usually in combination with other TAMs)</td>
</tr>
<tr>
<td></td>
<td>≥3 TAMs*</td>
</tr>
<tr>
<td></td>
<td>Q151M (esp. with A62V/F77L/F116Y) or K65R or T69SSX (insertion)*</td>
</tr>
<tr>
<td></td>
<td>(Potential resensitizing effect associated with L74V, Y181C and M184V)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>M184V + 3 of the following: M41L, D67N, L74I, L210W, T215Y/F, 219Q/E</td>
</tr>
<tr>
<td></td>
<td>≥5 of the following: M41L, D67N, L74I, L210W, T215Y/F, 219Q/E</td>
</tr>
<tr>
<td></td>
<td>K65R or Y115F or L74V</td>
</tr>
<tr>
<td></td>
<td>Q151M (esp. with A62V, F77L, F116Y) or T69SSX (insertion)*</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>M184V/I or T69SSX (insertion)* or K65R (resistance possible)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>M184V/I or T69SSX (insertion)* or K65R (resistance possible)</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>L74V, esp. with T69D/N or TAMs</td>
</tr>
<tr>
<td></td>
<td>Q151M (esp. with A62V/F77L/F116Y) or T69SSX (insertion)*</td>
</tr>
<tr>
<td></td>
<td>K65R</td>
</tr>
<tr>
<td></td>
<td>T215Y/F and ≥2 of the following: M41L, D67N, K70R, L210W, K219Q/E</td>
</tr>
<tr>
<td>Tenofovir DF (TDF)</td>
<td>T69SSX (insertion)*</td>
</tr>
<tr>
<td></td>
<td>≥3 TAMs with M41L or L210W (only partial resistance)</td>
</tr>
<tr>
<td></td>
<td>≥3–5 of the following: M41L, E44D, D67N, T69D/N, L210W, T215Y/F, 219Q/E, K65R or K70E/G</td>
</tr>
<tr>
<td></td>
<td>(Potential resensitizing effect associated with L74V and M184V)</td>
</tr>
</tbody>
</table>

TAMs = thymidine analog mutations
* T69SSX in combination with T215Y/F and other TAMs leads to a high degree of resistance to all NRTIs and tenofovir

Table 8: Mutations on the reverse transcriptase gene leading to NNRTI resistance

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>Relevant resistance mutations and patterns</th>
<th>Further mutations associated with resistance</th>
</tr>
</thead>
</table>
Table 9: Mutations on the protease gene leading to PI resistance

<table>
<thead>
<tr>
<th>PIs</th>
<th>Relevant resistance mutations and patterns</th>
<th>Further mutations associated with resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir/r</td>
<td>I84V/A or 48V/M ≥3 of the following: L10F/I/M/R/V, K20I/M/R/T, L24I, I62V, G73CST, 82A/F/S/T and L90M or ≥4 of the following: L10I/R/V, I54V/L, A71V/T, V77I, V82A/F/S/T and L90M Possible L76V-associated resensitizing effect</td>
<td>≥2 PRAMs*</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>D30N, I84A/V, N88S/D, L90M</td>
<td>V82A/F/S/T and at least 2 of the following: L10I, M36I, M46I/L, I54V/L/M/T, A71V/T, V77I, I84V/L/M/T, A71V/T, V77I, I84V ≥2 PRAMs*</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>I50V, L76V together with other PI mutations V32I plus I47V ≥6 of the following: L10F/I/V, K20M/R, E35D, R41K, I54V/L/M, L63P, V82A/F/T/S, I84V or ≥3 of the following: L10I/R/V, L33F, M36I, M46I/L, I54L/M/T, V32I, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I47V and L90M or ≥3 of the following: L10F/I/V, L33F, M46I/L, I47V, I54L/M/V/A/T/S, A71I, G73S/A/C/T, V82A/F/C/G and L90M</td>
<td>≥2 PRAMs*</td>
</tr>
<tr>
<td>Atazanavir/r (300/100 mg QD)</td>
<td>≥7 mutations/points of the following: K20M/R/V, L33F, E35G, N43T, M46L, I47V, ISOL/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V; V82L/T and I84V with twofold points score Score &gt;10 of the following: I10V (+1), L24I (-2), M36I (+2), N43T (+2), M46L (+1), I47V (+6), ISOL/V (-4) ISOL/M/V (+3), ISOL/M/V (+4)</td>
<td>6 mutations/points of the following: K20M/R/V, L33F, E35G, N43T, M46L, I47V, ISOL/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V; V82L/T and I84V with twofold points score Score 3-10 from I10V (+1), L24I (-2), M36I (+2), N43T (+2), M46L (+1), I47V (+6), ISOL/V (-4) ISOL/M/V (+3), ISOL/M/V (+4)</td>
</tr>
</tbody>
</table>
Table 9 (continued)

<table>
<thead>
<tr>
<th>PI</th>
<th>Relevant resistance mutations and patterns</th>
<th>Further mutations associated with resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I54L (-7) Q58E (+5), T74P (+6), L76V (-2), V82L/T (+5), N83D (+4), I84V (+2)</td>
<td>I54L (-7) Q58E (+5), T74P (+6), L76V (-2), V82L/T (+5), N83D (+4), I84V (+2)</td>
</tr>
<tr>
<td></td>
<td>Possible L76V-associated resensitizing effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Further resistance-ass’d mutations: I54S, I84C</td>
<td></td>
</tr>
</tbody>
</table>

Darunavir/r

≥4 of the following: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V (with V32I, I50V, I54M, L76V and I84V having a higher impact)

Further resistance-ass’d mutations: L10F, E35N, I47A, V82L, G48M, V82F

≥3 of the following: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V (with I50V, I54M, L76V and I84V having a higher impact)

* PRAMs (protease inhibitor resistance-associated mutations) include the following mutations: L33I/F/V, V82A/F/S/T, I84V and L90M. They lead to high PI cross-resistance

Table 10: Mutations leading to entry inhibitor resistance

<table>
<thead>
<tr>
<th>Fusion inhibitor</th>
<th>Resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-20</td>
<td>G36A/D/E/S/V or I37V or 38A/M/E/K/V or Q39R Q40H/K/P/R/T or N42T/D/S or N42T+(N43S/N43K) N43D/KH/S or L44M or L44M+ G36S or L45M/L/Q</td>
</tr>
<tr>
<td>CCR5 antagonists</td>
<td>Individual mutations described as resistance-associated; no consistent pattern</td>
</tr>
</tbody>
</table>

The reduction in susceptibility is generally higher for double than for single mutations

Table 11: Mutations on the integrase gene leading to raltegravir resistance (and probably cross resistance to elvitegravir)

<table>
<thead>
<tr>
<th>Integrase inhibitors</th>
<th>Resistance mutations (Resistance pathways and key mutations)</th>
<th>Other mutation- and resistance-profiles conferring or increasing resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>Q148H/G/K/R/E N155H Y143H/R/C The appearance of additional mutations produces an increase in the level of resistance.</td>
<td>L74M E92Q/V T97A E138A/K G140A/S V151I/A/L E157Q G163R/K S230R E157Q</td>
</tr>
</tbody>
</table>
Table 11 (continued)

<table>
<thead>
<tr>
<th>Integrase inhibitors</th>
<th>Resistance mutations (Resistance pathways and key mutations)</th>
<th>Other mutation- and resistance-profiles conferring or increasing resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir</td>
<td>T66I/A E92Q T97A S147G Q148R N155H E157Q S230R</td>
<td>H51Y L68Q V72I Q95K E138K G140S</td>
</tr>
</tbody>
</table>

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PART 3

AIDS
11. Opportunistic Infections (OIs)

CHRISTIAN HOFFMANN

In Western industrialized countries, many opportunistic infections (OIs) that in previous years were considered prevalent are now quite rare. This is particularly true for infections associated with severe immunodeficiency, such as CMV and MAC. The incidence of these OIs has been reduced to less than one-tenth of their frequency in the pre-HAART era (Brooks 2009, Buchacz 2010). ART has not only decreased the incidence of OIs, but it has also changed the course of OIs considerably. In the early years of the AIDS epidemic, the life expectancy of individuals diagnosed with their first AIDS defining illness was at most two to three years. Today, however, many patients now live with AIDS for 15 years or longer. In our own clinical study of 144 patients with cerebral toxoplasmosis, data from 1990–1993 indicated a 5-year survival rate of 8%; it climbed to 30% by 1994–1996, then to 80% since 1997 (Hoffmann 2007).

Up to 90% of patients who develop AIDS or severe opportunistic infections are unaware of their HIV status. Typically, these patients seek medical attention late and when their overall health condition is serious. Since AIDS remains life-threatening, every HIV clinician should be familiar with the diagnosis of OIs and their respective therapy. Even with recent improvements, many challenges still exist. First, there is still no adequate treatment available for diseases such as PML or cryptosporidiosis. Second, resistance to treatment has become an increasing problem in OIs such as PCP. Even today OIs like PML have a mortality rate comparable to that of a non-Hodgkin lymphoma (ART-CC 2009). Third, ART does not always lead to immediate improvement. ART may even complicate things, given the atypical course of a variety of diseases with ART (see the separate sub-chapter on “Immune Reconstitution Inflammatory Syndrome”, IRIS). Unfortunately, there are no detailed guidelines for OI prophylaxis outside the US, and the US recommendations were last updated in 2008 (www.aids.info); these cannot always be adopted elsewhere. Moreover, in small HIV centers or regions with low HIV prevalence, diagnostic problems for many OIs may occur, due to a lack of familiarity with and inability to recognize these rarer pathogens. Therefore, it is highly recommended that specimens be sent to specialized reference laboratories. If needed, further advice can be sought from a specialized clinician or a clinical HIV center.

The predominant rule for nearly all OIs is that the poorer the immune status of the patient, the earlier the invasive diagnostic procedures should begin. The primary aim should not be to spare patients the unpleasant procedures associated with extensive diagnostic testing. Moreover, diagnostic tests must be repeated if the results are inconclusive and nothing is identified the first time. Also, treatment should be initiated rapidly.

The second rule is that many OIs can be excluded if the immune status is known. Table 1 indicates the CD4 cut-off values and the rates of certain OIs.

Table 1: Important cut-offs for CD4 T cells, above which particular AIDS-related illnesses are unlikely. However, exceptions are always possible

<table>
<thead>
<tr>
<th>No cut-off</th>
<th>Kaposi's sarcoma, pulmonary tuberculosis, HZV, bacterial pneumonia, NHL</th>
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<tbody>
<tr>
<td>&lt;250/μl</td>
<td>PCP, esophageal candidiasis, PML, HSV</td>
</tr>
<tr>
<td>&lt;100/μl</td>
<td>Cerebral toxoplasmosis, cryptococcosis, miliary tuberculosis, HIV</td>
</tr>
<tr>
<td>&lt;50/μl</td>
<td>CMV retinitis, atypical mycobacteriosis</td>
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</table>
The third OI rule is that if ART is not already in place, then it should be started as quickly as possible. Immune reconstitution is the best protection against relapses or other OIs. For patients with some OIs, such as PML or cryptosporidiosis, which have no specific therapy, starting ART is the best hope. Especially in these cases there is no time to waste. ART should also be started rapidly in cases of PCP or toxoplasmosis. Although OI therapy is not without toxicity and problems regarding interactions the choice of antiretroviral drugs has increased making it easier to react to side effects. In ACTG 5164, a total of 282 subjects with an acute OI (63% PCP) were randomized to initiate ART immediately or after OI treatment (Zolopa 2009). At 48 weeks significantly less mortality and AIDS-related infections occurred in the group starting ART immediately. CD4 T cell counts also increased more rapidly. The risk of changing ART was slightly higher in the immediate group, although not the number of adverse events, hospitalizations or cases of IRIS. ACTG A5164 provides clear arguments for immediate initiation of ART when PCP is diagnosed. However, this does not necessarily apply to all OIs (Lawn 2011). Two randomized studies in patients with cryptococcal meningitis (Makadzange 2010) and tuberculous meningitis (Torok 2011) showed unfavorable effects when starting ART too early (see chapter on Late Presenters).

The following chapter is intended to be a relevant practical overview and does not include clinical rarities. The literature cited refers to interesting reviews and, almost exclusively, to controlled studies and when applicable, randomized studies.

References
Pneumocystis Pneumonia (PCP)

This interstitial pneumonia caused the majority of AIDS deaths in the early years of the HIV epidemic. In the last 20 years, there has been significant progress made in understanding this organism, especially through DNA analysis (Review: Thomas 2004). Although pneumocystis was previously classified as a protozoan, it was established in 1988 that it is in fact an unusual type of fungus (Edman 1988). In the 1990s, it was recognized that every host, whether rat, mouse, monkey or human, has its own specific pneumocysts. It also became clear that Pneumocystis carinii (P. carinii), which was first described in 1910, does not occur in humans at all, but only in rats. The Pneumocystis species that affects humans is now referred to as Pneumocystis jiroveci, and “carinii” has now been taken out of the name, although the abbreviation PCP remains (Stringer 2002).

Today, the majority of patients diagnosed with PCP are not on antiretroviral drugs, because many of them either do not know their HIV infection status or do not want to know it. In Europe between 1997–2004, among 760 cases of so-called “late presenters” who were diagnosed with HIV infection and AIDS at the same time, PCP (35%) was the most frequent OI (Mussini 2008).

PCP is a life-threatening disease, which should be treated by an HIV specialist. It often requires mechanical ventilation and still continues to have a high fatality rate of up to 10% (Morris 2008, Walzer 2008). Factors associated with mortality are older age, low hemoglobin level, and low partial pressure of oxygen breathing room air at hospital admission (Walzer 2008, Miller 2010). Moreover, relapses seen frequently in the past have become rare, thanks to ART and prophylaxis. Scar tissue formation may result in susceptibility to recurring pneumothoraces. PCP may rarely occur in relation to immune reconstitution inflammatory syndrome (see below). Extra-pulmonary manifestations of pneumocystis infections are also considerably rare. They may affect the liver, but many other organs may be involved.

Signs and symptoms

Every clinician should be familiar with the classic triad of PCP symptoms that include dry cough, subfebrile temperatures, and dyspnea on exertion; should ask patients specifically about their symptoms; and should measure the patients’ respiratory rates. A subacute course that allows differentiation from the productive cough, acutely high fever, pain and less common dyspnea-associated bacterial pneumonia is typical. Oral thrush is a frequent symptom in patients with PCP. Also, substantial weight loss of several kilos in the weeks before PCP diagnosis is common. These and other symptoms may be more subtle in cases with suboptimal prophylaxis (rare). Weeks and sometimes even months may go by before the diagnosis of PCP is made. It is noteworthy to state that decompensation – as with all interstitial pneumonias – often occurs much faster than expected. It is not rare for a patient to suddenly require ventilation after weeks of antibiotic therapy prescribed by the primary health care provider, especially when even “broad spectrum” antibiotics do not help. A patient with significant exertional dyspnea or even resting dyspnea should be directed immediately to hospital.

Diagnosis

If there is clinical suspicion of PCP determined by a physical examination with attention given to respiratory rate, oral thrush, and significant findings on auscultation, then a chest x-ray should follow without delay and, if possible, a high resolution computed tomography (HRCT) of the lungs. The chest x-ray often shows relatively characteristic findings with a butterfly-shaped (perihilar) interstitial infiltrate. In the
early stages, focus is on the mid- and lower fields. Indistinct, diffuse changes are more easily visible on HRCT than on a chest x-ray. A CT scan also allows a fairly certain distinction from other pulmonary infections (Hidalgo 2003). However, in cases where nothing pathological is visible on CT scan to an experienced radiologist, then rapid initiation of treatment is still justified even without a definitive diagnosis – particularly in the presence of the classic triad of symptoms, low CD4 T cell count and no previous PCP prophylaxis. Almost always present is partial respiratory insufficiency, which should be confirmed by arterial blood gas analysis. Lactate dehydrogenase (LDH) is often elevated and may have limited use as a predictive parameter for the course of disease. A high LDH is an unfavorable sign and may reflect the severity of the PCP. In contrast, CRP is often normal, provided there are no other concurrent infections. Sputum specimens are generally not useful (Review: Cruciani 2002), so that a bronchoalveolar lavage (BAL) is usually necessary. This can lead to detection of pneumocysts even after several days of treatment. Therefore, it is not essential to wait for the BAL to start treatment. The lab should be specifically alerted to possible PCP. The routine test for detecting Pneumocystis in the BAL is direct immunofluorescence assay (DFA). A real-time PCR assay also seems to be an accurate diagnosis method and could replace the DFA (Fillaux 2008).

Performing the BAL as early as possible also allows for the timely diagnosis of co-infections (CMV, pneumococci). It should be noted that respiratory insufficiency can deteriorate with BAL. Full blood count, transaminases and kidney function must be monitored during treatment and baseline values should be determined at this point. Newer diagnostic approaches include antibody testing (Bishop 2003) and measurement of S-adenosylmethionine, an agent that pneumocysts require but cannot produce. S-adenosylmethionine levels are significantly reduced in patients with PCP (Skelly 2008). It is currently not foreseeable, whether these tests, which spare patients the discomfort of bronchoscopy, will be available for routine diagnostic testing in the future. This also applies to other serum markers such as beta-D-glucan or antibody tests (Desmet 2009, Watanabe 2009, Djawe 2010, Gingo 2011, Sax 2011).

**Treatment**

**General**

Treatment should be initiated immediately if there is clinical suspicion. In cases of mild PCP (BGA: PO$_2$ >70–80 mm Hg), ambulatory treatment can be attempted. In very mild cases, even oral medication can be considered. This may well be possible in cooperation with a competent HIV nursing service. If such monitoring is not possible, if respiratory deterioration occurs, and in all cases with resting dyspnea, immediate hospitalization is advised. If ventilation becomes necessary, patients have a poor prognosis, even today (Crothers 2005, Walzer 2008). Non-invasive methods (like CPAP) may be beneficial if used from an early stage. This helps particularly in prevention of pneumothoraces (Confalonieri 2002).

The ACTG study shows the advantages of starting ART with PCP treatment (Zolopa 2009, see above). Another retrospective study showed improved survival in patients who began ART while hospitalized (Morris 2003). Possible cumulative toxicities and allergies with this approach, which may necessitate discontinuation of both PCP and HIV, treatment can be largely avoided today (Watson 2002).

**Drugs**

Acute therapy should last for 21 days. The drug of choice is cotrimoxazole. The dose of three 960 mg tablets three times daily is possible in milder cases. However, these higher oral doses are also associated with poor gastrointestinal tolerability. Some case
reports have observed positive effects with lower doses, but controlled studies are lacking (Thomas 2009). All severe cases should be treated intravenously in hospital. Due to possible clinical deterioration, which is probably a result of the bursting of pneumocysts in the alveoli, 1 mg/kilo prednisone BID should always be simultaneously co-administered with the PCP therapy for 5–10 days. There should be no hesitation to use steroids, especially in patients with poor blood gases. On steroids, significantly less patients need intubation (Briel 2006). Important: clinical deterioration during the first week of treatment is still not uncommon. Initial treatment should be re-evaluated after one week at the earliest, and only after exclusion of infections such as CMV.

The high doses of cotrimoxazole require monitoring of full blood count, electrolytes, renal function parameters and transaminases at least three times weekly. The main problems in addition to myelotoxicity as well as liver and kidney problems include a rash that usually occurs after the middle of the second week of treatment and is often accompanied by drug fever. The rash is seen in up to 30% of patients (Fisk 2009) – patients should be checked daily for skin changes! If an exanthema occurs, one can attempt to interrupt treatment for one or two days, and then continue with half-dose steroids. Otherwise, cotrimoxazole must be discontinued and replaced with alternative treatments.

All alternatives to cotrimoxazole are less effective. In cases of intolerability or history of sulfonamide allergy, intravenous pentamidine is the drug of second choice. An induction therapy is administered over the first few days (200–300 mg in 500 ml 5% glucose or 0.9% NaCl), and half the dose can then be given from day 6. This treatment is very toxic, which is why we have not used it for many years. Severe compensations of electrolyte and blood glucose levels (both hyper- and hypoglycemia) are possible, as well as pancreatitis, arrhythmia and renal failure. Initially, daily monitoring of blood glucose, electrolytes and renal parameters is necessary.

In very mild cases of PCP, treatment with daily pentamidine inhalations (300–600 mg daily for three weeks) can be attempted (Arasteh 1990, Montgomery 1995). However, experiences have not all been positive (Conte 1990, Soo 1990), and the current US guidelines advise against inhalatory acute therapy (Benson 2004). Instead of pentamidine, treatment with atovaquone suspension (better than the tablets used in the past) or a combination of clindamycin and primaquine is possible. However, data on these alternative therapies is only available for mild to moderately severe cases of PCP (Hughes 1993, Dohn 1994, Toma 1998). According to a meta-analysis, clindamycin-primaquine seems very promising as second-line treatment for PCP in patients who fail treatment with cotrimoxazole (Benfield 2008) and is superior to pentamidine (Helweg-Larsen 2009).

In the past few years, these alternative agents (intravenous pentamidine, atovaquone, clindamycin, primaquine) have been used only in exceptional cases. It should be mentioned that a 10-day initial therapy of a high dose cotrimoxazole is achievable in almost all patients, most of whom are then already significantly better. If exanthema or toxicity forces the interruption of cotrimoxazole between day 10 and 14, daily pentamidine inhalation can be administered in the third and last week of acute therapy. As this is not toxic, it can usually be started in parallel to ART. However, a study on this strategy has yet to be published.

**Prophylaxis**

Patients with less than 200 CD4 T cells/µl (<14%) are at high risk of PCP. Above these values, the occurrence of PCP is rare. Therefore, these patients are treated prophylactically, ideally with cotrimoxazole. Daily dosages may be slightly more effective than three times weekly (El Sadr 1999). The gradual lead-in administration over a
A period of 14 days is supposed to prevent allergic reactions, but is cumbersome (Para 2000). In cases of a mild or moderate allergy to co-trimoxazole, desensitization after several weeks is possible (Leoung 2001), and should definitely be attempted. Although dapsone and pentamidine inhalations are almost equally effective (Bozzette 1995, Bucher 1997), co-trimoxazole prophylaxis is better for preventing bacterial infections such as enteritis, sinusitis and pneumonia (DiRienzo 2002). More importantly, co-trimoxazole simultaneously provides reliable protection for cerebral toxoplasmosis. Pediatric co-trimoxazole suspension can be used for desensitization, by slowly increasing exposure over six days from 12.5, 25, 37.5, 50 and 75 to 100% of the dose in the 480 mg tablet. In a study of almost 200 patients, no cases of severe allergy occurred, and there was a reduction of fever and headaches. Approximately three quarters of all patients are thus able to tolerate co-trimoxazole again. However, re-exposure should only be attempted after an interval of eight weeks (Leoung 2001). Monthly inhalation of pentamidine is a well-tolerated alternative. However, coughing may occur. Asthma attacks are rare, and pneumothoraces are even rarer. A suitable inhalation system should be used, after administration of a beta-sympathomimetic to dilate the bronchi. The loading dose (300 mg TID for the first 5 days) frequently used in the past is no longer a universal standard. In patients with severe pulmonary disease, inhalation is probably less effective.

Further options are problematic. Dapsone has poor gastrointestinal tolerability, is quite myelotoxic and often leads to elevation of LDH. LDH, an important diagnostic parameter, can therefore not be utilized during treatment with dapsone (Ioannidis 1996). Atovaquone was proven to be of comparable efficacy to co-trimoxazole, dapsone and pentamidine in two multicenter studies (El-Sadr 1998, Chan 1999), and since then, is considered to be a good alternative for PCP prophylaxis. The oral suspension has better tolerability than the tablet formulation (Rosenberg 2001). A significant disadvantage of atovaquone for long-term prophylaxis is the disproportionately high cost (in some European countries approx. 1000 euro/month).

### Treatment/Prophylaxis of PCP (daily doses, if not otherwise specified)

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Duration: always at least three weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe to moderately</td>
<td>Co-trimoxazole 5–6 amp. at 480 mg TID plus prednisolone 2–2–0 tbl. at 20 mg (5–10 days)</td>
</tr>
<tr>
<td>Severe PCP</td>
<td></td>
</tr>
<tr>
<td>Mild PCP</td>
<td>Co-trimoxazole 3 tbl. at 960 mg TID</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Pentamidine 200–300 mg IV for 5 days (4 mg/kg), then halve dose</td>
</tr>
<tr>
<td></td>
<td>In very mild cases: daily inhalations with 300 mg Atovaquone suspension 5–10 ml BID (750–1500 mg BID)</td>
</tr>
<tr>
<td></td>
<td>Clindamycin 1 amp. at 600 mg IV q 6–8 h plus primaquine 1 tbl. at 30 mg QD</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Below 200 CD4 T cells/μl; after PCP episode</td>
</tr>
<tr>
<td>First choice</td>
<td>Co-trimoxazole 1 tbl. at 480 mg QD or Co-trimoxazole 1 tbl. at 960 mg 3 x/week</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Pentamidine 300 mg 1–2 x/month Dapsone 2 tbl. at 50 mg QD Dapsone 1 tbl. at 50 mg QD plus pyrimethamine 2 tbl. at 25 mg/week plus leucovorin 2 tbl. at 15 mg/week Atovaquone suspension 5 ml BID (750 mg BID)</td>
</tr>
</tbody>
</table>

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PCP prophylaxis regimens can be discontinued fairly safely with sufficient immune reconstitution: a recent meta-analysis showed that more than 200 CD4 T cells/µl for three months is required (Costiniuk 2011). PCP has only rarely been described in cases with CD4 T cell counts greater than 200 cells/µl after stopping prophylaxis (Degen 2002, Mussini 2003). If the viral load is suppressed, even lower CD4 cells are possible. In an analysis of 23,412 patients from 12 European cohorts who started taking ART after 1997, the incidence of primary PCP was very low among patients who had virologically suppressed HIV infection, were receiving ART, and who had CD4 cell counts of between 101–200 cells/µL (COHERE 2010). However, there are no controlled studies addressing this issue.

**Resistance issues, current controversies**

Stopping prophylaxis not only reduces side effects and costs, but also avoids other negative developments: the proportion of co-trimoxazole-resistant bacteria is constantly increasing among HIV-infected patients (Martin 1999). The worldwide use of co-trimoxazole has also affected pneumocysts. Resistance analyses were previously difficult since this particular organism, even almost 100 years after its discovery, can not be cultured. However, it is now possible to sequence sections of the genome encoding for dihydropteroate synthetase (DHPS). DHPS is an important enzyme involved in the folate metabolism of many organisms, and is targeted by sulfonamides such as sulfamethoxazole (SMX) and dapsone. The first mutations in the DHPS gene in pneumocysts were discovered in 1997. A further study showed DHPS mutations in 43%, while the gene region for dihydrofolate reductase (DHFR), targeted by trimethoprim (TMP) and pyrimethamine, did not show a single relevant mutation. In contrast to SMX, there seems to be no selective pressure associated with TMP – a suspicion that has to be analyzed, that TMP is not effective against pneumocysts (Ma 1999). Recently, however, even DHFR-mutations have been proven (Nahimana 2004). In addition, studies in large groups of patients have demonstrated that the frequency of sulfa resistance mutations has significantly increased in recent years. Resistance correlated significantly with the duration of prior prophylaxis and its failure (Helweg-Larsen 1999). However, it remains unclear whether DHPS mutations should affect decisions on PCP therapy or lead to a change in treatment (Review: Matos 2010).

The sequencing of the Pneumocystis genome has uncovered other possibly relevant findings: it seems highly likely that PCP is caused by a new infection, rather than the reactivation of an existing infection as previously assumed (Wakefield 2003). Asymptomatic HIV patients with frequent detection of pneumocysts may have reservoirs (Wakefield 2003), as well as HIV-negative patients on corticosteroid therapy (Maskell 2003) and patients with active PCP. Several reports also exist on nosocomial outbreaks (Schmoldt 2008, Le Gral 2012, Sassi 2012). However, other authors doubt patient-to-patient transmission (Wohl 2002), and isolation of PCP patients is still not generally recommended (Thomas 2004).

Pneumocysts do not always cause a manifest pneumonia: in healthy patients pneumocystis colonization has been observed (Ponce 2010, Vargas 2010). Colonized patients have been reported to represent a potential infectious source (Le Gral 2012). Pneumocysts may also play a role in chronic obstructive lung diseases (Morris 2008).
References


Cerebral toxoplasmosis

Although the incidence in Europe has been drastically reduced as a result of ART (Abgrall 2001), cerebral toxoplasmosis (or toxoplasmic encephalitis, TE) remains the most important neurological OI in HIV-infected patients. TE almost always results from the reactivation of a latent infection with *Toxoplasma gondii*, an intracellular parasite that infects birds, mammals and humans. Prevalence rates vary considerably worldwide (Porter 1992). Whereas *Toxoplasma gondii* is relatively rare in the US, seroprevalence rates in some regions within central Europe are as high as 90%. *Toxoplasma gondii* has an affinity to the CNS. Extracerebral organ manifestations (heart, muscle, liver, intestine, lung) are rare and often only detected at autopsy. Cerebral toxoplasmosis is potentially life threatening, and treatment is complicated. In severe cases, there may be residual neurological syndromes with significant disabilies, like hemiparesis. It is not rare to see a lifelong susceptibility to seizures as a result of defective healing. It should be noted that relapses may occur even after long periods of time due to intracerebral persistence.

In Western countries, there is some evidence that the situation of an HIV-infected patient developing TE in recent years differs from TE patients seen during the early years of the HIV epidemic (Hoffmann 2007). Patients with TE today usually are not taking antiretroviral therapy or prophylaxis of any sort. They are likely to be diagnosed with HIV at the time of TE diagnosis, and TE is much more frequently the AIDS-defining illness in these patients than in the pre-HAART era.

**Signs and symptoms**

Clinical symptoms depend on the localization of lesions with acute or peracute onset within a few days. The major signs include focal neurological deficits such as paresis, speech problems or sensory loss (Porter 1992). A febrile psychosyndrome with confusion is also a frequent early sign. It is not unusual to see epileptic seizure as the initial presentation, in the absence of other symptoms. Headaches with fever or subfebrile temperatures are always suspicious. Meningitic signs, however, are less typical. Atypical manifestations in patients with immune reconstitution on ART have been described (Ghosn 2003).

A fairly rare, but important manifestation is Toxoplasma chorioretinitis. It causes impairment of vision, is an important differential diagnosis to CMV retinitis and may occur on its own (Rodgers 1996). Toxoplasma chorioretinitis should be treated in exactly the same way as cerebral toxoplasmosis.

**Diagnosis**

Cerebral toxoplasmosis seldom occurs above a CD4 T cell count of 100 cells/µl; over 200 CD4 T cells/µl it is very rare (Bossi 1998). In contrast, it should be expected below 100 CD4 T cells/µl. A CT or MRI scan of the head should be performed promptly within a week in every case of focal neurological deficit, but also if seizures occur in significantly immunocompromised patients. In this instance, an MRI is superior to a CT scan and almost always shows more visible lesions. A third of cases have solitary lesions, a third have several (2–5) and a third have multiple lesions. In approximately nine out of ten cases, ring enhancement is found around the lesions, often accompanied by edema. Hemorrhage may occasionally occur.

For all radiologically detected lesions, the most likely diagnosis is cerebral toxoplasmosis. In addition, the most important differential diagnosis is an “atypical” cerebral toxoplasmosis. Furthermore, the more lesions there are, the more likely the diagnosis
of toxoplasmosis. However, the distinction between toxoplasmosis and a bacterial abscess or a cerebral lymphoma may be difficult. Other rare differential diagnoses include PML, infarcts, tuberculomas and cryptococcomas. “HIV-unrelated” diseases such as brain tumors or vascular diseases should also be considered.

A brain biopsy is not obligatory. Suspicion of toxoplasmosis (clinically and radiologically) justifies a treatment attempt before it comes to this. Response to therapy then confirms the diagnosis. However, if the patient does not improve clinically within one week, or even worsens, then stereotactical brain biopsy cannot be avoided, and in this case, should not be postponed. The cerebrospinal fluid (CSF), which also does not necessarily have to be analyzed if there are clear radiological findings (several lesions with contrast enhancement), usually shows moderate pleocytosis and slightly elevated total protein. Our experience with toxoplasma PCR from CSF has not been good. A negative result never excludes toxoplasmosis.

An updated serology should be available for every patient. Up to 97% of patients with cerebral toxoplasmosis have IgG antibodies, and so a negative result, which should be repeated in another lab if there is any doubt, makes toxoplasmosis unlikely. Some clinicians use levels of IgG titers or increased titers as indicators (Derouin 1996), but this approach has not been properly validated. IgM is only rarely positive, and therefore usually does not help. PCR from the blood has little relevance (Review: Bretagne 2003).

Treatment

Treatment of cerebral toxoplasmosis is difficult. The most frequently used combinations are usually effective (resistance has not yet been convincingly described), but require modification in at least half of the patients due to side effects – particularly allergies. Sulfadiazine and clindamycin are presumably equally effective in combination with pyrimethamine (Dannemann 1992). One large European study demonstrated a trend, though not significant, in favor of sulfadiazine (Katlama 1996). Co-trimoxazole may also be an option. According to a Cochrane analysis, the available evidence fails to identify a best regimen that can be considered the gold standard (Dedicoat 2006).

We recommend that sulfadiazine and pyrimethamine be used for an initial attempt as oral treatment. In cases of sulfonamide allergy, sulfadiazine should be substituted with oral or intravenous clindamycin from the beginning. In addition, all disoriented patients should receive clindamycin infusions, at least for adherence reasons. Because of the high rate of allergies with sulfadiazine, some clinicians oppose clindamycin. We do not share this perspective, since clindamycin is also allergenic. Moreover, clindamycin can cause pseudomembranous colitis.

A loading dose for pyrimethamine during the first few days has been propagated since the first published study (Leport 1988). However, it has not been proven necessary. Even the dosages vary. For example, in the US, 200 mg is recommended for the first day (followed by 50–75 mg depending on body weight); in many European countries, 100 mg is often given for three days, followed by 50 mg. It should be noted that, in contrast to clindamycin, pyrimethamine is also active in the presence of an intact blood-brain barrier, and therefore, is sometimes the only effective agent. Due to the myelotoxicity of sulfonamides and pyrimethamine, which inhibits transformation of folic acid to folinic acid, it is imperative to substitute sufficiently with folinic acid, which unfortunately is expensive. Folic acid, which is much cheaper, is ineffective since it cannot be converted in the presence of pyrimethamine (Luft 2000). Good results have also been reported with intravenous co-trimoxazole, with administration of the same dosages as for PCP (Canessa 1992, Béraud 2009). In two ran-
domized studies in patients with ocular or cerebral toxoplasmosis, co-trimoxazole was as effective as sulfadiazine/pyrimethamine (Torre 1998, Soheilian 2005). If allergies or intolerance to both sulfonamides and clindamycin occur, then a combination of atovaquone and pyrimethamine is an alternative (Chirgwin 2002). A combination of azithromycin plus pyrimethamine could be another alternative (Bosch-Driessen 2002).

Acute therapy lasts for a period of four to six weeks, or longer for the less effective reserve therapies. Treatment success can be assessed clinically in the first 14 days. While an improvement in the symptoms can often be observed within a few days, a patient who has not improved after two weeks of therapy or has even deteriorated, probably does not have toxoplasmosis. If this occurs, the diagnosis has to be reviewed and a brain biopsy must be performed. Changing the TE therapy is not useful in such cases and just expends valuable time. Antiretroviral therapy should be initiated as soon as possible. Drugs with the potential of allergic reactions (abacavir, when HLA testing is not possible, NNRTIs, fosamprenavir, darunavir) should be avoided. A control MRI is recommended for stable patients after two weeks at the earliest. Significant resolution of lesions is often only visible after four weeks. In cases of increased intracranial pressure or extensive edema, steroids are given (8 mg dexamethasone q 6–8 h). Steroids should be given for a limited time, as there is a significantly increased risk of aspergillosis. All treatment combinations require initial monitoring of blood count, glucose, transaminases and renal parameters at least three times weekly. Maintenance therapy with the reduced dose should only be initiated if lesions have shrunk by at least 75%.

Prophylaxis

Exposure prophylaxis: IgG-negative patients can protect themselves from primary infection by not eating raw or undercooked meat (lamb, beef, pork, game, etc). It has not been proven, despite widespread opinion, that infection occurs by mere contact with cats, the definitive hosts of Toxoplasma gondii. To date, the only study that has seriously investigated this conjecture could not prove endangerment as a result of proximity to cats (Wallace 1993). Nevertheless, stricter measures of hygiene should be followed (e.g., gloves should be used when handling the litter box).

Primary prophylaxis: All IgG-positive patients with less than 100 CD4 T cells/µl require primary prophylaxis. The drug of choice is co-trimoxazole. In cases of co-trimoxazole allergy, desensitization may be considered (see PCP). An alternative is dapsone plus pyrimethamine or high-dose dapsone. Primary prophylaxes can be discontinued safely if CD4 T cells are above 200/µl for at least three months.

Maintenance therapy/secondary prophylaxis: In the absence of immune reconstitution, patients with cerebral toxoplasmosis require lifelong maintenance therapy or secondary prophylaxis, as there are otherwise recurrences in nearly all cases. It usually consists of half the dose of the acute therapy (Podzamczer 2000). Clindamycin is presumably less suitable as it cannot cross the blood-brain barrier (Luft 2000). Co-trimoxazole seems to be not as effective for secondary prophylaxis, but should be considered because it is simple. However, it definitely requires higher doses than those used to treat PCP (Ribera 1999, Duval 2004). With immune reconstitution (at least six months above 200 CD4 T cells/µl), secondary prophylaxis can probably be stopped (Benson 2004, Miro 2006). When possible, an updated MRI scan should be available beforehand. If there is enhancement, then it may mean that lesions have become active even after years – and there is a risk of a recurrence. A recurrence even after five years has been observed, despite CD4 T cells being around 200/µl.
### Treatment/prophylaxis of cerebral toxoplasmosis (daily doses, if not otherwise specified)

<table>
<thead>
<tr>
<th><strong>Acute therapy</strong></th>
<th><strong>Duration:</strong> always at least four weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td><strong>Sulfadiazine + Pyrimethamine</strong></td>
</tr>
<tr>
<td><strong>Sulfadiazine</strong></td>
<td>2–3 tbl. at 500 mg QD <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Pyrimethamine</strong></td>
<td>2 tbl. at 25 mg BID (for 3 days, then halve dose) <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Leucovorin</strong></td>
<td>3 x 1 tbl. at 15 mg/week</td>
</tr>
<tr>
<td><strong>First choice</strong></td>
<td><strong>Clindamycin + Pyrimethamine</strong></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>1 amp. at 600 mg IV QD or 1 tbl. at 600 mg qid <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Pyrimethamine</strong></td>
<td>2 tbl. at 25 mg BID (for 3 days, then half dose) <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Leucovorin</strong></td>
<td>3 x 1 tbl. at 15 mg/week</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td><strong>Atovaquone + Pyrimethamine</strong></td>
</tr>
<tr>
<td><strong>Atovaquone</strong></td>
<td>suspension 10 ml bid (1500 mg BID) <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Pyrimethamine</strong></td>
<td>2 tbl. at 25 mg BID (for 3 days, then half dose) <strong>plus</strong></td>
</tr>
<tr>
<td><strong>Leucovorin</strong></td>
<td>3 x 1 tbl. at 15 mg/week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Maintenance therapy</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>As for acute therapy</strong></td>
<td>As for acute therapy, but half dose</td>
</tr>
<tr>
<td><strong>Discontinue if &gt;200 CD4 cells/μl for &gt;6 months (if MRI is normal or without contrast enhancement)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Possibly</strong></td>
<td><strong>Co-trimoxazole</strong></td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole 1 tbl. at 960 mg QD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Primary prophylaxis</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td><strong>Co-trimoxazole</strong></td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole 1 tbl. at 480 mg QD</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td><strong>Dapsone</strong></td>
</tr>
<tr>
<td></td>
<td>Dapsone 2 tbl. at 50 mg QD</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td><strong>Dapsone + Pyrimethamine</strong></td>
</tr>
<tr>
<td></td>
<td>Dapsone 1 tbl. at 50 mg QD <strong>plus</strong></td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine 2 tbl. at 25 mg/week <strong>plus</strong></td>
</tr>
<tr>
<td></td>
<td>Leucovorin 2 tbl. at 15 mg/week</td>
</tr>
</tbody>
</table>

This and other cases (Stout 2002, Ghosn 2003) have shown that quantitative measurement of CD4 T cells on ART does not always reflect the quality of the TG-specific immune response. As a result, there have been increasing efforts in recent years to improve the characterization of this specific immune response via ELISPOT. Studies have shown that the Toxoplasma-specific immune response remains poor in approximately 10–20% of patients on ART, despite good CD4 T cell counts (Fournier 2001, Miro 2003). In the future, ELISPOT testing may allow identification of patients who are at risk of recurrence despite good CD4 counts and who should therefore continue with secondary prophylaxis.

### References


CMV retinitis

Infections with cytomegalovirus are widespread. In many countries, seroprevalence is around 50–70%, and above 90% in MSM. In severely immunocompromised individuals, (CD4 count below 50 cells/µl), reactivation of CMV infection can lead to retinitis. In the past, CMV retinitis was a common AIDS-associated illness, leading to blindness in up to 30% of patients. It occurs mainly in untreated patients, who are often first diagnosed with HIV infection on presentation (Jacobson 2000). An inflammatory CMV retinitis, usually with severe vitritis, is also possible in the course of IRIS (see below). If CMV retinitis is not diagnosed and treated promptly, then the patient’s sight is at risk. Impairment of vision is almost always associated with lesions, which are no longer reversible even with adequate treatment. This is why CMV retinitis remains a dangerous illness, although the prognosis has significantly improved with ART (Goldberg 2003, Salzberger 2005, Thorne 2006).

Other manifestations of disseminated CMV infection are rare (15%), and can affect every organ. The lung (pneumonia), esophagus (ulcers), colon (colitis) and CNS (encephalitis) are most frequently involved. Sinusitis may also occur (Jutte 2000). The clinical signs of these CMV diseases depend on the organ affected. Diagnosis is often difficult and may only be possible on histology (Goodgame 1993). There is insufficient data on the treatment of these manifestations, so systemic therapies are usually chosen along with treatment for CMV retinitis (Whitley 1998).

Newer studies have suggested that CMV infection plays a role in the pathogenesis of artery disease and that CMV-induced T cell immunopathology could contribute to HIV-associated atherosclerosis (Parrinello 2012, Sacre 2012). There is also an association between CMV infection and altered immune reconstitution (Appay 2011, Hunt 2011).

Signs and symptoms

Any visual impairment occurring peracutely or acutely, such as blurred vision or floaters – especially unilaterally – should prompt an immediate (same day, if possible) ophthalmological examination of the patient. Symptomatic CMV retinitis is an emergency. Once there is a black spot in the visual field, it will be permanent. Involvement of the posterior pole (zone 1 retinitis) accounts for approximately one half of incident visual acuity loss. Cataract and retinitis-related retinal detachment are also common causes of vision loss (Thorne 2006).

All CMV treatment regimens can prevent progression of lesions, but not reverse them. Eye pain, burning, increased production of tears, and conjunctival irritation are not typical. However, many patients suffer from systemic symptoms such as fever and weight loss.

Diagnosis

Diagnosis is made by fundoscopy. Assessment of the usually peripheral, whitish exudates is dependent on the experience of the ophthalmologist. However, this can frequently be a problem, due to the rare occurrence of CMV retinitis nowadays. Unfortunately, incorrect diagnoses do happen and retina are lost. Therefore, if the primary ophthalmologist remains undecided, then it is best to start with oral valgancyclovir and transport the patient to a larger clinical center with ophthalmologists who are experienced in HIV. Furthermore, it is essential that the ophthalmologists receive information about the patient’s immune status. In cases of poor immune status and CD4 count less than 100/µl, chorioretinitis caused by Toxoplasma
Toxoplasma gondii is the most important differential diagnosis. CMV retinitis can almost be excluded at CD4 T cell counts above 100/µl; other viral infections (HSV, VZV) or even neurosyphilis should then be considered. CMV lesions may also be confused with cotton wool spots, which are not rare in patients with high HIV viral load. Multiple small lesions without hemorrhage or exudates are almost always cotton wool spots, and almost never CMV retinitis. Bilateral involvement is also usually the exception. Vitritis is rare, except with immune reconstitution syndrome.

CMV serology (IgG almost always positive, IgM variable) is seldom helpful for diagnosis. CMV PCR or a blood test for pp65 antigen to detect antibodies against a CMV-specific phosphoprotein may be more useful. CMV retinitis or a recurrence is unlikely with a negative PCR or pp65 result. The higher the levels of CMV viremia, the higher the risk of CMV disease. Patients with positive CMV PCR have a 3–5-fold elevated risk (Casado 1999, Nokta 2002). Positive CMV PCR is also independently associated with a poor prognosis for the patient (Deayton 2004, Jabs 2005, Wohl 2005). As with Toxoplasma gondii, there have been efforts to determine the antigen-specific immune response more precisely (Jacobsen 2004), although such testing is not yet routine.

**Treatment**

CMV treatment should always be initiated promptly and strictly monitored by fundoscopy at least once a week in the beginning. Photodocumentation is advisable. Initially, an intensive induction therapy is administered for two to three weeks, until there is scar formation of the lesions. HIV clinicians and ophthalmologists should work closely together, particularly during the induction therapy, and when possible, communicate several times a week. Induction therapy is followed by maintenance therapy at a reduced dose.

ART in particular has dramatically improved the prognosis of patients. That said, all diagnosed patients should start ART without delay. This can restore CMV-specific immune responses (Komandouri 1998), so that CMV viremia may disappear even without specific therapy after a few weeks (Deayton 1999, O’Sullivan 1999). However, if retinitis is present, CMV-specific treatment should be started, as immune reconstitution may take several months.

**Systemic treatment**

Valgancyclovir, a prodrug of gancyclovir with good oral absorption, is the first choice in CMV treatment. In a randomized study (Martin 2002) on 160 patients with retinitis, the results were impressive: valgancyclovir tablets were just as effective as gancyclovir infusions. However, the toxicity profile of both agents was comparable. This means, in cases of oral treatment, that the blood count has to be frequently monitored as for infusions and that the indication has to be equally carefully set. Treating a positive IgM serology (without any further diagnosis) with valgancyclovir is not only expensive, but also usually an unnecessary risk.

Other options for systemic treatment have become less important, and are only used in cases of recurrence. If there is intolerability or more rarely (Martin 2007) resistance to valgancyclovir (Drew 1999), then foscarnet remains an option. This, however, requires daily infusions. Further problems with this drug include nephrotoxicity, and very painful penile ulcers. Very intensive hydration of the patient is therefore necessary in all circumstances. However, there are some experts in the field who prefer intravenous CMV treatment in advanced cases.

There are no direct comparative studies available for cidofovir, which is also used occasionally. The benefit of the long half-life (once weekly dosing possible) is outweighed by the considerable renal toxicity of this drug (Plosker 1999). We observed
creatinine elevations in every second patient treated, despite the fact that a strict infusion plan was closely followed (see Drugs section).

New anti-CMV drugs are not expected for the next years. Maribavir recently failed to show a benefit in Phase III studies (Snydman 2011). Monoclonal antibodies (MSL-109) or compounds such as cyclopropavir or BAY 38-4766 are still in early phases of development (Review: Prichard 2011).

Additional treatment with G-CSF (filgrastim) improved survival in one analysis of three large studies enrolling patients with CMV retinitis in the years 1990–1997. In particular, there was a reduction of bacterial infections. However, the reason for this positive effect remains unclear. Thus, administration of filgrastim is presently not generally recommended (Davidson 2002).

**Local treatment**

Several options for local treatment of CMV retinitis have been tested (Review: Smith 1998). Although such treatments can be safely administered by experienced ophthalmologists and are associated with few complications (infections, hemorrhage), disadvantages remain. Weekly intravitreal injections of gancyclovir or foscarnet, or pellet implantation (Vitraset®, must be replaced every 6–9 months) do not protect from infection of the contralateral eye or from extraocular manifestations (Martin 1999). The same is true for fomivirsen (Vitravene®), an antisense-oligonucleotide for intravitreal injection, which is astonishingly effective even with multiresistant CMV strains (Perry 1999). These local treatments have become less important since ART and valgancyclovir and some have been taken off the market.

**Treatment/prophylaxis of CMV retinitis** (daily doses, if not otherwise specified)

<table>
<thead>
<tr>
<th>Treatment of choice</th>
<th>Duration: always at least three weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Valgancyclovir</td>
</tr>
<tr>
<td>Alternative</td>
<td>Gancyclovir</td>
</tr>
<tr>
<td>Alternative</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Alternative</td>
<td>Gancyclovir + Foscarnet</td>
</tr>
<tr>
<td><strong>Maintenance therapy</strong></td>
<td>Discontinue when &gt;100–150 CD4 cells/μl &gt;6 months</td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Valgancyclovir</td>
</tr>
<tr>
<td>Alternative</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Alternative</td>
<td>Cidofovir</td>
</tr>
<tr>
<td><strong>Primary prophylaxis</strong></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Prophylaxis**

**Primary prophylaxis:** In the prospective studies that have been performed, no primary prophylaxis regimen has been convincing. There is also no effective vaccine. Therefore, the most important method for prevention in patients with CD4 counts below 200 cells/μl is still fundoscopy every three months. With good immune reconstitution, intervals between examinations can be extended. It is important to perform a fundoscopy in severely immunocompromised patients prior to starting ART. This
allows detection of smaller lesions, which may later present with severe inflammation during the course of immune reconstitution.

**Secondary prophylaxis:** After approximately three weeks of acute therapy, but at the earliest with scar formation of lesions, a reduced dose secondary prophylaxis (maintenance therapy) should begin, preferably with oral valgancyclovir (Lalezari 2002). However, the drug is not only very expensive but also just as myelotoxic as gancyclovir infusions. Discontinuation of secondary prophylaxis as quickly as possible is desirable for this OI (MacDonald 1998, Tural 1998, Jouan 2001), but it also requires strict ophthalmologic monitoring. According to US guidelines, discontinuation should occur at the earliest after six months of maintenance therapy and with an immune reconstitution above 100–150 CD4 T cells/µl. However, we have successfully stopped gancyclovir at lower CD4 T cell counts, if both HIV and CMV PCR in blood were below detection. One study showed that stopping after 18 months of ART/maintenance therapy can be safe above 75 CD4 T cells/µl (Jouan 2001). After stopping maintenance therapy, fundoscopy should be performed every four weeks over the first months.

The previously required life-long daily infusions of gancyclovir or foscarnet via port, pumps and nursing service are luckily now a thing of the past. If there are relapses during oral valgancyclovir, re-induction and maintenance therapy with foscarnet or possibly with cidofovir can be considered.

**References**


Pritchard MN, Kern ER. The search for new therapies for human cytomegalovirus infections.


Candidiasis

Candidiasis is an infection with yeast-forming fungi. Of the 150 Candida species known to date, only approximately 20 cause disease. By far the most frequent species is *C. albicans*. Other species such as *C. tropicalis*, *C. glabrata* and *C. krusei* are rare, but may respond less readily to treatment with azoles. Although it was commonly assumed that azole resistance is a problem particularly with albicans strains, this has not been the case to date (Sanglard 2002).

Candidiasis is an important indicator of immunodeficiency and should be seen as a reason to consider starting ART, even with good immune status. Esophageal candidiasis and even oral thrush often occur following other OIs. Fever, which is not a classic symptom of candidiasis, is a particular indication to be on the alert. If immune status is good, it must be remembered that there are also other reasons for thrush – alcoholism and steroid treatment are only two of many possibilities. In addition to candidiasis of the oropharynx and esophagus, vaginitis is a frequent problem in women (also occurring in healthy individuals). Candidemia occurs only rarely in HIV-infected patients, even with severe immunodeficiency.

Signs and symptoms

The oropharynx is usually affected, with taste disturbances and sometimes a burning sensation on the tongue. White, non-adherent plaques on the buccal mucosa, tonsillar ring and tongue confirm the diagnosis. Involvement of the tongue alone is rare. Occasionally, there may be atrophic candidiasis, which presents only with an erythematous mucosa.

Candida esophagitis usually occurs with oropharyngeal involvement, but in about one third of cases there is no oral thrush. It often presents with dysphagia (“drinking is ok, but food can’t go down”) and retrosternal pain. Some patients complain of nausea, although vomiting occurs only rarely.

Diagnosis

Diagnosis in the oropharynx can be made based on clinical appearance. A swab is not usually required. Characterization by culture or even determination of drug susceptibility (beware laboratory uncertainty!) is only advised if a treatment attempt with fluconazole or itraconazole has failed. Oral candidiasis is not to be confused with oral hairy leukoplakia (OHL). In contrast to candidiasis, the whitish, hairy plaques of OHL, on the sides of the tongue, cannot be scraped off. OHL is not caused by fungi but by EBV, and is an important disease marker for HIV, even if it is harmless and does not require treatment.

Candida esophagitis can also initially be diagnosed clinically. Dysphagia, retrosternal pain and oral candidiasis make the diagnosis very probable. Empiric fluconazole therapy reduces costs (Wilcox 1996). Upper GI endoscopy is only required if complaints persist. To distinguish fluconazole-resistant esophageal candidiasis from herpes or CMV esophagitis, samples of lesions should always be taken. In contrast, determination of serum antibodies or antigen is always unnecessary.

Treatment

With relatively good immune status at first presentation, treatment with topical antifungal agents such as nystatin, amphotericin B or miconazole can be attempted. However, systemic treatment is usually necessary. This is more effective and prevents relapses for longer (Pons 1997).
Fluconazole is the treatment of choice, and one week of oral treatment is usually sufficient (Sangeorzan 1994). According to a recently published trial, shorter treatment duration with higher dosages may be an option. In this large randomized study, a single dose of 750 mg of fluconazole was safe, well tolerated, and as effective as the standard 14-day fluconazole therapy (Hamza 2008). If symptoms persist for more than a week, a swab should be taken and the daily fluconazole dose may be increased to 800 mg for the second attempt. Itraconazole should only be used if the second treatment attempt fails and non-albicans strains have been found. It will be effective in approximately two thirds of cases (Saag 1997). Although itraconazole suspension is as effective as fluconazole (Graybill 1998), we do not primarily use it as plasma levels are unreliable and there are problems due to numerous interactions.

Several new and promising antimycotics have been developed in recent years. However, these should only be used in clear cases of fluconazole resistance. There is insufficient evidence on the superiority of these drugs in the treatment of non-resistant candidiasis (Pienaar 2006). Voriconazole is expected to be as effective as fluconazole, but is possibly not tolerated as well (Ruhnke 1997, Ally 2001). This may be also true for posaconazole (Vasquez 2006). Like amphotericin B, these new azoles should only be used for treatment of multi-azole resistant mycoses. The new antimycotic class of echinocandins has good efficacy, among them drugs such as caspofungin, micafungin or anidulafungin (Keating 2001, Villanueva 2001, Arathoon 2002, de Wet 2004, Reboli 2007). These drugs, which can only be administered intravenously, showed similar efficacy and tolerability to intravenous fluconazole for treatment of candida esophagitis in randomized studies (Villanueva 2001, de Wet 2004, Reboli 2007). Antiretroviral therapy should be initiated when such mycoses occur, particularly with multiresistant strains, as these usually disappear with sufficient immune reconstitution (Ruhnke 2000).

### Treatment/prophylaxis of candidiasis (daily doses)

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Duration: 5–10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>In mild cases</td>
<td>Topical e.g., amphotericin B, 1 lozenge QD or nystatin suspension 1 ml QD</td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Fluconazole Fluconazole 1 x 1 cap at 100 mg for oral candidiasis Fluconazole 1 x 1 cap at 200 mg for esophageal candidiasis (twice the dose on the first day in each case)</td>
</tr>
<tr>
<td>Alternative</td>
<td>Itraconazole Itraconazole 1–2 cap. at 100 mg BID or Itraconazole suspension 10–20 ml BID (1 ml = 10 mg)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

### Prophylaxis

No survival benefit has been demonstrated for any Candida prophylaxis to date (McKinsey 1999, Rex 2000, Goldmann 2005). In probably the largest randomized study on this issue, a reduction in oral candidiasis episodes as well as in invasive candidiasis was observed on long-term prophylaxis (Goldman 2005). The hypothesis that long-term prophylaxis will lead to the selection of resistant non-albicans strains (Vazquez 2001) was not confirmed in this study. Azole resistant infections were not seen more frequently in the long-term therapy group. Nonetheless, every immunocompromised patient should be screened for oral thrush at every visit.
References


Tuberculosis

CHRISTOPH LANGE, CHRISTIAN HERZMANN, GIOVANNI BATTISTA MIGLIORI, ANDREA GORI

About 12% of all infections with the Mycobacterium tuberculosis complex (MTB, including *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. canetti* and *M. microti*) occur in people living with HIV. In some African countries, up to 80% of tuberculosis (TB) patients are HIV-seropositive, making it the most important opportunistic infection worldwide (WHO 2010, UNAIDS 2010). Although numbers of coinfection have been declining in the latest WHO report, the prevalence of HIV among TB patients remains extremely high in Africa (46%), the Americas (17%) and South-East Asia (13%). High rates of coinfection are also found in some smaller European countries like Portugal (12%), Estonia (10%), Malta (9%) and Latvia (8%) as well as in the urban metropolitan areas of European low prevalence countries (e.g., Brussels 9%). (ECDC 2011, Pimpin 2011, WHO 2010).

The spread of the TB epidemic is closely related to the HIV prevalence in the general population (Corbett 2003). The incidence of TB is more than eight times higher in HIV-positive than in HIV-negative people (Corbett 2006). In addition, there is concern that HIV may enhance the spread of multidrug resistant (MDR) TB (Dubrovina 2008, Cox 2010). With about 30,000 MDR-TB cases notified worldwide in 2009, its prevalence among all TB cases is high with up to 19% in Eastern Europe, 14% in Central Asia and 16% in the Russian Federation in comparison to 1.3–1.8% in Africa (WHO 2010).

Despite a steadily increasing prevalence of HIV-1 infection in Western Europe and North America in recent years, the incidence of TB has continuously declined in countries where ART is available (Kirk 2000, Girardi 2000, Nahid 2006). However, clinical management of MTB/HIV-coinfected patients is complicated due to a wide range of drug interactions, overlapping side effects of ART and anti-tuberculosis medications and low compliance caused by pill burden.

Figure 1: HIV prevalence (%) in new TB cases (WHO 2010)
Interaction of HIV and MTB

HIV and MTB infections have synergic influence on the host immunoregulation. HIV infection impairs cell-mediated immunity largely through depletion of CD4 T lymphocytes. The impaired immunity leads to a higher susceptibility to MTB infection. In turn, it is likely that TB enhances the immunodeficiency related to HIV-infection (Toossi 2003). The incidence of primary TB and reactivated TB is greater in HIV-infected patients in comparison with HIV-seronegative individuals (Havlir 1999, Badri 2001). Although HIV-infected patients have a > 50 times higher risk of TB reactivation, it is now clearly demonstrated that most patients develop disease after recent transmission, emphasising the need for patient-to-patient infection control measures (Horsburgh 2010, Houben 2011, Sonnenberg 2001).

The incidence of post-primary TB ranges from 5–30% in HIV-infected subjects. The risk of active TB in patients with latent TB infection (LTBI) is approximately 8% per year in HIV-infected patients compared with a lifetime TB risk of 5–10% in HIV-seronegative individuals. In countries with a low TB prevalence HIV infected subjects have a 37-fold increased risk for TB, in countries with a high TB prevalence the risk is 21-fold increased (Getahun 2010). It has been shown that the risk of TB is already enhanced in the first year after HIV-seroconversion (Sonnenberg 2005). Low CD4 cell count, late presentation, low body mass index, anemia and a high HI viral load despite ART are known risk factors for the development of TB (Van Rie 2011). Despite adequate TB and HIV therapy, both morbidity and mortality remain increased in HIV-infected patients (Manas 2004, Whalen 2000). In the USA, TB mortality in 2006 was 9% in the general population but 20% in HIV infected subjects (CDC 2010).

While most opportunistic infections, including non-tuberculosis mycobacterial infections (NTM), occur almost exclusively in advanced stages of HIV-infection, TB is prevalent at any stage regardless of the CD4 T cell counts (Ackah 1995). More than 50% of pulmonary TB cases occur in patients having more than 200 CD4 T cells/µl.

Figure 2: Percentage of HIV positive TB cases in Europe, 2009 (ECDC 2011)
Clinical manifestations

In the early stages of HIV-infection the clinical symptoms of TB are similar to those in HIV-negative patients. Fever, fatigue, night sweats and weight loss are common. Pulmonary TB: As in HIV-negative cases, typical lesions of pulmonary TB in HIV-patients with more than 200 CD4 T cells/µl are upper-lobe lung infiltrates (with or without cavities). Tuberculosis granulomas are always present in these lesions. Cough and hemoptysis are frequent. Undefined lung opacities are often present on chest radiography as well as enlarged mediastinal lymph nodes. As immunodeficiency progresses, atypical pulmonary presentations or TB pleuritis become more frequent. Bronchopulmonary symptoms, such as cough and haemoptysis are often absent when TB occurs in the advanced stages of HIV infection. Because CD4 T lymphocytes are required for granuloma formation their cellular structure changes with increasing immunodeficiency (Diedrich 2011, Nambuya 1988). With the progression of immunodeficiency, hematogenous and lymphatic spread of mycobacteria is more common leading to miliary or disseminated TB or localized extrapulmonary TB (Elliott 1993, Kingkaew 2009).

Extrapulmonary TB occurs predominantly in patients with CD4 T cells below 200/µl, most commonly affecting the cervical lymph nodes (Schutz 2010). Lymph nodes are enlarged, hard and generally not painful on palpation. The formation of abscesses and draining fistulas as well as fever and malaise are common. Tuberculosis meningitis often emerges with ambiguous prodromal symptoms such as headache, nausea and vomiting followed by elevated temperature and clinical signs of meningeal irritation. The basal meninges are usually involved and cranial palsy of the III and VI nerves are common. Mono-, hemi- or paraparesis as well as loss of consciousness and seizures can occur. In any patient with symptoms and signs of meningitis, a lumbar puncture should be performed without delay.

Other extrapulmonary localizations include pericarditis, osteoarthritis, the urogenital tract and the skin. Tuberculosis lesions may involve adrenal glands causing Addison’s disease. Practically, any organ can be involved.

Miliary or disseminated TB: Clinical manifestations depend on multiple small granular lesions (lat. milium effusum) and their localization. Lungs may be involved and micro-nodular opacities are evident on chest x-ray. On radiological criteria alone, these lesions cannot be distinguished from pulmonary cryptococcosis. Miliary dissemination of TB can also involve the abdomen. In febrile patients with abdominal pain and ascites, peritoneal TB must be included in the differential diagnosis.

Diagnosis

The diagnosis is established based on clinical, radiological and microbiological findings. Diagnostic steps in the management of an HIV-infected patient with suspected TB do not differ from those with HIV-negative cases (Lange 2004). The differential diagnosis includes other infections such as NTM (e.g., M. avium complex), cryptococcosis, histoplasmosis, leishmaniosis, but also sarcoidosis, lymphoproliferative diseases, in particular non-Hodgkin lymphoma, and solid malignant neoplasia.

Radiology: Radiographic images of pulmonary TB can vary substantially. Pulmonary TB can mimic a variety of other pulmonary diseases and can be present without evident changes on chest radiography. However, typical chest radiographic findings
are ill-defined single or multiple opacities in the upper lobe, with or without cavities inside the opacities, and enlarged mediastinal lymph nodes. Calcifications and fibrotic scar formation may be either a sign of healed pulmonary TB or a clue of reactivated disease. In miliary TB, the chest radiography shows disseminated micronodular opacities. Patients with low CD4 T cell counts are less likely to present with typical radiographic changes but may have a normal chest X-ray, no cavities or a pleural effusion (Chamie 2010). In case of doubt, a chest CT scan is recommended whenever possible. If extrapulmonary TB is diagnosed, lung radiographic imaging as well as abdominal ultrasound should be performed to identify possible pulmonary disease, liver and spleen abscesses, thickening of the intestinal mucosa or ascites.

**Respiratory samples:** When pulmonary TB is suspected, three sputum samples should be collected on consecutive days for mycobacterial culture and direct sputum smear examination for acid fast bacilli (AFB). Sputum quantity (>3–5 ml) and its origin from the lower respiratory tract is essential, since smear microscopy for AFB and mycobacterial cultures remain sterile otherwise. If patients are unable to cough deeply or cannot produce sputum, induced sputum should be provoked by 10–15 minutes inhalation of hypertonic sodium (3%) chloride. The collection of early morning gastric aspirate is an alternative if bronchoscopy is not available. The aspirate should be buffered in phosphate solution immediately. Bronchoscopy is indicated when the clinical findings remain highly suspicious for TB. Bronchial secretions or bronchoalveolar lavage obtained by bronchoscopy do not allow a more sensitive or specific diagnosis of TB than sputum smear in patients with HIV infection (Conde 2000). However, bronchoscopy is very helpful in the differential diagnosis of TB and other diseases particularly since co-existence of several pulmonary diseases is frequent in patients with HIV-infection (Narayanswami 2003). Furthermore, histopathological examination of transbronchial biopsies may show typical tuberculosis granulomas. On the day after bronchoscopy, sputum should be collected as the microscopic yield is higher following the intervention even if no mycobacteria were detected in lavage fluid.

**Mycobacterial culture:** Sputum and all other biological materials (including heparinised blood, urine, fluids, biopsies) should always be sent for culture that detects MTB with a high sensitivity and specificity. The gold standard for the diagnosis of TB is culture identification of MTB after incubation of biological samples preferentially in liquid media or alternatively in solid media. Liquid media take less time (2–4 weeks) than solid media (3–5 weeks) until a positive result can be obtained. A mycobacterial culture is only considered negative if no mycobacteria are identified after 6–8 weeks of incubation. Non-tuberculous mycobacteria (NTM) usually grow much faster than MTB and can often be identified within two weeks of incubation. All new clinical isolates of MTB should undergo drug susceptibility testing for first-line and in case of MDR TB for second-line antibiotic regimens.

**Microscopy:** For sputum and all other biological materials direct microscopy should be performed after staining to detect AFB. The sensitivity of fluorescence microscopy (49%) is superior to conventional light microscopy (38%) (Cattamanchi 2009). Specificity of direct sputum microscopy is poor. At least 5,000–10,000 mycobacteria per slide are necessary to achieve a positive result in a routine setting. Approximately 50% of all patients with culture positive pulmonary TB are AFB smear negative on three consecutive sputum samples. AFB positive smears are present in approximately 5% of cases where pulmonary lesions are not visible on standard chest radiography (Ackah 1995). In addition, discrimination between MTB and other acid fast bacteria is not possible by microscopy. The differential diagnosis includes infections with NTM, nocardiae and rhodococci. Microscopy in HIV-infected patients with >200 CD4
T cells/µl and typical radiographic changes has the same yield as in HIV-seronegative patients. With advanced immunodeficiency, the likelihood of an AFB positive smear decreases (Chamie 2010). Biopsies of lymph nodes, pleura, peritoneum, synovia and pericardium and diagnostic fluid aspirates from all anatomic compartments are suitable for AFB microscopy and histological examination for typical granulomas.

**Nucleic acid amplification (NAAT):** Mycobacterial nucleic acid (DNA or RNA) can be detected in biological samples by a routine PCR test. MTB PCR test is faster than culture and more sensitive and specific than acid-fast staining. NAAT is especially helpful for differentiation of mycobacterial species when AFB are visible on microscopy. Under these circumstances, the sensitivity of MTB PCR is >95%. Unfortunately, the sensitivity decreases to 36–82% even for new diagnostic tools like the Cepheid Xpert when smear negative morning sputa are analysed directly (Rachow 2011, Boehme 2010). Because PCR can yield false negative results, reports should always be interpreted within the clinical context.

A major advantage of modern NAAT is the detection of resistance mutations within a few hours, enabling the physician to initiate an adequate antituberculosis drug regime.

In extrapulmonary TB, for example tuberculosis meningitis, where direct microscopy is often negative but a rapid diagnosis is needed, MTB PCR testing should be performed as part of the initial evaluation. For PCR analysis, biopsy samples should not be kept in formalin but rather be preserved in “HOPE” (Hepes-glutamic acid buffered organic solvent protection effect) media (Olert 2001).

**Tuberculin skin test (TST):** If no AFB are visible on microscopy but TB is still suspected, a TST, also known as purified protein derivative (PPD) test is recommended. A positive TST (or PPD) indicates an immunological memory to previous or ongoing contact with MTB. Positive TST results may also be found in patients who were BCG-vaccinated or who had contact with NTM. On the other hand, the TST in HIV positive patients with active TB has a sensitivity of only 31%. The sensitivity of TST is even more decreased, when CD4 cell counts decline (Syed Ahamed Kabeer 2009). The TST should only be administered intradermally according to the method described by Mendel and Mantoux. The standardized dose recommended by WHO and the International Union against Tuberculosis and Lung Diseases (IUATLD) is 2 Tuberculin Units (TU)/0.1ml PPD RT23/Tween 80. In the US and other countries, the standardized dose is 5 TU/0.1ml PPD-S, which is thought to be similar in strength. 48–72 hours after intradermal injection, the diameter of induration (not redness) of the injection site is measured along the short axis of the forearm (Sokal 1975). According to the Infectious Diseases Society of America (IDSA), the TST is positive if the induration diameter is ≥5mm in HIV infected persons (≥5 mm in HIV negative subjects). The IDSA guidelines for interpretation of the TST result are based on results of clinical studies that were conducted with 5 TU PPD-S in the US and therefore cannot be directly applied to other countries where different antigens are used.

**Interferon-γ Release Assay (IGRA):** Recently, IGRAs have been introduced for the diagnosis of MTB infection. They detect the secretion of IFN-γ by peripheral blood mononuclear cells (PBMC) that is induced by specific MTB peptides (ESAT-6 and CFP-10). However, the tests were developed to detect latent tuberculosis infection (LTBI, see below), not active disease (Chen 2011). Accordingly, the sensitivity of the Quantiferon TB-Gold in-tube test has a sensitivity of only 65% in HIV patients with active tuberculosis and shows no additional value in the diagnostic workup of HIV positive, AFB negative TB suspects (Syed Ahamed Kabeer 2009, Rangaka 2011). However, IGRAs are more sensitive and specific than the TST for diagnosis of MTB.
infection in patients with immunodeficiency (Chapman 2002, Pai 2004, Ferrara 2006, Rangaka 2007b, Jones 2007, Luetkemeyer 2007, Leidl 2009). Two IFN-gamma blood tests are currently available: an ELISA (Quantiferon TB-Gold in-tube test) and an ELISPOT (T-SPOT.TB Test). Two trials demonstrated a better sensitivity for the ELISPOT assay in HIV infection (Lawn 2007, Mandalakas 2008). Importantly, the ELISPOT test result is much less dependent on the level of CD4 T cells (Rangaka 2007a, Hammond 2008, Stephan 2008, Kim 2009), while the IFN-gamma response in the ELISA strongly correlates to the CD4 cell count (Leidl 2009). In patients with advanced immunodeficiency ELISA can therefore not be recommended for the diagnosis of LTBI. The sensitivity and specificity of the ELISPOT assay can possibly be improved further by relating them to the CD4 T cells of the patient (Oni 2010). Sequential IGRA measurements to monitor tuberculosis activity or treatment are not useful (Connell 2010, Lee 2010).

The detection of antibodies against mycobacterial components has no role in modern tuberculosis diagnostics.

**Therapy**

First-line drugs include rifampicin (RMP), isoniazid (INH), ethambutol (EMB) pyrazinamide (PZA) and streptomycin (SM). SM is only available as IM or IV formula and may thus not be considered “first-line”. INH and RMP are the most potent drugs. Second-line drugs include amikacin, capreomycin, cycloserine, levofloxacin, linezolid, moxifloxacin, prothionamide and rifabutin (RB).

Common cases of pulmonary TB can be treated with a standard 6-month treatment course, regardless of the HIV status. To prevent the development of drug resistance, active TB should always be treated with a combination of four drugs in the initial phase. The standard therapy consists of a 2 months course of RMP, INH, EMB and PZA, followed by a continuation phase therapy of 4 months with RMP and INH. Drug dosages are listed in Table 1. The four initial drugs should be administered until culture test results show drug susceptibility of MTB isolates.

Hospitalization is generally indicated to prevent the spread of the infection. As long as AFB are detected in the sputum or in the bronchoalveolar lavage, the patient should be treated in isolation. The duration of the infectious period in pulmonary TB depends on the extent of pulmonary lesions and cavities. Sputum should be regularly collected (weekly in the initial phase), evaluated for AFB by direct microscopy and for viable MTB by culture until the end of treatment. The infectiousness is considered to be very low once AFB are repeatedly absent in sputum smears. When at least three sputum samples obtained on different days are AFB negative, therapy can be continued as an outpatient. There appears to be no difference between HIV negative and HIV positive patients in the duration of therapy until the sputum becomes AFB negative and cultures remain sterile (Bliven 2010, Senkoro 2010). However, viable MTB can usually be cultured from sputum for a few weeks after microscopy has become AFB negative. Patients with MDR TB should be kept in isolation until both microscopy and sputum cultures remain negative.

Failure of therapy is associated with drug resistance, poor drug compliance or insufficient treatment duration (Sonnenberg 2001, Korenromp 2003). If sputum cultures are still positive after the initial phase of treatment or if the initial drug regimen was different from standard therapy (e.g., did not include RMP and INH), therapy should be extended to 9 months or longer (i.e., the continuation phase should be extended to 7 months or longer). Treatment is also longer than a standard 6 months course for AIDS patients, cavitary pulmonary TB and TB meningitis.
Adverse events

The most frequent and significant adverse events of antituberculosis drugs are listed in Table 1. INH should routinely be co-administered with prophylactic pyridoxine (vitamin B6) to prevent peripheral polyneuropathy. Before and during therapy with EMB, colour vision should be examined and monitored as this drug may affect the optic nerve. Dosages of EMB and PZA need to be adjusted in patients with impaired renal function. In patients with liver disease (including drug induced hepatitis), the choice of first-line drugs is limited as RMP, INH and PZA can worsen the liver injury. In these cases, a combination of EMB, streptomycin, cycloserine, moxifloxacin and/or linezolid may be administered. Since this second-line therapy is no different from that of MDR TB, these patients should be treated in specialized centres. Audiometric monitoring should be performed when streptomycin is used. Following the start of TB therapy, liver enzymes, serum creatinine and complete blood count should be monitored on a regular basis (e.g. in the initial phase every week, then every 4 weeks). Hyperuricemia is common when PZA is used. A mild polyarthralgia can be treated with allopurinol and non-steroidal antiphlogistic drugs. Arthralgia can also be induced by RMP and RB.

Table 1: Antituberculosis drug doses, side effects and drug interactions

<table>
<thead>
<tr>
<th>Antituberculosis drugs</th>
<th>Recommended dose</th>
<th>Common adverse events</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampicin (RMP)</strong></td>
<td>10 mg/kg</td>
<td>Elevation of liver enzymes, toxic hepatitis; allergy, fever; gastrointestinal disorders; discoloration (orange or brown) of body fluids; thrombopenia</td>
<td>Many drug interactions: induces cytochrome p450 (for ART drug interactions see Table 3) Monitor LFTs*</td>
</tr>
<tr>
<td>Also available in IV injection</td>
<td>&gt; 50 kg: 600 mg &lt; 50 kg: 450 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isoniazid (INH)</strong></td>
<td>5 mg/kg maximum 300 mg/day Administer with vitamin B6</td>
<td>Peripheral neuropathy; elevated liver enzymes, toxic hepatitis; CNS side effects: psychosis, seizures</td>
<td>Avoid d4T, ddI Avoid administration if pre-existing liver damage; avoid alcohol</td>
</tr>
<tr>
<td>Also available for IV or IM injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethambutol (EMB)</strong></td>
<td>40–55 kg: 800 mg/day 56–75 kg: 1.2 g/day 76–90 kg: 1.6 g/day</td>
<td>Optic neuritis; hyperuricemia; peripheral neuropathy (rare)</td>
<td>Antiacids may decrease absorption Baseline screen for visual acuity and colour perception (repeated monthly); contraindicated in pts with pre-existing lesions of optic nerve</td>
</tr>
<tr>
<td><strong>Pyrazinamide (PZA)</strong></td>
<td>30 mg/kg/day maximum 2.0 g/day</td>
<td>Arthralgia, hyperuricemia, toxic hepatitis, gastrointestinal discomfort</td>
<td>Hyperuricemia: uricosuric drug (allopurinol); monitor LFTs.</td>
</tr>
<tr>
<td><strong>Streptomycin</strong></td>
<td>0.75–1 g/day maximum cumulatative dose 50 g!</td>
<td>Auditory and vestibular nerve damage; renal damage; allergies, nausea, skin rash, pancytopenia</td>
<td>Audiometry; monitor renal function; should not be used in pregnancy</td>
</tr>
<tr>
<td>IV/IM administration only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antituberculosis drugs</td>
<td>Recommended daily dose</td>
<td>Common adverse events</td>
<td>Drug interactions Comments</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1 g/day Maximum cumulative dose 50 g!</td>
<td>Auditory and vestibular nerve damage</td>
<td>Audiometry; monitor renal function; do not use in pregnancy</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–30 mg/kg/day max 1 g/day &gt; 50 kg: 1 g &lt; 50 kg: 0.75 g maximum cumulative dose: 50 g</td>
<td>Renal damage, Bartter-like syndrome, auditory nerve damage</td>
<td>Audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10-15 mg/kg day maximum 1,000 mg/day</td>
<td>CNS disorders, anxiety, confusion, dizziness, psychosis, seizures, headache</td>
<td>Aggravates CNS side effects of INH and prothionamide Contraindicated in epileptics; CNS side effects occur usually within the first 2 weeks</td>
</tr>
<tr>
<td>Levofloxacin Also available for IV injection</td>
<td>500 or 1,000 mg/day</td>
<td>Gastrointestinal discomfort, CNS disorders, tendon rupture (rare)</td>
<td>Not approved for treatment in children; in adults rather use Moxifloxacin</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg /day</td>
<td>Thrombopenia, anemia, CNS disorders</td>
<td>Evidence for clinical use relies on case reports; expensive</td>
</tr>
<tr>
<td>Moxifloxacin Also available for IV injection</td>
<td>400 mg/ day</td>
<td>Gastrointestinal discomfort, headache, dizziness, hallucinations</td>
<td>Similar activity as rifampin, drug resistance is still rare</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>0.75–1 g/day</td>
<td>CNS disorders; liver damage, gastrointestinal discomfort</td>
<td>Slowly increase dosage; monitor LFTs</td>
</tr>
<tr>
<td>Rifabutin (RB)</td>
<td>300 mg/day</td>
<td>Gastrointestinal discomfort; discoloration (orange or brown) of urine and other body fluids; uveitis; elevated liver enzymes; arthralgia</td>
<td>Weaker inducer of p450 than rifampin; for ART drug interactions see Table 3. Monitor LFTs; generally preferred instead of rifampin in patients treated with ART drugs (see Table 3)</td>
</tr>
</tbody>
</table>

* LFTs: Liver function tests.  
** CNS: Central nervous system
Table 2: Re-introduction of TB drug following drug adverse event

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>50 mg</td>
<td>300 mg</td>
<td>5 mg/kg/day (max 300 mg/day)</td>
</tr>
<tr>
<td>RMP</td>
<td>75 mg</td>
<td>300 mg</td>
<td>10 mg/kg/day (max 600 mg/day)</td>
</tr>
<tr>
<td>PZA</td>
<td>250 mg</td>
<td>1,000 mg</td>
<td>25 mg/kg/day (max 2 g/day)</td>
</tr>
<tr>
<td>EMB</td>
<td>100 mg</td>
<td>500 mg</td>
<td>25 mg/kg/day for 2 months then 15 mg/kg/day</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>15 mg/kg/day (max 1 g/day)</td>
</tr>
</tbody>
</table>

Patients who exhibit severe adverse events should always be hospitalized for diagnosis and treatment. Drugs thought to be responsible for a given adverse event ought to be discontinued. If visual disturbance occurs on EMB, renal failure or shock or thrombocytopenia on RMP and vestibular dysfunction on streptomycin therapy, re-exposure to these agents must be avoided. Other drugs can be reintroduced one by one when symptoms resolve, beginning with the drug that is least likely to cause the adverse event. All drugs should be restarted at low dosages and dosages should be increased stepwise (Table 2). When no adverse effects occur after 3 days, additional drugs can be added. The drug that is most likely to be responsible for an adverse effect should be the last one to be restarted if no alternative is available.

If toxic hepatitis occurs, then all drugs should be stopped until the serum bilirubin and liver transaminases have normalized. In many cases, it is possible to re-introduce the causative drug (usually INH, RMP or PZA) with increasing dosage without further hepatic complications.

When second-line drugs are used it is usually necessary to prolong the standard treatment duration.

**ART and TB therapy**

Independent of the status of ART, uncomplicated non-cavitary pulmonary TB in HIV-infected patients can be treated using standard 6-months course with a similar success rate as in HIV-negative individuals (Burman 2001, Chaisson 1996, Hung 2003). If the therapeutic response is delayed (i.e., when sputum cultures are still MTB positive after 2 months of the initial phase), the TB therapy should be extended to at least 9 months.

A few issues must be considered regarding simultaneous ART and TB therapy.

**Paradoxical reaction:** Following initiation of TB therapy, patients already treated with ART present with paradoxical reactions (lymphadenopathy, fever or increasing pulmonary infiltrates) five times more often than ART naïve patients (Breen 2005). An acute exacerbation of a TH1 immune response against mycobacterial antigens seems to be responsible for the paradoxical reaction in ART experienced HIV/MTB co-infected patients (Bourgarit 2006).

**Unmasked TB and immune reconstitution inflammatory syndrome (IRIS):** Unmasked TB represents the progression of an undiagnosed subclinical TB disease which is already present before starting ART. The recovery of pathogen-specific immune responses during the initial months of ART trigger the unmasking of a subclinical disease. Screening strategies for underlying TB need to be carefully emphasized in order to prevent severe unmasking manifestations. All patients starting ART with an advanced immunodeficiency and principally those with access to ART programs in resource-limited settings, should undergo microscopic and culture screening for TB regardless of the presence or absence of symptoms.
A similar immunopathogenic mechanism is responsible for a form of tuberculosis progression termed IRIS. Patients with TB and advanced HIV infection can show a clinical progression of tuberculosis after ART is commenced. Even in the presence of TB treatment, ART is associated with immunoreconstitution and dysregulation resulting in the deterioration TB, mainly due to a strong inflammatory component (Lawn 2008). IRIS has been reported to occur in 25–60% of severely immunodeficient patients in the first three months of ART treatment and has been associated with a rapid immunologic and virologic response to ART (Michaelidis 2005, Lawn 2005a). The mortality of TB-IRIS was 10% in one Ugandan study (Worodria 2011). The criteria for the diagnosis of IRIS have been defined in an international consensus statement 2008 (Meintjes 2008). In summary, classic symptoms of TB are required (fever, lymphadenopathy, pulmonary consolidations, neurological symptoms, serositis). Notably, more than 10% of TB-IRIS cases in high prevalence countries are due to mycobacteria showing a previously undetected resistance to RMP (Meintjes 2009). Although IRIS can lead to paradoxical exacerbations, the diagnosis of TB must trigger the introduction of ART in HIV infected patients (OARAC 2011). During IRIS, both ART and TB therapy should be continued (OARAC 2011). A trial performed in South Africa found a clinical benefit of prednisolone administration for the treatment of IRIS (1.5 mg/kg for 2 weeks, followed by 0.5mg/kg for 2 weeks) (Meintjes 2010). However, data on IRIS therapy is sparse and no evidence based recommendations can be made yet.

**Adherence to therapy** is difficult to achieve due to the large number of ART and anti-tuberculosis drugs administered simultaneously and their overlapping toxicities. The most decisive determinant for the success of TB treatment is a good drug adherence for the entire duration of therapy. When compliance is impaired, the development of drug resistance and relapses are common. Therefore, WHO recommends that all patients with TB should be enrolled in directly observed therapy (DOT) programs.

**Drug interactions:** There are many pharmacological interactions between ART and anti-tuberculosis drugs (Table 3 and 4). Both RMP and protease inhibitors (PIs) are metabolized by cytochrome P450 3A. Concomitant therapy with PIs and RMP is generally not recommended (OARAC 2011, EACS 2009) (Table 3). The preferred antiretroviral regimen is efavirenz (<60kg: 600 mg QD; >60kg 800 mg QD) in combination with TDF+FTC when rifampin therapy is mandatory. In individual patients, screening for a CYP2B6 516G T polymorphism may be justified to determine the interaction between efavirenz and RMP (Kwara 2011). Alternatively efavirenz (standard dose) can be combined with rifabutin (450 mg QD) that has less cytochrome P450-3A inducing potential (OARAC 2011). The combination of nevirapine and RMP appears to achieve similar outcomes (Moses 2010).

A combination of 3–4 NRTIs (AZT, Abacavir, 3TC ± TDF) could represent a short-term option for patients with a viral load <100,000 copies/ml until TB treatment with RMP is completed. Rifabutin (150 mg three times weekly) can also be combined with boosted PIs, but one trial reported increased rates of neutropenia when combined with ATV/r (Table 4) (Zhang 2011). Other (off-label first line) regimens may include enfuvirtide (T-20) as it has no interactions with rifamycins (Boyd 2003). There are limited data about the combination of rifampicin and some other antiretroviral agents like tipranavir and maraviroc. Maraviroc should only be given under close observation. Rifampicin also induces the enzyme UGT1A1, leading to in-creased glucuronidation and reduced plasma levels of raltegravir (Wenning 2009) while Rifabutin increases the raltegravir AUC by 19% (OARAC 2011). No significant pharmacokinetic interactions were reported with tenofovir (Droste 2005).
Table 3: Recommendations for co-administering ART with Rifampin*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antiretroviral dosage adjustment</th>
<th>Rifampin dosage adjustment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PIs</td>
<td>No co-administration</td>
<td>No co-administration</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg (&lt;60 kg weight) or 800 mg (&gt;60 kg weight) OD</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No co-administration</td>
<td>No co-administration</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>No co-administration</td>
<td>No co-administration</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>600 mg BID</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>800 mg BID</td>
<td>None</td>
<td>TDM if possible as RAL levels decrease by 61 %</td>
</tr>
<tr>
<td>NRTI</td>
<td>Standard dose</td>
<td>Standard dose</td>
<td>Triple NRTI therapy not recommended</td>
</tr>
</tbody>
</table>

* EACS 2009, OARAC 2011, CDC 2007 (modified)

Table 4: Recommendations for co-administering ART with rifabutin*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antiretroviral dosage adjustment</th>
<th>Rifabutin dosage adjustment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PIs</td>
<td>Standard dose</td>
<td>150 mg every other day or 150 mg three times weekly</td>
<td></td>
</tr>
<tr>
<td>(LPV/r, FPV/r,DRV/r, SQV/r, ATV/r)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Standard dose</td>
<td>450 mg / day</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Standard dose</td>
<td>Standard dose</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td>Etravirine</td>
<td>No co-administration</td>
<td>No co-administration</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>ART without PI: standard dose</td>
<td>Standard dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>With TPV/r or FPV/r: 300 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>With other PI/r: 150mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Standard dose</td>
<td>Standard dose</td>
<td></td>
</tr>
</tbody>
</table>

* EACS 2009, OARAC 2011 (modified)

Priority: Treatment of active TB always has clinical priority over ART. Several studies suggested that simultaneous use of ART and anti-TB treatment in patients with less than 200 CD4 T cells, and most significantly in patients with less than 50 CD4 T cells (Havril 2011, Abdool 2011), could have a significant impact on survival (Blanc 2010, Schiffer 2007, Velasco 2009). Moreover, a recent randomized trial demonstrated that, at least in resource-limited settings, ART has the potential to reduce mortality even in patients with relatively conserved immune function (CD4 T cells 200–500 cells/µl) (Abdool Karim 2010, Karim 2009). When TB occurs in ART-naïve patients with 50–100 CD4 T cells/µl the mortality is high. Therefore simultaneous treatment of both infections is indicated (Dean 2002,
EACS 2009, OARAC 2011, Velasco 2009). It is recommended that TB therapy is initiated first. If TB therapy is tolerated, ART can be introduced within two weeks. Patients need to be monitored closely as the risk of paradoxical reaction is high and there are some overlapping toxicities.

In TB patients with CD4 T cells of 100–350/µl, anti-tuberculosis therapy must be started as soon as possible. The initiation of ART can be delayed for 4 weeks according to US guidelines and 8 weeks according to European guidelines (EACS 2009, OARAC 2011).

At a CD4 T cell count >350/µl, the US guidelines still recommend initiation of ART within 4–8 weeks after TB therapy was started. The European guidelines leave this decision at the physician’s discretion.

Patients who are already on ART when TB develops should remain on ART, although anti-retroviral regimen may need to be modified depending on the compatibility with anti-tuberculosis drugs (Dean 2002).

Patients with advanced immunodeficiency remain at high risk of developing TB despite ART, as function of the immune system is not fully restored by ART (Lange 2003, Lawn 2005a+b, Bonnet 2006, Sutherland 2006).

**Therapy of latent TB infection (LTBI)**

Latent tuberculosis infection (LTBI) is defined by a positive MTB specific immune response in the TST or an IGRA in the absence of active tuberculosis (Mack 2009). It is not clear which proportion of individuals with a positive MTB-specific immune response is indeed infected with viable MTB. Nevertheless, preventive chemotherapy is recommended for all HIV-infected individuals with a positive MTB-specific immune response in order to prevent active TB (Akolo 2010). HIV-infected persons should be given treatment if their reaction to the TST is ≥5mm. ELISPOT (T-SPOT.TB test) testing is superior to the TST and ELISA (Quantiferon-Gold in tube test) in HIV-infected individuals with low CD4 T cells (Leidl 2009).

The efficacy of prophylactic INH treatment in HIV-infected patients with LTBI has been demonstrated in several randomized studies (Bucher 1999, Elzi 2007). A 6-months prophylactic course of INH reduced the incidence of TB among HIV infected subjects from about 11.5 to 4–9 per 100 person-years (Grant 2005, Charalambous 2010). Therefore, a 6–9 months course of INH (300 mg daily) and pyridoxine is usually recommended for the treatment of LTBI. Alternatively, treatment with RMP (600 mg daily) can be offered. Other regimes consisting of rifapentine / INH weekly for 12 weeks, RMP / INH twice weekly for 12 weeks or INH daily for up to 6 years were not superior to the standard 6-months INH regime in HIV infected adults (Martinson 2011). In contrast, one study reported a 36-months INH regime to be superior to the standard 6-months course (Samandari 2011). A 2-months course of RMP+PZA was associated with adverse hepatic effects and is not recommended (Woldehanna 2004).

ART-naïve patients with negative TST do not benefit from either primary or secondary preventive chemotherapy of TB (Bucher 1999, Churchyard 2003). In addition, preventive chemotherapy with INH has no effect on the overall mortality (Woldehanna 2004). Although ART has a beneficial effect on the prognosis of HIV-positive patients with active TB, the effects of ART in LTBI are still unknown.

**Multidrug resistant (MDR) TB and extensively drug resistant (XDR) TB**

MDR TB means TB caused by MTB isolates resistant to at least RMP and INH, the two most efficient anti-TB drugs. Despite declining numbers of TB cases in many industrialized nations in recent years, the proportion of MDR TB is rising in many
countries. For example, in Germany, 2.2% of all MTB isolates were MDR in 2004, compared to 2.5% in 2004 (Eker 2008). Of these, 90% were isolated from migrants from the Russian Federation. In this geographical region, up to 50% of MTB show INH resistance, and up to 21% show multidrug resistance (WHO 2010). In these cases, selection of the correct drug regimen for treatment of LTBI and active TB becomes problematic.

XDR TB is defined by the WHO as to be resistant to at least RMP, INH, fluoroquinolones (moxifloxacin and levofloxacin) and to at least one injectable drug (aminoglycosides, capreomycin or kanamycin). Initial reports of a near 100% mortality of XDR-infected patients could not be confirmed in a meta-analysis (Gandhi 2006). However, a retrospective study from South Africa reported 30-day and 1-year mortality rates of 51% and 83%, respectively (Gandhi 2010). MDR TB continues to spread in South Africa despite good treatment adherence (Calver 2010). XDR TB has been already reported in at least 58 countries (WHO 2010). Until now, data on the management and prognosis of HIV/XDR TB coinfection is sparse.

Where possible, patients with MDR and XDR TB should be treated in specialized centers with second-line anti-tuberculosis drugs. Patients should not be discharged before repeated sputum cultures yield MTB negative results. In general, at least five anti-tuberculosis drugs that are in vitro active against the causative strain of MTB should be administered for 18–24 months after the sputum culture conversion. Long-term treatment with linezolid against MDR- and XDR TB has been associated with a high frequency of severe adverse drug events. Thus, linezolid should only be used when better options are not available (Migliori 2009).

Given the limited number of drugs available for the treatment of resistant MTB, the importance of tracing contact persons cannot be underestimated.

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tuberculosis immune reconstitution inflammatory syndrome in a cohort of TB/HIV patients commencing anti-

Atypical mycobacteriosis

Atypical mycobacterioses are usually synonymous with infections with *Mycobacterium avium complex* (MAC). Although MAC is by far the most frequent pathogen, numerous other atypical mycobacterioses exist that cause a similar disease pattern, such as *M. celatum*, *M. kansasii*, *M. xenopi* or *M. genavense*. MAC bacteria are ubiquitous and can be found in diverse animal species, on land, in water and in food. Exposure prophylaxis is therefore not possible. Consequently, isolation of infected patients is not necessary. While MAC may be detectable in the sputum or stool of asymptomatic patients (colonization), only patients with massive immunodeficiency and less than 50 CD4 T cells/µl develop disease (Horsburgh 1999). This used to include up to 40% of AIDS patients in the pre-HAART era (Nightingale 1992). The infection has now become very rare in industrialized countries (Karakousis 2004). However, it remains important, as it has developed into a completely new disease in the ART era. It previously occurred mainly with a chronic, disseminated course of disease, often in patients with wasting syndrome. MAC infections under ART are now almost always localized and related to immune reconstitution inflammatory syndrome (IRIS). The disease now occurs with manifestations that were previously never seen (see below).

Signs and symptoms

The symptoms of disseminated MAC infection are unspecific. When the CD4 count is less than 100 cells/µl, fever, weight loss and diarrhea should always lead to consideration of atypical mycobacteriosis. Abdominal pain may also occur. As described above, disseminated MAC infection has now become rare. Localized forms of atypical mycobacterioses are far more frequent. These include, above all, lymph node abscesses, which may occur practically everywhere. We have seen abscesses in cervical, inguinal and also abdominal lymph nodes, some of which developed fistulae and resolved only slowly even after surgical intervention. Any abscess appearing whilst on ART (with severe immunosuppression) is highly indicative of MAC! In addition to skin lesions, localized forms include osteomyelitis, particularly of the vertebrae, and septic arthritis (observed: knee, hand, fingers).

Diagnosis

Diagnosis of the disseminated form is difficult. Blood cultures (heparinized blood) should always be sent to a reference laboratory. Although atypical mycobacteria usually grow more rapidly than TB bacteria, the culture and differentiation from TB may take weeks. In cases presenting with anemia, bone marrow aspiration is often successful. If atypical mycobacteria are detected in the stool, sputum or even bronchoalveolar lavage BAL, it is often difficult to distinguish between infection requiring treatment and mere colonization. In such cases, treatment should not be initiated if general symptoms are absent. This is also true for *Mycobacterium kansasii* (Kerbiriou 2003).

Laboratory evaluations typically show elevated alkaline phosphatase (AP) – a raised AP in severely immunosuppressed patients should make us think of MAC. Similarly, MAC infection should be considered in any cases of anemia and constitutional symptoms. Cytopenia, particularly anemia, often indicates bone marrow involvement. Ultrasound reveals enlargement of the liver and spleen. Lymph nodes are often enlarged, but become apparent due to their number rather than their size (Gordin 1997). Here, differential diagnoses should always include TB or malignant lymphoma.
Direct specimens should always be obtained for localized forms, as identification of the organism from material drained from the abscess is usually successful.

**Treatment**

Treatment of MAC infection detected from culture is complex. Similarly to TB, monotherapy does not suffice. Since 1996, many clinicians prefer the combination of a macrolide (clarithromycin or azithromycin) with ethambutol and rifabutin (Shafran 1996). In the past, this treatment was given lifelong; today it is generally considered sufficient to treat for at least six months and until a ART-induced increase in the CD4 T cell count to above 100 cells/µl has been achieved. After publication of data indicating that rifabutin may be omitted from the regimen (Dunne 2000), the multicenter randomized ACTG 223 study demonstrated a survival benefit with the triple combination C+R+E compared to C+E and C+R – mortality rates were halved in the triple combination arm (Benson 2003).

Due to the high potential for interactions, rifabutin can be discontinued after several weeks when clinical improvement is observed. The clarithromycin dose should not exceed 500 mg BID. In at least two randomized studies, there was a significantly higher number of deaths in the treatment arms with a higher clarithromycin dose, for reasons that remain unclear (Chaisson 1994, Cohn 1999). Instead of clarithromycin, azithromycin can also be given, which is cheaper and interacts less with cytochrome P450 enzymes. Azithromycin and clarithromycin have comparable efficacy in combination with ethambutol (Ward 1998).

In disseminated illnesses, treatment should be monitored through regular blood cultures. Cultures must be negative by eight weeks at the latest. In the localized form, the response can be assessed better clinically. Every MAC therapy has a high potential for side effects and drug interactions. Concomitant medications, including ART, should be carefully examined – dose adjustments are frequently required and there may be contraindications (see Drugs section).

Reserve drugs such as amikacin, quinolones or clofazimine are only required in rare cases today. It is important to perform resistance testing for all atypical mycobacterial infections with species other than *M. avium complex*.

We have generally stopped treatment of localized MAC infections when the abscess has healed – which usually takes several months. In individual cases, steroids may be helpful temporarily. However, there are no specific guidelines for treatment of local MAC infections.

**Prophylaxis**

In the US, large placebo-controlled trials have shown that the macrolides, clarithromycin and azithromycin, as well as rifabutin, significantly reduce MAC morbidity and mortality when used for primary prophylaxis in severely immunocompromised patients (Havlir 1996, Nightingale 1992, Pierce 1996, Oldfield 1998). Prophylaxis also saves costs (Sendi 1999). However, MAC infections are more rare in Europe. As a result, and because of concerns over compliance and development of resistance, few patients in Europe receive primary MAC prophylaxis (Lundgren 1997). For patients failing currently available ART regimens and without new treatment options, prophylaxis with a macrolide should be considered at low CD4 T cell counts (<50 cells/µl). Weekly dosing with azithromycin is convenient for patients and has comparable efficacy to daily rifabutin (Havlir 1996).

Primary prophylaxis and maintenance therapies can be discontinued quite safely at CD4 T cell counts above 100/µl (Currier 2000, El Sadr 2000, Shafran 2002, Aberg
2003). It is possible that even partial viral suppression suffices for MAC-specific immune reconstitution (Havlir 2000). Complete recovery as a result of immune reconstitution is possible (Aberg 1998).

**Treatment/prophylaxis of MAC** (daily doses, if not specified otherwise)

<table>
<thead>
<tr>
<th><strong>Acute therapy</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment of choice</strong></td>
<td>Clarithromycin + ethambutol + possibly rifabutin</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>Azithromycin + ethambutol + possibly rifabutin</td>
</tr>
<tr>
<td><strong>Maintenance therapy</strong></td>
<td>As for acute therapy, but without rifabutin. Discontinue if &gt;100 CD4 T cells/μl &gt;6 months</td>
</tr>
<tr>
<td><strong>Primary prophylaxis</strong></td>
<td>Consider for CD4 cells below 50/μl. Discontinue if &gt;100 CD4 T cells /μl &gt;3 months</td>
</tr>
<tr>
<td><strong>Treatment of choice</strong></td>
<td>Azithromycin 2 tab. at 600 mg/week</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>Clarithromycin 1 tab. at 500 mg BID</td>
</tr>
</tbody>
</table>

**References**


Herpes simplex

Infections with herpes simplex viruses are a frequent problem for HIV-infected patients (Chang 1995). Chronic disease is frequent, particularly with severe immunodeficiency (below 100 CD4 T cells/µl). Two viruses should be distinguished. HSV-1 is transmitted by direct contact with mucosal membranes such as kissing, and causes the typical, itchy perioral blisters on the lips, tongue, gums, or buccal mucosa. HSV-2 is sexually transmitted and leads to lesions on the penis, vagina, vulva and anus. HSV-2–associated lesions significantly increase the risk of transmission of HIV (Freeman 2006, Ouedraogo 2006, see Prevention). In severe cases, other organs may be affected. These include mainly the esophagus (ulcers), CNS (encephalitis), eyes (keratitis, keratoconjunctivitis, uveitis) and respiratory tract (pneumonitis, bronchitis). In such cases and with persistence of lesions for a period of more than four weeks, herpes simplex infection is an AIDS-defining illness.

Signs and symptoms

The typical blisters itch and burn. Oral involvement may impair food intake. In cases of genital or anal herpes (proctitis), urination and defecation can be very painful. Extensive lesions may occur with severe immunosuppression. Regional lymph nodes are often enlarged. The clinical symptoms of disseminated disease depend on the organs affected.

Diagnosis

Diagnosis of oral, genital or perianal herpes can often be made clinically. If there is doubt, then swabs should be taken, placed in viral culture media, and quickly transported to the laboratory. The diagnosis of organ manifestations usually requires histology. Diagnosis is particularly difficult for HSV encephalitis, as cerebrospinal fluid often does not help. Serologies are only useful if they are negative, therefore making HSV infection improbable.

Treatment

In general, every treatment, whether topical, oral or systemic, is more effective when started early. For patients with a good immune status and only discrete lesions, topical treatment with acyclovir cream or ointment is adequate. Penciclovir cream is probably as effective as acyclovir (Chen 2000) and allegedly less irritant, although significantly more expensive. The nucleoside analog acyclovir remains the treatment of choice for systemic treatment. Acyclovir inhibits the DNA polymerase of herpes viruses. Resistance is rare, despite the fact that this agent has been used since 1977 and numerous generics are now available (Levin 2004). Acyclovir is usually well tolerated and effective against both HSV-1 and HSV-2. Severe cases with mucocutaneous or organ involvement should be treated immediately intravenously. As CNS levels are lower than in plasma, the dose should be increased to treat encephalitis. If acyclovir is to be given intravenously, renal blood values should be checked. Valacyclovir and famcyclovir are equally effective alternatives to acyclovir (Ormrod 2000, Conant 2002), though substantially more expensive. The main advantage is their improved oral bioavailability; they require less frequent dosages. In cases of recurrent genital herpes lesions shorter therapeutic regimens (i.e., two days of famciclovir) may be as effective as standard 5-day courses (Bodsworth 2008).
Brivudine remains a good alternative for HSV-1 and HZV (zoster). However, it is possible that this dihydropyrimidine dehydrogenase inhibitor causes mitotoxicity and reduces the efficacy of HIV drugs (U. Walker 2005, personal communication). Foscarnet should only be used in exceptional cases due to its toxicity. However, it may be helpful in extensive, refractory cases.

Newer drugs, unlike acyclovir, that do not inhibit DNA polymerase but rather helicase, another herpes virus enzyme, have been effective in clinical trials (Tyring 2012). However, additional studies are warranted to define the potential of helicase inhibitors.

A local anesthetic that can be produced by the pharmacist can be prescribed in addition for painful mucocutaneous lesions. Unfortunately, the approved tetracaine solution (HervirosTM) has been taken off the market. Some pharmacists can, however, confect something similar in-house.

**Prophylaxis**

Primary prophylaxis is not recommended. However, a meta-analysis of almost 2000 patients in eight randomized studies showed that acyclovir can reduce the risk of both HSV and HZV disease by more than 70%. Even mortality was reduced by 22% (Ioannidis 1998). The introduction of ART has changed the relevance of this data. Nevertheless, it can still make sense, even today, to treat persistent recurrences with long-term low-dose acyclovir or valacyclovir (Dejesus 2003, Warren 2004). However, short bursts of subclinical genital HSV reactivation are frequent, even during high-dose acyclovir therapy (Johnston 2012). Herpes simplex vaccines are still in early stages of development (Belshe 2012).

**Treatment/prophylaxis of HSV infection (daily doses)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Acyclovir 1 tab. at 400 mg 5x/day</td>
</tr>
<tr>
<td>Severe cases</td>
<td>Acyclovir ½-1 amp. at 500 mg TID (5-10 mg/kg tid) IV</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Valacyclovir 2 tab. at 500 mg TID</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Famciclovir 1 tab. at 250 mg TID</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Brivudine 1 tab. at 125 mg QD</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Interactions between HIV and herpes simplex**

Prevalent HSV-2 infection is associated with a three-fold increased risk of HIV transmission among both men and women (Freeman 2006, see the Prevention section in the ART chapter). Large randomized studies could demonstrate that during anti-HSV therapy, HIV replication is also inhibited. During treatment with acyclovir, HIV plasma viremia is decreased by 0.33 log (Ludema 2011). High dose valacyclovir resulted in a slightly greater reduction of HIV replication (Mugwanya 2011). This reduction is at first sight not very impressive, but nevertheless it is significant. These results have recently revived the significance of acyclovir therapy (Vanpouille 2009) despite the fact that acyclovir does not prevent the transmission of HIV (Celum 2008+2010, Watson-Jones 2008). This old drug has become interesting again. Possibly new derivatives will be developed that are better tolerated and more effective in terms of antiviral potency towards HIV.
References


Herpes zoster

Herpes zoster is the reactivation of an earlier infection with varicella virus, which subsequently maintains a lifelong residence in the spinal ganglia. Herpes zoster episodes can occur even in HIV+ patients with relatively good immune status, and are also seen during immune reconstitution (Martinez 1998). Given the high incidence of zoster episodes in HIV+ patients, herpes zoster can be regarded as an indicator disease for HIV infection (Søgaard 2012). With more advanced immunodeficiency, herpes zoster tends to become generalized. In addition to involvement of one or more dermatomes, dangerous involvement of the eye (affecting the ophthalmic branch of the trigeminal nerve, “herpes zoster ophthalmicus”, with corneal involvement) and ear (herpes zoster oticus) may occur. Most feared is involvement of the retina with necrotizing retinitis. The neurological complications include meningoencephalitis, myelitis and also involvement of other cranial nerves (Brown 2001).

Signs and symptoms

There are often prodromal signs with headache, malaise, and photophobia, accompanied only rarely by fever. The affected areas are initially hypersensitive, and then become pruritic and/or painful within hours or days. Pain can precede lesions by several days. Lesions often show segmental, yet always unilateral, erythema with herpetiform blisters within one or more dermatomes. Lesions ulcerate, are often hemorrhagic, and gradually dry up. They should be kept dry and clean to avoid bacterial superinfection. Involvement of several dermatomes often leaves treatment-resistant pain syndromes with zoster neuralgia. Post-herpetic neuralgia can be assumed if pain persists for more than a month (Gnann 2002).

Diagnosis

Cutaneous involvement usually allows clinical diagnosis of herpes zoster. However, diagnosis may be difficult especially on the extremities and in complicated zoster cases. Typical cases do not require further diagnostic tests. If there is uncertainty, a swab may be taken from a blister and sent to the laboratory in viral culture media. An immunofluorescence assay is presumably more reliable. HZV encephalitis is only detectable through analysis of CSF by PCR. Herpes zoster oticus should be considered in cases of unilateral, peracute hearing loss, which is not always visible from the outside. Either examine the ear yourself or consult an ENT specialist! For visual impairment the same rules apply as for CMV retinitis – refer the patient to the ophthalmologist as quickly as possible.

Treatment

Monosegmental zoster can be treated on an outpatient basis with oral acyclovir. Rapid initiation of treatment is important. Systemic therapy is always necessary, and doses are higher than for HSV. Lesions dry up more rapidly if calamine lotion is used, which also relieves pain. Gloves should be worn, given that the lesions are highly infectious initially. Likewise, unvaccinated individuals without a history of chickenpox should not come into close contact with a case of herpes zoster. Analgesics (novaminsulfone, or better still tramadole) should be given generously. Any complicated, multi-segmental or facial herpes zoster should always be treated with intravenous therapy. As with HSV, several alternatives for treatment include valacyclovir, famcyclovir and brivudine (see HSV). There is still controversy if the unpleasant post-herpetic neuralgia allegedly occurs less frequently under these drugs than under acyclovir (Li...
2009, McDonald 2011). Valacyclovir, famcyclovir and brivudine are not licensed for treatment of immunocompromised patients. They are also substantially more expensive than the numerous acyclovir formulations. Acyclovir resistance may occur in the thymidine kinase gene, but is rare (Gershon 2001, Saint-Leger 2001). In these cases, foscarnet can be given. Novel anti-HZV drugs are still in early phases of development (Review: Andrei 2011).

Pain management of post-herpetic neuralgia is problematic. Carbamazepine or gabapentine only partially help. Steroids are generally not advised (Gnann 2002). Since November 2007 lidocaine medicated plasters (Versatis®) are licensed in Europe which can be pasted to painful areas. Side effects are local skin irritation. Herpetic lesions should be healed before use (Garnock-Jones 2009). In 2009, the FDA approved Qutenza® 8% patch for the management of neuropathic pain due to postherpetic neuralgia (PHN). Qutenza® delivers a synthetic form of capsaicin, the substance in chili peppers that gives them their heat sensation, through a dermal delivery system. The patch is applied by a physician or a healthcare professional.

Prophylaxis

Varicella vaccination seems to be fairly safe and effective for patients with more than 400 CD4 T cells/µl (Gershon 2001, Weinberg 2010). It should be considered if HZV serology is negative. In individuals with negative serology and exposure to highly infectious HZV, administration of hyperimmunoglobulin (2 mg/kg IV) may be attempted in individual cases. Long-term primary prophylaxis is not advised. Some dermatologists prefer long-term low dose therapy if there are persistently recurring episodes.

<table>
<thead>
<tr>
<th>Treatment/prophylaxis of HZV infection (daily doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute therapy</strong></td>
</tr>
<tr>
<td>Duration: at least 7 days</td>
</tr>
<tr>
<td>Treatment of choice: Acyclovir 1 tab. at 800 mg 5x/day</td>
</tr>
<tr>
<td>Severe cases: Acyclovir 1-2 amp. at 500 mg TID (10 mg/kg tid) IV</td>
</tr>
<tr>
<td>Alternatives: Valacyclovir 2 tab. at 500 mg TID</td>
</tr>
<tr>
<td>Alternatives: Famciclovir 2 tab. at 250 mg TID</td>
</tr>
<tr>
<td>Alternatives: Brivudine 1 tab. at 125 mg QD</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
</tr>
<tr>
<td>Not recommended</td>
</tr>
</tbody>
</table>

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Progressive multifocal leukoencephalopathy (PML)

PML is a severe demyelinating disease of the central nervous system. It is caused by JC virus (JCV), a polyoma virus found worldwide. JCV was named after the initials of the first patient John Cunningham, from which this simple DNA virus was first isolated in 1971 (Major 1992). Therefore, JC has no connection, as is often wrongly assumed, with Jakob-Creutzfeldt syndrome. As seroprevalence is high, at up to 80%, latent persistent infection is assumed. Kidneys and bones seem to be important reservoirs. Only impaired cellular immunity leads to reactivation of JCV and manifestation of disease. It seems certain that JCV reaches the CNS via leukocytes, and then affects mainly oligodendrocytes and consequently the cells which comprise the myelin sheaths. Destruction of these is as macroscopically apparent as multifocal demyelination. The main focus of the disease is the white matter of the cerebral hemispheres, but in some cases, the cerebellum, the grey matter may also be affected. PML is a classic opportunistic infection and can occur in patients with hematological diseases or during therapy with monoclonal antibodies such as rituximab, natalizumab or efalizumab (Yousry 2006, Carson 2009, Major 2010). However, HIV patients are by far the largest patient group. Severe immunodeficiency is frequently seen, but not obligatory for development of PML. In contrast to CMV or MAC infection, PML does not always indicate the final stages of HIV infection. Although CD4 T cells are usually below 100/µl at manifestation of disease, PML may also occur at above 200 CD4 T cells/µl. The decrease in incidence is not as marked as with other OIs. After cerebral toxoplasmosis, it is now probably the second most common neurological OI (Antinori 2001).

Prognosis was poor in the pre-HAART era. The median interval between the onset of the first symptoms and death was between 3 and 6 months. Patients usually died of secondary complications after being bedridden for many weeks. The prognosis is slightly better at CD4 counts above 200/µl (Berger 1998). Disease progression seems to be much slower on ART, and even complete remission seems possible (Albrecht 1998). However, these effects are not as impressive as for other OIs: in a Spanish study of 118 PML patients on ART, 64% were still alive 2.2 years after diagnosis (Berenguer 2003). Complete remission is not the rule, even with sufficient ART. They mainly occur in cases of inflammatory PML, which occurs in the course of immune reconstitution inflammatory syndrome (IRIS) (Du Pasquier 2003, Hoffmann 2003, Tan 2009). The number of CD4 T cells and the JC virus-specific immune response seem to be relevant as prognostic markers, although the JCV viral load does not seem relevant (Khanna 2009, Marzocchetti 2009). Today PML is still the OI with the highest mortality (ART-CC 2009).

Signs and symptoms

Although there is a broad spectrum of PML symptoms due to the variety of localized areas of demyelination, the clinical signs and course of the disease have several common characteristics. In addition to cognitive disorders, which may range from mild impairment of concentration to dementia, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as speech and even visual deficits. We have seen several blind patients with PML. These deficits may be isolated and initially present as discrete changes in coordination, rapidly leading to considerable disabilities. Epileptic seizures may also occur. Loss of sensibility, fever, and headache are rare and are usually more typical of cerebral toxoplasmosis.
Diagnosis

Clinical suspicion of PML should be rapidly confirmed radiologically. But beware: a CCT scan is not helpful – it does not clearly reveal hypodense lesions. An MRI is much more sensitive to detecting both the number and size of lesions than a CCT and usually shows high signal intensity lesions in T2 weighted imaging and in FLAIR sequence, which are hypointense in T1W and often do not show gadolinium enhancement or mass effect. ART may result in inflammatory courses that involve significant enhancement (see IRIS). Exclusion of grey matter is typical – since this is a leukoencephalopathy. Furthermore, it should be noted that the lesions are almost always asymmetrical.

An MRI often allows clarification between cerebral toxoplasmosis or lymphoma. However, the huge, extensive lesions covering an entire hemisphere that are often shown in the literature are not always present. Every PML starts small – very discrete, localized, solitary lesions can occur and certainly do not exclude the diagnosis. PML can occur anywhere in the brain, and there are no typically susceptible areas. Lesions are often parieto-occipital or periventricular, but the cerebellum may also be involved. It is important that the images are assessed by a radiologist or clinician familiar with PML. Even then, it is difficult to distinguish PML from HHV-6 infection (Caserta 2004) or HIV leukoencephalopathy (Langford 2002).

Clinicoradiological diagnosis is therefore not definitive. Examination of cerebrospinal fluid is essential. Generally, if there is no other coinfection, unspecific inflammatory signs are absent although the total protein content is usually slightly elevated. Pleocytosis is rarely seen, and more than 100/3 cells in the CSF make PML unlikely. CSF should always be tested for JCV. Newer PCR methods have a sensitivity of around 80% and a specificity of over 90%. A CSF sample should be sent to a JCV-experienced laboratory.

PML is very probable in cases of clinicoradiological suspicion and positive JCV PCR. In such cases, brain biopsies are no longer recommended. Nevertheless, negative PCR does not exclude the diagnosis. Levels of JCV viral load may vary significantly and do not correlate with the extent of lesions (Eggers 1999, Garcia 2002, Bossolasco 2005). Unfortunately, JCV PCR is even less useful – many patients with PML have a low or undetectable JCV CSF viral load while on ART (Bossolasco 2005). Stereotactic brain biopsy may become necessary in individual cases.

Treatment

A specific PML treatment is not available. Foscarnet, interferon, immune stimulants, steroids or cytosine arabinoside are not effective (Hall 1998). Cidofovir and camptothecin are the two newer drugs currently being discussed. It is feared that these drugs will have a similar fate in controlled studies. Camptothecin is an alkaloid cytostatic, which inhibits topoisomerase I, a nuclear enzyme that is required for DNA and therefore for JCV replication (O’Reilly 1997). Currently, only data from case studies and a small series of patients exist in which 3 out of 12 patients experienced clinical improvement under the camptothecin-derivate topotecan (Vollmer-Haase 1997, Royal 2003). However, one patient died while taking topotecan, which shows high hematoxicity. Results of randomized studies are missing and this approach can not be recommended outside clinical studies.

The nucleotide analog cidofovir, which is licensed for CMV retinitis, showed some positive effects. According to an analysis of 370 patients from numerous studies (De Luca 2008), a real benefit has not been proven. Our experiences have been rather disappointing and, in a retrospective analysis of 35 patients, cidofovir was even associated with a poorer prognosis. However, this chiefly reflects the frustration of
patients and clinicians – cidofovir was mainly used in cases of progressive disease (Wyen 2004). There may no longer be an argument for the use of cidofovir in PML patients.

In recent years, 5-HT2a inhibitors and/or serotonin receptor antagonists have been proposed for PML treatment. It has been shown that the serotonergic receptor SHT2AR could act as the cellular receptor for JCV on human glial cells (Elphick 2004); the blockade could represent a therapeutic goal. Case studies for some agents such as risperidone and mirtazapine, which block serotonergic receptors, exist already (Verma 2007, Focosi 2007+2008, Cettomai 2009). However, controlled studies are missing. This is also the case for mefloquine (Brickelmeier 2009).

It should be an absolute priority to optimize ART in cases of PML. Improvement of the JC virus-specific immune response which is often observed within immune reconstitution determines the patient’s further progress to a large extent (Khanna 2009, Marzocchetti 2007+2009, Gasnault 2011). Our early observation that prognosis significantly improved on ART (Albrecht 1998) was confirmed by several other groups (Clifford 1999, Dworkin 1999, Gasnault 1999+2008, Tantisiriwat 1999, Berenguer 2003, Khanna 2009). Since synergy between HIV and JCV has been demonstrated in vitro, maximal HIV suppression should be the goal. Although progression of disease has been described with sufficient antiretroviral therapy, ART often remains the only real hope for patients. There is also some evidence that intracerebral penetrating antiretroviral agents such as AZT, FTC, abacavir, nevirapine and lopinavir are more efficient regarding survival of patients with PML (Gasnault 2008). There is one small pilot trial suggesting that an intensive 5-drug ART may improve survival of patients with PML (Gasnault 2011).

### Treatment/prophylaxis of PML

<table>
<thead>
<tr>
<th>Treatment/prophylaxis of PML</th>
<th>Acute therapy</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of choice ART</td>
<td>The most important goal is maximal HIV suppression and immune reconstitution. Use intracerebral penetrating agents such as AZT, FTC, abacavir, nevirapine and lopinavir</td>
<td>Do not exist</td>
</tr>
<tr>
<td>Experimental</td>
<td>Only within clinical trials (risperidone? mirtazapine?)</td>
<td></td>
</tr>
</tbody>
</table>

### Prophylaxis

There is none. Exposure prophylaxis is also not possible.

### References


Bacterial pneumonia

Bacterial pneumonia occurs even with a relatively good immune status (>200 CD4 T cells/µl). It is not as closely associated with immunodeficiency. Furthermore, the decrease in incidence since the HAART era has been more moderate than for other opportunistic infections. Only recurring, radiologically and culturally detected acute pneumonia (more than one episode in the last 12 months) is considered AIDS-defining. As with HIV-negative patients, community-acquired pneumonia should be distinguished from nosocomial pneumonia. Travel history is important, particularly for community-acquired pneumonia.

The bacteria that are most frequently found to cause community-acquired pneumonia in HIV infected patients are Pneumococcus and Hemophilus influenza. Mycoplasma is important to consider, particularly in younger patients. Klebsiella, Staphylococcus aureus and Pseudomonas aeruginosa are other common pathogens. Legionella are rare.

Intravenous drug users develop community-acquired pneumonia significantly more often than other patient groups. Comorbidity, alcohol over-use and current smoking are other risk factors (Grau 2005). Therapy interruption and cigarette smoking were also major risk factors in SMART (Gordin 2008). Abstinence from smoking significantly reduces the risks of bacterial pneumonia (Bénard 2010). Earlier reports about increased incidence of bacterial pneumonia on a T-20 containing regimen have not been confirmed (Trottier 2005, Kousignian 2010). Low CD4 T cell counts and an existing liver cirrhosis are major risk factors for severe cases (Manno 2009, Madeddu 2010). Nosocomial pneumonia is often caused by hospital germs (Klebsiella, Staphylococcus, Pseudomonas). In such cases, treatment depends on local resistance patterns and experience (Gant 2000, Vogel 2000).

Signs and symptoms/diagnosis

Acute, usually high, fever and productive cough are typical. Breathing may be painful because of accompanying pleuritis, but real dyspnea is rare. Auscultation almost always allows distinction from PCP. If something can be heard, then PCP is unlikely. Chest radiography secures the diagnosis. CRP is significantly elevated, LDH usually normal. It is essential to take several blood cultures at body temperatures above 38.5˚C before starting treatment. A major problem regarding the blood culture is that diagnosis takes time (24–48 hours) and is not so sensitive. However it is the only procedure that allows a resistance test. Sputum culture is a simple method allowing determination of etiology in approximately half of all cases – however, its overall utilization remains controversial and results strongly depend on the clinician’s experience (Cordero 2002). This also applies to the pneumococcal antigen determination in urine and the diagnosis of other specific viruses which are not recommended in current guidelines (Tessmer 2010).

Treatment

General

Treatment of bacterial pneumonia in HIV patients is similar to that in HIV-seronegative patients. Therapy should always begin empirically, without waiting for sputum or blood culture results. Many HIV patients with bacterial pneumonia can be treated as outpatients. Patients with poor immune status below 200 CD4 T cells should be hospitalized, as well as patients with high fever (above 39.5˚C), poor compliance, signs of organ failure, CNS disorders (confusion) or poor vital signs (tachypnea, tachycardia, hypotonia) and older patients (above 65 years).
Sufficient hydration is important in all patients. If patients remain in ambulatory care, then this is an indication that they should drink a lot (more than 2 liters of water daily). The use of supportive therapy with expectorants or mucolytics such as N-acetylcysteine or antitussives is controversial. On adequate therapy, improvement can be expected within 48–72 hours. If patients, especially the severely immunocompromised, have a persistent fever, then the treatment must be reconsidered after 72 hours, at the latest. It should be noted that the current first-line therapies are not effective against *Pseudomonas aeruginosa*.

**Medication**

Different drugs are possible for ambulatory treatment. Even an attempt with penicillin may be justified in some circumstances – depending on local rates of Pneumococcus and *Hemophilus influenzae* resistance. It should be noted that HIV-infected patients frequently develop allergies.

**Empiric treatment/prophylaxis of community-acquired bacterial pneumonia** (daily doses) – there may be significant differences in price!

<table>
<thead>
<tr>
<th><strong>Outpatient</strong></th>
<th><strong>Duration:</strong> 7–10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Amoxicillin + clavulanic acid 1 tab. at 875/125 mg TID</td>
</tr>
<tr>
<td>Mild</td>
<td>Clarithromycin 1 tab. at 500 mg BID</td>
</tr>
<tr>
<td>Mild</td>
<td>Roxithromycin 1 tab. at 300 mg QD</td>
</tr>
<tr>
<td>Mild</td>
<td>Cefuroxime 1 tab. at 500 mg BID</td>
</tr>
<tr>
<td>Mild</td>
<td>Cefpodoxime 1 tab. at 200 mg BID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Inpatient</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Piperacillin (+ tazobactam) + macrolide</td>
</tr>
<tr>
<td>Severe</td>
<td>Ceftriaxone + macrolide</td>
</tr>
<tr>
<td>Severe</td>
<td>Cefuroxim + macrolide</td>
</tr>
</tbody>
</table>

**Prophylaxis**

| Vaccination (pneumococcal polysaccharide) | Pneumovax 23™ pre-filled syringe IM |

Aminopenicillins are effective against *Hemophilus influenza* and various gram-negatives. However, when combined with clavulanic acid, active against beta-lactamase-producing bacteria, they are associated with more gastrointestinal complaints. Newer oral cephalosporins have a broader spectrum against gram-negatives, while at the same time have good efficacy against Pneumococcus and Hemophilus. They are, however, expensive.

Macrolides are advantageous for atypical bacteria such as Mycoplasma, Chlamydia and Legionella – but the proportion of macrolide-resistant Pneumococcus is increasing (14% in Germany). Efficacy is also limited in some Hemophilus strains.
For quinolones, it should be noted that ciprofloxacin has no or only weak efficacy against many important pathogens. Therefore only newer quinolones should be used. However, in 2009, a ‘Dear Doctor’ letter was sent to European health care professionals, describing the rare occurrence of fulminant hepatitis and the Stevens-Johnson syndrome or toxic epidermal necrolysis in patients using moxifloxacin. These side effects must be placed in the overall balance of pros and cons of moxifloxacin as compared to the alternatives. If patients are hospitalized, then intravenous administration is possible initially. In this case, at least two antibiotics should be combined. Targeted treatment after isolation of the pathogen, and, in particular, treatment of nosocomial pneumonia, should depend on local resistance patterns and the recommendations of the in-house microbiologist.

**Prophylaxis**

The Pneumovax® vaccine provides effective protection. It should be utilized in all HIV patients with >200 CD4 T cells/µl. However, newer data suggest that Pneumovax® has a significant, independent protective effect against pneumococcal disease, regardless of CD4 lymphocyte count (Penaranda 2007). Although it does not avert pneumonia in all cases it seems to have a positive effect on the further course of the treatment (Imaz 2009).

**References**


Cryptosporidiosis

Cryptosporidiosis is a parasitic intestinal disease with fecal-oral transmission. It is mainly caused by the protozoon *Cryptosporidium parvum* (two genotypes exist, genotype 1 is now also known as *C. hominis*) and may affect both immunocompetent and immunocompromised hosts (Review: Chen 2002). First described in 1976, cryptosporidia are among the most important and most frequent causes of diarrhea worldwide. Important sources of infection for this intracellular parasite include animals, contaminated water and food. The incubation period lasts approximately 10 days. While diarrhea almost always resolves within a few days in otherwise healthy hosts or in HIV-infected patients with CD4 counts greater than 200 cells/µl, cryptosporidiosis is often chronic in AIDS patients. Particularly in severely immunocompromised patients (<50 CD4 T cells/µl), diarrhea may become life-threatening due to water and electrolyte loss (Colford 1996). Only chronic, and not acute, cryptosporidiosis is AIDS-defining.

**Signs and symptoms**

The typical watery diarrhea can be so severe that it leads to death as a result of electrolyte loss and dehydration. Up to twenty bowel movements a day are not uncommon. Tenesmus is frequent, along with nausea and vomiting. However, the symptoms are highly variable. Fever is usually absent. Additionally, the biliary ducts may occasionally be affected with the elevation of biliary enzymes. Pancreatits is also possible.

**Diagnosis**

When submitting stool samples, the laboratory should be informed of the clinical suspicion. Otherwise, cryptosporidia are often overlooked. If the lab is experienced and receives the correct information, usually just one stool sample is sufficient for detection. In contrast, antibodies or other diagnostic tests are not helpful. The differential diagnosis should include all diarrhea-causing pathogens.

**Treatment**

No specific treatment has been established to date. Diarrhea is self-limiting with a good immune status; therefore, poor immune status should always be improved with ART – and this often leads to resolution (Carr 1998, Miao 2000). To ensure absorption of antiretroviral drugs, symptomatic treatment with loperamide and/or opium tincture, a controlled drug prescription, at its maximum dosage, is advised. If this is unsuccessful, then treatment with other anti-diarrheal medications, perhaps even sandostatin, can be attempted. Sufficient hydration is necessary and infusions may even be required.

Recent reviews confirm the absence of evidence for effective agents in the management of cryptosporidiosis (Abubakar 2007, Pantenberg 2009). We have observed good results with the antihelminthic agent nitazoxanide (*Cryptaz®*). Nitazoxanide proved to be effective in a small, randomized study (Rossignol 2001). In 2005 it was licensed in the US for treatment of cryptosporidia-associated diarrhea in immunocompetent patients. Nitazoxanide is not approved for AIDS patients and showed no effects in a double-blind randomized study in HIV-infected children with cryptosporidia (Amadi 2009).

Rifaximine (*Xifaxan®, 200 mg*) is a nonabsorbed rifampicin derivative, already licensed in the US as an anti-diarrheal. The first data with AIDS patients are very promising (Gathe 2008).
Paromomycin (Humatin®) is a nonabsorbed aminoglycoside antibiotic and has shown favorable effects on diarrhea in small uncontrolled studies (White 2001). In one double-blind randomized study, however, there was no advantage over placebo (Hewitt 2000). Potentially, there is an effect in combination with azithromycin (Smith 1998).

**Treatment/prophylaxis of cryptosporidiosis (daily doses)**

<table>
<thead>
<tr>
<th>Treatment/prophylaxis</th>
<th>Acute therapy</th>
<th>Curative attempt</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic</strong></td>
<td>Loperamide + opium tincture</td>
<td>Octreotide</td>
<td>Exposure prophylaxis: no tap water</td>
</tr>
<tr>
<td></td>
<td>(Loperamide 1 cap. at 2 mg 2–6 times daily or loperamide solution 10 ml (10 ml = 2 mg) 2–6 times daily and/or Opium tincture 1% = 5–15 drops QD)</td>
<td>Sandostatin solution for injection 1 amp. at 50 μg SC BID or TID (increase dose slowly)</td>
<td></td>
</tr>
<tr>
<td><strong>Curative attempt</strong></td>
<td>Nitazoxanide</td>
<td>Rifaximin 2 tab. at 200 mg BID</td>
<td></td>
</tr>
<tr>
<td><strong>Curative attempt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Prophylaxis**

There is no generally accepted prophylaxis, although retrospective analyses have reported a protective effect of rifabutin and clarithromycin (Holmberg 1998). The importance of good hygiene and not drinking tap water should be emphasized to patients, at least in countries with limited access to clean, adequate drinking water. Contact with human and animal feces should be avoided. The tendency for patients to become ill during the summer months can often be linked to swimming in rivers or lakes. Cryptosporidia are resistant to most disinfectants. In hospitals and other medical facilities, the usual hygienic measures, such as wearing gloves, are adequate. Moreover, patients do not need to be isolated. However, they should not be put in the same room with other significantly immunocompromised patients.

**References**


Cryptococcosis

Infection with the yeast Cryptococcus neoformans is a rare AIDS-defining illness in Europe. In the US and especially in Southeast Asia, cryptococcosis occurs much more frequently and is considerably one of the more prominent AIDS-defining illnesses worldwide. Presumably transmitted via inhalation, bird droppings are a key reservoir for C. neoformans. This pulmonary infection may remain subclinical in immunocompetent patients, but is almost always followed by disseminated disease in HIV+ patients. Apart from the lungs, the main manifestation after hematogenic spread is in the CNS. For this reason, a CSF examination is obligatory in every suspected case. However, isolated skin manifestations and lymphadenitis can also occur. Organ involvement, such as in the urogenital or gastrointestinal tract, is rare. Cryptococcosis almost always occurs with severe immunodeficiency. In a collection of 114 cases, 87% had less than 100 CD4 T cells/µl; the median CD4 count was 30 (Weitzel 1999). Cryptococcosis is fatal if untreated. Treatment is lengthy, complicated and should be managed only on an inpatient basis. Relapses were frequent in the pre-HAART era and occurred in at least 15% of cases. In addition, cryptococcosis occurs relatively frequently in the presence of an immune reconstitution inflammatory syndrome. Prognosis has much improved over the last years. In one study from France, the mortality rate per 100 person-years was 15.3 in 1996–2000, compared with 63.8 in the pre-HAART era although early mortality did not differ between the two periods (Lortholary 2006).

Signs and symptoms

The CNS manifestation with encephalitis is the most frequent manifestation (ca. 80%). Patients complain mainly of headaches, fever and confusion or clouding of consciousness which progresses rapidly over a few days. Disorders of gait, hearing, and vision may occur, as well as paresis, particularly of the cranial nerves. In such cases intracranial pressure is almost always increased. However, meningeal symptoms are usually absent. In the course of an immune reconstitution syndrome, clinical symptoms are often atypical and characterized by extensive abscesses (Manfredi 1999).

Pulmonary disease leads to symptoms of atypical pneumonia with unproductive cough and chest pain. Skin lesions can initially resemble molluscum contagiosum, and later become confluent in the form of larger, ulcerative lesions.

Diagnosis

Cryptococcosis is life-threatening, and the mortality rate in larger studies is between 6 and 25% (Saag 2000). There is no time to lose during diagnostic testing. Rapid examination of the lungs (HRCT) and CNS in particular (MRI) should be initiated in every suspected case (e.g., positive cryptococcal antigen test). The chest x-ray usually does not reveal much; therefore, an HRCT scan must be performed if pulmonary involvement is suspected. The spectrum of morphology on the image is very variable. Diffuse, small lesions similar to tuberculosis may occur, but there can also be sharply defined infiltrates reminiscent of bronchopneumonia. Cavitation and bronchiectasis may also be present. Every attempt should therefore be made to clearly identify the causative organism by BAL. An MRI scan of the head should always be performed if there are neurological symptoms. However, in contrast to toxoplasmosis and primary CNS lymphoma, it usually does not reveal much, and isolated or multiple mass lesions (cryptococcomas) are
very rare. Nevertheless, intracranial pressure is often increased and a fundoscopy (papillary edema) should be performed.
The most important test for cryptococcosis is lumbar puncture after a fundoscopy and/or an MRI. Diagnosis can be made via India ink stain in almost all cases. CSF must be examined even in cases with pulmonary or other manifestations to exclude CNS involvement. Cryptococcal antigen (CrAg) in the blood (titer >1:8) is a good parameter and should always be determined, especially in patients with low CD4 T cell counts (Jarvis 2011). Blood cultures are also often positive. With cutaneous involvement, the diagnosis is usually made from a biopsy.

**Treatment**

In cases of CNS involvement an immediate combination of antimycotics is urgently recommended followed by maintenance therapy with fluconazole (Saag 2000). Fluconazole alone is not sufficient, as recently shown by two randomized trials from Africa. In these trials, mortality of cryptococcal meningitis was unacceptably high. Within the first weeks, 54–59% of the patients died (Longley 2008, Makadzange 2009). Combination prevents resistance and allows reduction of acute therapy to 4–6 weeks. The choice of combination is not clearly defined. In some countries, combination therapy with the three antimycotics amphotericin B, flucytosine and fluconazole is often used for meningitis. The triple therapy leads to complete remission of meningitis in around 80% of cases (Weitzel 1999), and consequently the possibility of a slightly higher rate than under dual therapy with amphotericin B and flucytosine as favored in the US (van der Horst 1997).

However, other data raises questions as to the superiority of triple therapy. According to the measurements of cryptococcal clearance in the CSF, in a small, randomized study of 64 patients in Thailand, the combination of amphotericin B and flucytosine was the most effective treatment (Brouwer 2004). It was even significantly better than triple therapy and also amphotericin B and fluconazole. Amphotericin B at a dosage of 1 mg/kg plus is possibly more rapidly fungicidal than is standard-dose amphotericin B (Bicanic 2008). If amphotericin B is not available, the combination of flucytosine and fluconazole is better than fluconazole alone (Nussbaum 2010). Nevertheless, in view of the toxicity of flucytosine, available in many countries only in infusion and not in tablet form, the combination of amphotericin B and fluconazole is preferable. In a Phase II study the high doses of 800 mg fluconazole daily was most effective (Pappas 2009). A newer study showed that the efficacy of high dose fluconazole is equivalent to flucytosine (Loyse 2012).

In addition to having significantly lower toxicity, liposomal amphotericin (Ambisome®) is slightly more effective than conventional amphotericin B (Lenders 1997, Hamill 1999). However even Ambisome®-containing combinations are highly toxic. Daily monitoring of kidney and liver enzymes, blood count and electrolytes are recommended. Fluconazole should be administered as an infusion, particularly if patients seem confused.

In untreated patients, ART is typically started during the acute phase of treatment. Caution should be taken with tenofovir, given an observed case of renal failure requiring dialysis after treatment with tenofovir and amphotericin B. Since there is also a higher risk for the development of IRIS, the optimal time for initiation of ART is still under debate. In ACTG 5164, early ART was an advantage (Zolopa 2009). In a small African study on seriously ill patients, however, mortality was increased in patients starting ART immediately after diagnosis (Makadzange 2010).

In cases of isolated pulmonary involvement (CSF-negative) or other extracerebral manifestations, treatment without flucytosine can be completed (acute therapy with amphotericin B and fluconazole) within two instead of four weeks. If there is a pos-
itive cryptococcal antigen test without evidence of CNS, pulmonary or other infection, then treatment can consist of fluconazole alone. Treatment success is monitored based on the clinical course and repeated lumbar punctures. CSF is negative in approximately 60% of cases after two weeks (Saag 2000). When this is the case, maintenance therapy or secondary prophylaxis can be started, though not sooner than after four weeks of acute therapy. The quicker the CSF shows to be negative, the better the prognosis (Bicanic 2009, Chang 2012). If there is increased intracranial pressure, then CSF drainage may become necessary (Graybill 2000). Steroids are ineffective (Saag 2000).

**Prophylaxis**

Pre-exposure prophylaxis does not seem to exist. A survival benefit has not not demonstrated and primary prophylaxis against Cryptococcus neoformans is not recommended even in endemic areas such as Thailand (McKinsey 1999, Chariyalertsak 2002). Recently, in a large double-blind randomized placebo-controlled trial in Uganda on 1719 patients with negative CrAg on screening, fluconazole prophylaxis was shown to prevent cryptococcal disease while waiting for and in the early weeks of antiretroviral therapy, particularly in those with CD4 counts of less than 100 cells/µl. However, all-cause mortality was not reduced (Parkes-Ratanshi 2011). Fluconazole is given as secondary prophylaxis or maintenance therapy. It is significantly more effective than itraconazole. For example, in a large randomized study, the relapse rate in the fluconazole arm was only 4% compared to 23% in the itraconazole arm, resulting in discontinuation of the study before completion (Saag 1999). Fluconazole can probably be discontinued with sufficient immune reconstitution (above 200 CD4 cells/µl, undetectable viral load for three to six months), as demonstrated in several studies (Aberg 2002, Kirk 2002, Vibhagool 2003, Mussini 2004), and after at least six months of maintenance therapy. It is prudent to check for cryptococcal antigen before stopping (Mussini 2004). Positive antigen tests require continuation of treatment as the risk of relapse is high, especially in patients with high antigen titres (Lortholary 2006).

**Treatment/prophylaxis of cryptococcosis** (daily doses, unless specified otherwise), see also Drugs section for further details

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Duration: always at least six weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of choice</td>
<td>Amphotericin B Amphotericin B 0.5–0.75 mg/kg QD or liposomal amphotericin B 3 mg/kg QD (preparation by pharmacy) plus fluconazole 1 bottle at 200 mg IV BID or fluconazole 1 cap. at 200 mg BID plus flucytosine* flucytosine 1 bottle at 250 ml (2.5 g) IV QD (= 100–150 mg/kg distributed in four separate doses)</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>Discontinuation possible from &gt;200 CD4 cells/µl &gt;3–6 months</td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Fluconazole Fluconazole 1–2 cap. at 200 mg QD</td>
</tr>
<tr>
<td>Alternative</td>
<td>Itraconazole Itraconazole 2 cap. at 100 mg BID</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*Note: We usually omit flucytosine. In this case the daily doses of fluconazole should be 800 mg. Instead, we begin with ART during the acute therapy phase in these patients who are almost always ART-naïve.
Salmonella septicemia

Infection with non-typhoid Salmonella, which typically only causes enteritis in healthy individuals, can lead to severe septicemia in immunocompromised patients (Jacobs 1985). A newer study indicates that impaired immunity against nontyphoidal Salmonella bacteremia in HIV infection results from excess inhibitory antibodies against Salmonella lipopolysaccharides, whereas serum killing of Salmonella is induced by antibodies against outer membrane proteins (MacLennan 2010).

In Central Europe, Salmonella septicemia is rare in HIV patients, and accounts for less than 1% of AIDS cases. In the Swiss cohort of over 9000 patients, only 22 cases of recurring salmonellosis were documented over a period of nine years (Burkhardt 1999).

In Southern Europe as well as Africa, salmonellosis is much more frequent. Infected food, particularly poultry, is most widely recognized as a reservoir for Salmonella. In most cases, relapses are frequent. In addition to septicemia, atypical infections with osteomyelitis, empyema, pulmonary abscesses, pyelonephritis or meningitis have been described (Albrecht 1992, Nadelman 1985). Recurring, non-typhoid Salmonella septicemia is considered an AIDS-defining illness. The risk of recurrent septicemia decreased significantly in the ART era (Hung 2007).

Signs and symptoms/diagnosis

Patients are often severely ill. Chills and high fever are usually present. If treatment is delayed, there is always a danger of septic shock. Diarrhea may be absent. Blood cultures mainly lead to isolation of enteritis-causing strains such as S. enteritidis and S. typhimurium. The pathogens causing typhoid or paratyphoid fever, S. typhi and S. paratyphi, are rare.

Treatment

Ciprofloxacin is the treatment of choice (Jacobson 1989). Although oral bioavailability is good, intravenous dosing is preferable. In the US the resistance situation is relatively good (Forrest 2009). In contrast to Asia, where rates of ciprofloxacin resistance have clearly increased and risen to up to 30% (Hung 2007). In these cases, cephalosporins such as cefotaxime or ceftriaxone have proven to be effective. One week of treatment with ciprofloxacin or ceftriaxone is usually enough. Maintenance therapy should continue for 6–8 months and not be stopped too early (Hung 2001). However, lifelong secondary prophylaxis, which was propagated in the past (Nelson 1992), no longer seems necessary.

Treatment/prophylaxis of Salmonella sepsis (daily doses)

<table>
<thead>
<tr>
<th></th>
<th>7–14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute therapy</td>
<td></td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Ciprofloxacin 1 bottle at 200 mg IV BID</td>
</tr>
<tr>
<td>Alternative</td>
<td>Ceftriaxone 1 bottle at 2 g IV QD</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>For relapses</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 1 tab. at 500 mg BID (6–8 months)</td>
</tr>
</tbody>
</table>

Prophylaxis

Drug prophylaxis is not recommended. However, HIV patients should generally be advised to pay attention to food hygiene, especially in warmer countries.
References


Immune reconstitution inflammatory syndrome (IRIS)

For the first time, in mid-1997 and early 1998, two groups described atypical manifestations of CMV retinitis (Jacobsen 1997) and MAC disease with abscess formation (Race 1998) in HIV+ patients within a few weeks of initiation of ART. Although the pathogens, pathogenesis and localization were very different, all these illnesses had a distinct inflammatory component and were associated with significant immune reconstitution in these patients. Consequently, it was suspected early on that these presentations could constitute a syndrome during which a latent infection present at initiation of therapy is fought more effectively by the recovering immune system (Overview: French 2009). Infections are not the only cause of IRIS. Malignancies and other diseases have also been described as IRIS-related (see below). The International Network for the Study of HIV-associated IRIS (INSHI, http://www.med.umn.edu/inshi/) has established the following consensus criteria for diagnosis of IRIS:

1. Response to ART (at least one log₁₀ copies/mL decrease in HIV RNA)
2. Clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation.
3. Symptoms cannot be explained by expected clinical course of a previously recognized and successfully treated infection, medication side effect or toxicity, treatment failure or complete non-adherence.

One must differentiate between subclinical infections first appearing on ART (“unmasking IRIS”) and clinically evident infections already existing at therapy initiation, which often paradoxically become worse during therapy (“paradoxical IRIS”). IRIS in many publications today is often a collection of bizarre, sometimes grotesque case reports, which have actually only one thing in common: an unexpected, usually clinically impressive infection, differing significantly from the course of disease seen during the pre-HAART era. Nevertheless, IRIS has three rules:

1. Anything is possible.
2. Nothing is as it was in the pre-HAART era.
3. IRIS does not mean that ART has failed. In fact, patients usually have a good prognosis.

How frequently does IRIS occur? Due to the lack of a definition in the early years of ART, the data vary substantially. In our experience, a frequency of 5–10% in patients with less than 200 CD4 T cells/µl is realistic. Very low CD4 T cells, a high viral load before initiation of therapy or a rapid drop of HIV RNA on ART seem to be important predictive factors for IRIS. If one focuses on patients who were already infected with mycobacteria or cryptococcus neoformans before ART was started, IRIS rates of 30% can be reached (Müller 2010).

Mycobacterial IRIS. For MAC, the number of published cases with grotesque, fistular lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritis or meningitis is too large to be cited here. After a total of 83 patients started ART with a CD4 T cell count of less than 200/µl, only six mycobacterioses, among these four MAC infections, were observed within the first weeks of therapy (Hoffmann 1999). Lymph node abscesses usually occur during the first weeks of ART. IRIS cases with Mycobacterium xenopi or kansasii have also been described (Chen 2004, Phillips 2005).

There are now numerous reports on tuberculosis (John 1998, Chien 1998), reminiscent of the “paradoxical” reactions to TB treatment known in the 1950s. All of these patients suffered an initial deterioration while on correct tuberculostatic treatment and ART-induced immune reconstitution. By the same token, meningitis as well as marked lymphadenopathy with unspecific histology can complicate the course of
disease, yet both respond astonishingly rapidly and well to steroids. Prednisolone was very effective in a recent placebo-controlled trial (Meintjes 2010).

An early or immediate start of ART in therapy-naïve patients facilitates the occurrence of IRIS. In four large randomized trials the risk of IRIS increased when ART was started immediately in patients with TB, especially in those with low CD4 T cells (Abdool 2011, Blanc 2011, Havlir 2011, Wondvossen 2012). In all studies, however, the increased risk did not lead to increased mortality. This may be different in patients with tuberculous meningitis. In this population, at least one randomized trial showed a less favorable outcome with early ART (Torok 2009).

**CMV IRIS.** In addition to mycobacteriosis, numerous cases of unusual CMV infections under ART have been published. In patients with previously diagnosed CMV retinitis, IRIS developed in 38% (Müller 2010). Inflammatory CMV retinitis with vitritis that may lead to visual impairment, papillitis and macular edema, can now be described as a distinct syndrome, differing significantly from the course of CMV retinitis seen in the pre-HAART era (Jacobson 1997, Karavellas 1999). Neovascularization endangers vision even after resolution (Wright 2003). As with MAC disease, *in vitro* studies have shown that the CMV-specific immune response is improved most significantly in those patients developing vitritis (Mutimer 2002, Stone 2002).

Inflammatory CMV manifestations are not limited to the retina and may involve other organs.

**PML IRIS.** The course of inflammatory PML that occurs during IRIS is different from the infaust prognosis seen during the pre-HAART era (Collazos 1999, Kotecha 1998, Cinque 2001, Miralles 2001). Clinical symptoms are often more fulminant initially, and on radiology, there is a contrast enhancement which is otherwise atypical for PML, that may resolve over time. Patients have a better prognosis, and PML seems to resolve completely (Hoffmann 2003, Du Pasquier 2003). It appears that a number of patients with inflammatory PML, who have been asymptomatic for years, live without any residual symptoms. However, fatal cases of inflammatory PML have also been reported (Safdar 2002). Previously documented experiences indicate that steroids are ineffective, although there have been accounts of positive results (Nuttall 2004, Tan 2009).

**Cryptococcal IRIS.** Numerous cases with inflammatory courses of disease have been described (Overview: Haddow 2010). Together with MAC/TBC and CMV, cryptococci are probably the most influential pathogens that contribute to IRIS. In particular, severely immunocompromised patients who start with ART after cryptococcal therapy should be watched closely for the first few weeks and months. Newer studies show that 10–20% of patients with coinfections develop a cryptococcal IRIS (Sungkanuparph 2009, Müller 2010). The MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. Cryptococcal antigen in the CSF is positive, although culture remains negative (Boelaert 2004). The intracranial pressure is often particularly high (Shelbourne 2005). As well as meningitis, lymphadenitis can also occur (Skiest 2005).

**IRIS induced by other infections.** A variety of contemporary case studies have documented the induction of IRIS by the following infections: leishmaniasis (Jiménez-Expósito 1999), penicilliosis (Ho 2010), histoplasmosis (De Lavaissiere 2008), pneumocystosis (Barry 2002, Koval 2002, Godoy 2008, Jagannathan 2009, Mori 2009), toxoplasmosis (Martin-Bondel 2011) or herpes (Fox 1999). Herpes zoster and hepatitis B or C episodes also seem to occur on ART, particularly during the first weeks (Behrens 2000, Chung 2002, Manegold 2001, Martinez 1998, Domingo 2001). HHV-8-associated Kaposi’s sarcoma can worsen significantly on ART in the presence of IRIS (Bower 2005, Leidner 2005, Feller 2008). Increasing dermatological problems...
such as exacerbation of pre-existing folliculitis or skin disease have also been reported (Handa 2001, Leholoeniya 2006, Pereira 2007, Iarikov 2008). There are even reports about parvovirus and leprosy (Nolan 2003, Couppie 2004, Bussone 2010, Watanabe 2011).

IRIS and other diseases. Diseases other than OIs are now recognized to occur as IRIS. These include autoimmune diseases such as Graves’ disease, lupus, Sweet’s and Reiter’s syndromes, Guillain-Barré syndrome, acute porphyria, gout and sarcoidosis, to name but a few (Bevilacqua 1999, Behrens 1998, Fox 1999, Gilquin 1998, Makela 2002, Mirmirani 1999, Neumann 2003, Piliero 2003, Sebeny 2010, Rasul 2011). Even two cases of Peyronie’s disease, a fibrosis of the penis, were reported (Rogers 2004). These reports raise the question of whether all of these manifestations are truly induced by immune reconstitution or perhaps merely chance occurrences. While most reports initially offered little information on the etiology beyond purely hypothetical discussions, it has recently become apparent that changes in the cytokine profile are involved in the pathogenesis of IRIS, together with an activation of the cellular immune response. However, it seems that the mechanisms differ according to disease and genetic profile (Price 2001, Shelbourne 2005).

Consequences

Patients starting ART with less than 200 CD4 T cells/µl and particularly those who have a high viral load require close clinical monitoring during the first weeks. Close attention should be given especially in cases where very immunocompromised patients suddenly feel physically “affected,” express subfebrile conditions, and want to start ART “after thinking about it for a long time.” Latent infections are often present in such cases and rapidly become apparent as immune reconstitution occurs – the poorer the immune status and the longer its duration, the greater the danger of IRIS. Although newer studies prove that infection parameters such as CROP, D-dimer or cytokines such as IL-6 or IP-7 are predictive of IRIS or OI (Rodger 2009, Antonelli 2010, Porter 2010) it is not generally practiced in routine diagnosis. However chest radiography, abdominal ultrasound and fundoscopy should be included in routine investigations of such patients before beginning treatment. Moreover, clinical examination which nowadays are often gladly overlooked should be taken seriously. Some authors suggest that MAC prophylaxis start even before ART in severely immunocompromised patients seems problematic, even though prophylaxis cannot prevent MAC IRIS (Phillips 2002+2005). Still, prospective clinical studies have yet to prove whether administration of IL-2 or GM-CSF is worthwhile, as was recently postulated (Pires 2005). Mycobacterioses in particular should be treated generously with steroids. This has been confirmed in a randomized trial (Meintjes 2010). One should always be prepared for atypical localizations, findings and disease courses of opportunistic infections. Generally speaking, the prognosis of IRIS is usually good. Mortality of patients developing IRIS is reportedly not higher than that of patients without IRIS (Park 2006).

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**Wasting syndrome**

Wasting syndrome is defined as involuntary weight loss of at least 10% of original body weight accompanied by persistent diarrhea (at least two bowel movements daily for more than 30 days) or extreme fatigue and/or fever without apparent infectious etiology. With thorough and competent work-up, a specific causative agent can usually be found for wasting syndrome because it is essentially a classical exclusion diagnosis and really more of an epidemiological instrument than a specific disease. Although previously a very frequent condition, wasting syndrome has become rare today. For example, in a large study conducted in the year 2000, only 14% of patients indicated having lost more than 10% of their original body weight (Wanke 2000). Rates are higher in intravenous drug users (Campa 2005). Weight loss remains an independent risk factor for mortality, even in the HAART era, and every patient should be weighed regularly. In one large study, mortality risk in patients with a loss greater than 10% of body weight was more than four to six times higher than that of patients with stable body weight (Tang 2002). Patients with classic wasting syndrome are often extremely weak and the risk for opportunistic infections is significantly elevated (Dworkin 2003). There is also cognitive impairment in these patients (Dolan 2003).

**Diagnosis**

The causes of wasting syndrome are complex. First, it is necessary to exclude or treat opportunistic infections (TB, MAC, cryptosporidiosis and microsporidiosis). If none are found, then several reasons remain that may contribute, even in combination, to wasting syndrome. These include: metabolic disorders, hypogonadism, poor nutrition and malabsorption syndrome (Overview: Grinspoon 2003). Consequently, a thorough patient history is extremely beneficial. Does the patient have a sensible diet? How are meals distributed throughout the day? Is the patient depressed? Which drugs (ART) are being taken? Distinction from antiretroviral-induced lipoatrophy (d4T/ddI) is often difficult. Significant weight loss also occurs frequently on interferon (Garcia-Benayas 2002), but rapidly resolves after finishing treatment. In addition, hypogonadism should be ruled out with the measurement of testosterone. While there are several simple tests for malabsorption syndromes, it is prudent to start with testing albumin as well as TSH and cholesterol levels. Further tests such as D-xylose absorption or biopsies of the small intestine should only be initiated after consulting with a gastroenterologist. Other tests, such as DEXA, densitometry, bioelectrical impedance analysis, etc, should be conducted in centers experienced with AIDS wasting syndrome to determine the patient’s body composition.

**Therapy**

Wasting syndrome always requires competent diet counseling. Exercise, if possible, is also good. Of course, they only have limited success. Supportive parenteral nutrition only helps if there are problems with absorption (Kotler 1990, Melchior 1996). Effective ART, ideally without drugs that cause lipoatrophy such as d4T or ddI, and possibly even omitting nucleoside analogs completely, is ideal. Severe lipoatrophy may require complete omission of nucleoside analogs (see Chapter on Nuke-sparing). Beyond this, many kinds of drug treatment have been attempted. However, these have limited success and are often problematic. Megestrol acetate, a synthetic gestagenic hormone, shows some benefit as an appetite stimulant in wasting syndrome, as demonstrated in some studies (Von Roenn 1994,
Mulligan 2006). Its side effects are those typically associated with steroids, including induced hypogonadism, which should always be avoided, especially in cases of wasting syndrome. As a result, it is not widely nor currently recommended that this drug be used.

Dronabinol, the main active ingredient in marijuana, has been licensed in the US since 1985 as Marinol®, and may be prescribed for pharmacy formulation as drops or hard gel capsules. This drug is certainly attractive for many patients and sometimes actively demanded. Prescription should be carefully considered, particularly in view of the significant cost associated with the medication. In some European countries, dronabinol costs approximately 600 euros per month for the usual dose of 5 mg TID. Without a clear diagnosis of wasting syndrome, communication with the insurance company may minimize substantial payment problems. Some health insurances and other payors reject the request. The effect on wasting syndrome is moderate at best, if detectable at all (Beal 1995). It tends to be even weaker than megestrol acetate (Timpone 1997).

Hypogonadism, a frequent condition of patients with wasting syndrome, calls for the measurement of testosterone levels. If the age-dependent levels are low, then testosterone substitution has proven itself useful, both for weight gain and quality of life (Grinspoon 1998). A dose of 250 mg testosterone is given IM every 3–4 weeks, and there are a variety of less expensive generic names. The effect is sustained, even with long-term use (Grinspoon 1999). If testosterone levels are normal, substitution is not indicated. In women, one should exercise caution when administering androgenic hormones. Other anabolic steroids are available in addition to testosterone, such as oxandrolone or nandrolone (Gold 2006, Sardar 2010). Although possibly more effective than testosterone, these drugs are commonly associated with other side effects, particularly those related to the liver (Corcoran 1999). Positive effects have been demonstrated with the anabolic steroid oxymetholone in a small, double-blind, randomized study (Hengge 2003). However, extremely high elevation of transaminases have been observed.

High costs and side effects have limited the use of recombinant human growth hormones (rHGH), for which long-term data is still not available (Mulligan 1993, Schambelan 1996). However, the results of a recent metaanalysis suggest that growth hormones may be more effective than anabolic steroids or testosterone in wasting syndrome (Moyle 2004). Common adverse events with rHGH therapy include blood glucose elevations, arthralgia, myalgia, and peripheral edema, but these usually respond to dose reduction or drug discontinuation (Review: Gelato 2007).

References


Several opportunistic infections that rarely occur in central Europe or have become increasing rare due to the introduction of ART include: aspergillosis, bacillary angiomatosis, histoplasmosis, isosporiasis, coccidioidomycosis (*Coccidioides immitis*), visceral leishmaniasis, microsporidiosis, *Penicillium marneffei* mycosis, and rhodoccosis. In addition to affecting HIV+ patients more frequently than immunocompetent individuals, these infections are also considered to have more severe courses of disease and more frequent recurrences in HIV-infected patients than in HIV-negative patients. Despite this, according to the current CDC/WHO classification, only histoplasmosis, isosporiasis, and coccidioidomycosis are AIDS-defining.

**Aspergillosis**

Aspergillosis occurs almost exclusively in severely immunocompromised patients but is not classified as AIDS-defining. In the largest cohort described worldwide to date, in a study of 342 cases of invasive aspergillosis, almost all of the patients had less than 50 CD4 T cells/µl (Mylonakis 1998). Although the lungs are largely susceptible to pneumonia or tracheobronchitis, almost all other organs can be compromised, particularly the CNS. Sinusitis or abscesses in kidney or liver are other manifestations (Hunt 2000, Mylonakis 2000).

For the most part, aspergillosis occurs in HIV patients on long-term and in some cases excessively long steroid treatment for another OI. Severe neutropenia (<1000 leucocytes) is another risk factor. Found in over 90% of invasive aspergillosis cases, *Aspergillus fumigatus* is by far the most frequent pathogen. Other important aspergillus pathogens are *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans*. The severely ill patients complain of fever, cough, dyspnea and chest pain. Hemoptysis frequently occurs.

The only way to reach a reliable diagnosis is biopsy. A serum antigen test on Galactomannan, a component of the cell wall of Aspergillus (not exclusively, also other mycoses) may support the diagnosis. Chest x-rays often remain inconspicuous. In the HRCT, bilateral, multifocal and nodular lesions may be the most common radiological characteristic, while Halo and crescentic signs occur occasionally.

Treatment should be initiated immediately. Suspicion of aspergillosis justifies a treatment attempt without definitive diagnosis, i.e., biopsy results. Each delay worsens a potentially unfavorable prognosis substantially. At present voriconazole is considered treatment of choice (Schwartz 2005). In contrast to other antifungal drugs, voriconazole penetrates well into the CNS. In patients with invasive aspergillosis, initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B (Herbrecht 2002). Voriconazole is given at a dosage of 4 mg IV/kg BID (loading dose: 6 mg/kg BID on day 1, oral therapy with 200 mg BID starting from day 7). Main adverse events are visual disturbances (20%) and (reversible) increases of liver enzymes.

An alternative approach is amphotericin B, whose inferiority to voriconazole is questioned by some (Jorgensen 2006). The effect of combinations is not proven (Garbati 2012). Salvage therapy includes lipid-based formulations of amphotericin B, caspofungin, high-dose itraconazole or posaconazole (Dockrell 2008). A systematic steroid therapy should be stopped if possible and every patient should receive antiretroviral treatment immediately. Some case reports describe that permanent therapy can be dropped if immune reconstitution is sufficient (Yoganathan 2009).
References


Bacillary angiomatosis

Bacillary angiomatosis in HIV patients was first described in the 1980s (Review: Maguina 2000). Bacillary angiomatosis is caused by the rickettsial species Bartonella henselae and Bartonella quintana (“Rochalimaea” until the beginning of the 1990s). While Bartonella henselae is typically associated with cats, its primary host, and cat fleas, its vector; Bartonella quintana frequently affects homeless patients and is associated with poor hygiene and social-economic conditions. Several possible reservoirs have been discussed for such cases (Gasquet 1998). In a Spanish study of 340 HIV-infected patients, 22% patients reacted to one or more Bartonella antigens. Of all the studied seroprevalence factors, only age was statistically significant (Pons 2008). Reportedly, Bartonella occurs more often in North and South America than in Europe. In Brasil, the seroprevalence was 38% (Lamas 2010). In a study of 382 febrile HIV+ patients in San Francisco, Bartonella was found to be the causative organism in 18% (Koehler 2003).

Bacillary angiomatosis remains a significant differential diagnosis in all cases with skin lesions of unknown etiology. The pseudoneoplastic, vascular skin proliferation is quite often clinically and histologically mistaken for Kaposi’s sarcoma or hemangioma. The vascular nodules or tumors may be isolated, but are usually multiple and reminiscent of fresh Kaposi’s sarcoma, with cherry red or purple nodules. One quarter of the cases may have bone involvement with painful osteolytic foci (AP elevation). Here, the skin lesions sometimes resemble dry hyperkeratotic changes such as those seen in psoriasis. Different organs may be affected. In a collection of 21 cases, 19 patients had skin, 5 bone and 4 liver involvement (Plettenberg 2000). Manifestations in lymph nodes, muscle, CNS, eye, gingiva and gastrointestinal tract have also been reported.

Diagnosis of BA is difficult. The gram-negative bacteria are only visible on biopsy samples stained with Warthin-Starry silver stain. If this stain method is not applied, then bacillary angiomatosis will not be found. Moreover, pathologists should be informed of the suspected diagnosis, as the Warthin-Starry silver stain is not routinely performed. PCR is also possible. Reference labs should be contacted for further diagnostic details.

Treatment of bacillary angiomatosis is with erythromycin (at least four weeks with 500 mg QD) or clarithromycin. Relapses are common, which is why some physi-
cians favor therapy for at least three months. Supposedly effective, doxycyclin is the therapy of choice for CNS involvement. Since transmission is generally via cats, US guidelines recommend not having cats as pets. Preferably, cats should be healthy and older than one year; and scratches should be avoided.

References

Histoplasmosis

*Histoplasma capsulatum* is a dimorphic mold, found largely in moist soil and without a capsule despite its name. The Southern and Midwestern of regions of the US as well as Central America and Africa are endemic areas. Inhalation of microconidia, the spores of *H. capsulatum*, can cause granulomatous disease in the lungs of immunocompetent individuals. In HIV patients with impaired immunity (85% have less than 100 CD4 T cells/µl), infection leads to an acute, life-threatening disease with dry cough, fever, dyspnea and malaise (Gutierrez 2005, Mora 2008). Miliary TB and PCP are important differential diagnoses. Disseminated courses of disease may also occur, in which the fungus can be detected in bone marrow or by liver biopsy (Albrecht 1994). Skin ulcerations, oropharynx or CNS involvement may also occur (Scheinfeld 2003, Wheat 2005, Antonello 2011). Hepatosplenomegaly is common, occurring in almost 90% of the patients (Mora 2008).

Histoplasmosis is an AIDS-defining illness whose pathogen like that of cryptococcal antigen can be reliably detected in the blood with an antigen test. Laboratory evaluations often reveal significantly elevated LDH and alkaline phosphatase as well as transaminases.

Amphotericin B should be given as initial treatment. Liposomal amphotericin B (3 mg/kg daily for 14 days) is not only less toxic, but possibly also more effective (Johnson 2002). In milder cases, itraconazole (200 mg BID or TID) is effective, and can also be used as a secondary prophylaxis. It is significantly more effective than fluconazole (Wheat 2002), but is associated with a high risk of interactions, particularly with ritonavir, but also with efavirenz (Crommentuyn 2004, Andrade 2009, Hills-Nieminen 2009). In such cases a modification of the doses is often necessary. With regard to other OIs, secondary prophylaxis for histoplasmosis can be discontinued if immune reconstitution is sufficient (Goldman 2004). Initiation of ART and the subsequent immune reconstitution may reveal undiagnosed latent disseminated histoplasmosis (Nacher 2006).
References


Isosporiasis

*Isospora belli* is an ubiquitous intestinal parasite. While rare in Europe, it is a issue of great concern in the developing world, especially in the tropics and subtropics (Lagrange-Xelot 2008). In India *Isospora belli* was the most frequent diarrhea infection after cryptosporidiosis in HIV+ patients (Kulkarni 2009). Similar to cryptosporidiosis, this microbe may cause epidemic-type outbreaks in immunocompetent hosts. Patients suffer at a minimum with enteritis-like complaints and occasionally, also experience very severe watery diarrhea, abdominal pain, cramps and nausea. In immunocompromised patients, chronic diarrhea and malnutrition may occur (Review: Goodgame 1996). Fever is seldom seen. Median CD4 T cell count in patients with *Isosporiasis* is 150, slightly higher than in cases of cryptosporidiosis and microsporidia. Chronic isosporiasis with diarrhea lasting for more than four weeks is AIDS-defining. Detection of the relatively large oocysts is possible via normal stool sampling for parasites, as well as in acid-fast stains. Blood tests usually reveal eosinophilia (Certad 2003).

Treatment is co-trimoxazole (960 mg daily for one week). Ciprofloxacin is slightly less effective (Verdier 2000). Relapse is common despite co-trimoxazole maintenance therapy (Lagrange-Xelot 2008).

References


Coccidioidomycosis

Infection with the mold Coccidioides immitis is endemic in the Southwestern US and therefore, needs to be considered when presented with patients who have been in this region. (Review: Galgiani 2005, Ampel 2007). Laboratory personnel also should also be informed of the high risk of infection, even in suspected cases. After inhalation of spores, the primary manifestation begins in the lungs (Pappagianis 1993). Approximately 1–3 weeks after exposure, a pneumonia-like illness develops with fever, cough, chest pain and general malaise. The infection, although often symptomatic, usually resolves in immunocompetent patients without sequelae. Occasionally, there is residual cavitation which in some cases require surgical intervention (Jaroszewski 2009). Disseminated coccidioidomycosis beyond the lung and Hilar lymph nodes (for example chronic meningoencephalitis) occurs only in significantly immunocompromised patients with CD4 counts of less than 250 cells/µl (Ampel 2007, Drake 2009). Disseminated coccidioidomycosis is an AIDS-defining illness. Prognosis was poor in the pre-HAART era. In an analysis of 602 patients with disseminated coccidioidomycosis, mortality after one year was 63% (Jones 1995). With ART the course of this illness is mostly less severe (Massanat 2010).

Serology is not very helpful in immunodeficient patients. Diagnosis is mostly made by cultures or histological materials (Adam 2009). Due to high infection risks, laboratory staff should be informed when in doubt of coccidioidomycosis. Amphotericin as well as azoles are effective (Hernandez 1997), and should be, if necessary, combined (Ampel 2007). Detailed recommendations for the different situations (meningeal or disseminated cases must be treated more intensively) can be found (Galgiani 2005). Fluconazole should be given as maintenance therapy at high doses (400 mg). In cases of chronic refractory meningitis, posaconazole is also an option (Schein 2011).

In the past few years, it seems that the disease has become rarer as a result of ART, and that maintenance therapy can be discontinued when CD4 cells are greater than 250/µl with only initial pulmonary involvement. However, lifelong treatment is still recommended for cases of meningeal involvement (Woods 2000, Galgiani 2005, Ampel 2007).

References

Leishmaniasis (visceral)

Leishmaniasis is an infectious disease that is caused by 20 species pathogenic for humans belonging to the genus Leishmania, a protozoa transmitted by sand flies. One must differentiate between the cutaneous and the visceral forms of leishmaniasis (Kalar Azar), the manifestation form depends on the species (L. donovani, L. infantum, L. chagasi). According to WHO, there are 12 million people infected with leishmaniasis worldwide, with approximately 350 million living in risk areas. With such numbers, leishmaniasis is one of the most important parasitosis. In Europe, leishmaniasis is common and countries around the Mediterranean, such as Spain, Portugal, France and Italy are affected the most. The following link provides a global overview: www.who.int/leishmaniasis/leishmaniasis_maps/en/index.html.

Visceral leishmaniasis appear more frequently in HIV-infected patients. In Spain, on third of all patients with visceral leishmaniasis have HIV (Gil-Prieto 2011). While important, leishmaniasis is still not an AIDS-defining illness. A review of 15 cases in Germany showed that all HIV patients were significantly immunosuppressed (usually less than 100 CD4 T cells/µl). A few patients had not been in endemic areas for several years (Albrecht 1998). Bone marrow involvement is reflected by the almost obligatory pancytopenia, which may be particularly severe in HIV patients (Pintado 2001). Other symptoms include fever, hepatosplenomegaly, and mucocutaneous lesions. The diagnosis is usually made from bone marrow aspirate.

Treatment of visceral leishmaniasis is difficult (Review: Olliaro 2005). Pentavalent antimony compounds such as sodium stibogluconate (Pentostam®) or or meglumine antimoniate (Glucantime®) have been used for about 60 years (usual dosage: 20 mg/kg IV or IM daily for 28 days). However, these drugs are extremely toxic. Myalgia, arthralgia, cardiotoxicity and chemical pancreatitis often lead to discontinuation (Laguna 1999). Combination therapies are possibly more effective and allow for shorter therapy (van Griensven 2010, Sundar 2011).

The German Association for Tropical Medicine still recommends liposomal amphotericin B (Ambisome®) as the treatment of choice (2–5 mg/kg daily). However, recent trials have suggested that effectiveness of liposomal amphotericin is limited in HIV-coinfected patients (Rijtmeier 2011, Sinha 2011). Classic amphotericin B is also effective (Lachaud 2009). The only orally bioavailable leishmaniasis drug and a promising new drug, due to its good tolerability and efficacy, is miltefosine (Impavido®), an alkylphosphocholine analog that was licensed in Europe in 2004. Although clarity is still needed as to how miltefosine inhibits leishmania metabolism, a Phase III study in India demonstrated it as highly effective (Sundar 2002). Another randomized study in Ethiopia showed that among HIV-infected patients with leishmaniasis, miltefosine was less effective than sodium stibogluconate, but tolerability was better (Ritmeijer 2006). The doses was 100 mg daily (~2300 euros/month). We have successfully treated some patients with miltefosine to date. Another option may be paromomycin, an aminoglycoside which seems to be effective as at least two randomized studies from India have shown (Sundar 2007+2011). In Europe paromomycin (Humatin®) has so far only been licensed as a gastrointestinal drug for local use. As a secondary prophylaxis pentamidine may be effective (Patel 2009). In contrast, fluconazole seems to show no effects (Rybniker 2009). Relapses are frequent and occur in almost half of all cases. ART seems to change this – another argument for inclusion in the AIDS classification (de La Rosa 2002, Fernandez-Cotarelo 2003).

References
Microsporidiosis

Microsporidiosis is an important cause of diarrhea in HIV+ patients. Microsporidia are obligate intracellular protozoa. At least four genera, with Enterocytozoon bieneusi considered the most noteworthy, are described as pathogenic in humans. Even in Germany, microsporidia were previously among the most recurrent diarrhea-causing microbes. Furthermore, in the pre-HAART era, microsporidia could be found in approximately one-third of all patients. Some studies documented up to two-thirds of all HIV-infected patients with chronic diarrhea (Sobotka 1998). The incidence of microsporidiosis has been reduced significantly due to ART; consequently, it is now only diagnosed occasionally. Although microsporidiosis is not AIDS-defining, chronic microsporidiosis almost always occurs in severely immunocompromised patients with CD4 T cell counts of less than 50 cells/μl.

Diarrhea may be very severe; watery, though not bloody; and accompanied by abdominal pain, nausea and vomiting. Fever is almost always absent. While myositis, keratoconjunctivitis and sinusitis have rarely been described, infections of the biliary ducts are considered common.

In light of the fact that microsporidia, like cryptosporidia, are very small, an experienced lab is desirable for detection. Those who have never seen them or who are not asked to explicitly test for them will probably not detect them. Culture has not generally been established. Direct detection is most successful with specialized staining methods. Special transport or preparation is not necessary.
Although effective, albendazole (1–2 tab. at 400 mg BID for 4 weeks) is not most advantageous in every case. For example, *Enterocytozoon bieneusi* is often resistant to albendazole. Repeated positive reports in such cases, especially from France, give an account of treatment with fumagillin (watch for thrombocytopenia), but these case numbers remain low (Molina 2002). Case reports (Bicart-See 2000) are also available for nizoxanide (see cryptosporidiosis). There have also been positive reports of symptomatic treatment with thalidomide. ART-induced immune reconstitution, however, seems to have the greatest effect (Carr 1998+2002, Maggi 2000).

### References


### Nocardia

Nocardia are aerobic bacteria or actinomycetes that occur worldwide. Several species exist that cause pneumonia as well as systemic disease. In a survey of 30 cases of HIV+ patients with nocardiosis, pulmonary manifestation occurred in 21 cases (Uttamchandani 1994). Pulmonary manifestation of nocardiosis is often confused with tuberculosis. Extrapulmonary manifestation may occur in the skin, brain, nerves, muscle and bone. The immune response to Nocardia is cellular. As a result, there is generally an increased risk of pulmonary or systemic disease in immunosuppressed patients. In HIV-infected patients, however, opportunistic infections with Nocardia are rare. Patients are usually significantly immunocompromised (Javaly 1992, Uttamchandani 1994). Nocardia respond well to sulfonamides such as sulfadiazine even in HIV-infected patients (Pintado 2003). In cases of suspected nocardiosis, an experienced laboratory should be consulted.

### References


### Penicillium marneffei

Most fungi belonging to the Penicillium species are not pathogenic. One exception is *Penicillium marneffei*, which is a problem mainly for HIV patients in Southeast Asia (Le 2011). In these areas, it is the most frequent fungal infection in AIDS beside cryptococcosis, and is considered AIDS-defining by many clinicians (but is not included in the CDC classification). The known reservoirs for *Penicillium marneffei* are humans, rats and dogs.
Lungs and skin are the organs most frequently affected (Ma 2005). The clinical symptoms consist of prolonged high fever, lymphadenopathy, weight loss, malaise, cough and hemoptysis, diverse cutaneous and mucocutaneous lesions (reminiscent of molluscum contagiosum) and abnormal liver enzymes. There is often hepatosplenomegaly. Disseminated cases also occur (Ma 2005).

Definitive diagnosis relies upon the identification or isolation of *P. marneffei* in clinical specimens (blood, bone marrow, sputum). However, conventional culture usually takes at least three days. The use of the Galaktomannan antigen assay may facilitate earlier diagnosis of *Penicillium marneffei* infection for HIV-infected patients in endemic areas (Huang 2007).

There are no randomized studies which have evaluated different treatment options for *P. marneffei* infections. Amphotericin B, voriconazole and itraconazole are effective treatments (Supparatpinyo 2007, Ustianowski 2008). To prevent relapses, however, patients who have had the disease should take itraconazole as a permanent prophylaxis (Supparatpinyo 1998). Primary prophylaxis is not recommended even with longer stays in endemic areas (Chariyalertsak 2002). The only patient we have seen with *Penicillium marneffei* had spent several months on vacation in Thailand (Sobottka 1996).

**References**


**Rhodococcus**

*Rhodococcus equi* (previously *Corynebacterium equi*) is a sporeless, gram-positive intracellular pathogen, which is ubiquitous in air, water and soil. *R. equi* has been found on all continents, and was first identified as a pathogen in young horses. For half a century, only veterinarians were interested in this microorganism, but in the last two decades, it has been found more and more frequently in humans, primarily in significantly immunocompromised patients. In these patients, it causes severe granulomatous or abscess forming pneumonia, and sometimes also disseminated infection. The coryneform bacteria seen in sputum cultures are often confused with normal diphtheroid flora found in the mouth and therefore not diagnosed.

In 1986, the first case with respect to an AIDS patient was described (Samies 1986). In a collection of 78 cases, mostly AIDS patients with less than 50 CD4 T cells/µl were affected. The main symptoms were fever, dyspnea and unproductive cough (Capdevila 1997). Cavitation, mainly in the upper lobes, is frequently seen radiologically (Capdevila 1997, Marchiori 2005). Rhodococci are best detected in sputum and blood cultures (Torres-Tortosa 2003).
Erythromycin, azithromycin, ciprofloxacin, rifampin and vancomycin are effective, and some of these drugs can be combined. However, treatment is difficult and complete recovery is rare, even with ART (Plum 1997, Sanz-Moreno 2002, Ferretti 2011). Surgical measures may also be necessary if there is extensive cavitation. Survival of patients treated with ART is much higher than that of patients who did not receive ART (Torres-Tortosa 2003, Topino 2010).

References

Trypanosoma cruzi

Trypanosoma cruzi is a protozoan that is transmitted via contaminated feces of triatomid bugs (assassin bugs), found almost exclusively on the American continent. It causes Chagas disease, one of the most frequent causes of cardiomyopathy in South America. HIV-infected patients are more frequently affected and have higher levels of parasitemia (Sartori 2002), probably due to the fact that the Trypanosoma-specific immune response is mainly cellular in nature. In addition, a more frequent occurrence in HIV-infected patients is meningoencephalitis, which is usually severe and radiologically not distinguishable from cerebral toxoplasmosis or primary cerebral lymphoma. Most probably it is a reactivation (Diazgranados 2009, de Almeida 2011). In HIV-infected patients from South America, Trypanosoma infection should therefore be considered in the differential diagnosis (Silva 1999, Cordova 2008, Llenas-Garcia 2012). Whenever possible, lumbar puncture should be performed because of the high accuracy for early diagnosis. However, treatment (for example benznidazole) is rarely successful and mortality is high (Sartori 2007, Cordova 2008). Possibly itraconazole or ketoconazole are also effective (de Almeida 2009).

References
Kaposi’s sarcoma (KS) is the most common malignancy in patients with HIV infection. In 1981, the simultaneous occurrence of KS with pneumocystis pneumonias in young gay men led to the first descriptions of AIDS. This entity is designated after the Hungarian dermatologist Moritz Kaposi who first described the “classical” KS 100 years earlier. Classical KS predominantly occurs in elderly, but otherwise healthy people from the Eastern Mediterranean area. It affects often only the skin at the lower extremities and thereby, clearly differs from HIV-associated KS which will be the focus of the following chapter.

In contrast to classical KS, HIV-associated KS may affect all skin and mucous membranes. Lymph nodes and internal organs such as stomach, gut, lung or liver may also be involved. The progression of HIV-associated KS is very variable and reaches from small lesions, remaining stable for years, to extremely aggressive courses, in which progression may lead to death within a few months.

Compared to the 1980s and early 1990s, when KS was one of the most common AIDS illnesses, prevalence of KS today is relatively low (Francesci 2010). Since the early years of AIDS, the incidence has fallen to less than a tenth (Grabar 2006, Simard 2011) of what it was. In addition, the clinical course of KS has changed with the introduction of antiretroviral therapy. The refractory variants with an aggressive, devastating and often fatal course which were seen in the pre-HAART era have became a rarity today. However, there are still some very aggressive cases occurring today, typically only a few weeks or months after introduction of antiretroviral therapy. This so-called IRIS-associated KS often comes with rapid visceral lesions and mortality is high (Crane 2005, Achenbach 2012). High HHV-8 and HIV viremia seem to be risk factors for this IRIS-associated KS (Letang 2009).

Pathogenesis

The cellular origin of the spindle cells (considered the KS tumor cells) is still controversial. Newer investigations suggest lymphatic, endothelial cells (Dupin 2006). Since 1994, it is well known that KS is induced by an infection with the human herpesvirus-8 (HHV-8) or Kaposi’s sarcoma-associated herpesvirus (KSHV). HHV-8 can be always detected in the tumor tissue, and the level of HHV-8 plasma viremia correlates quite well with KS progression (Laney 2007). In HIV-infected patients with KS, a significant HHV-8 viremia is frequently found (Marshall 2010). Transmission of HHV-8 occurs predominantly via saliva (Pauk 2000), but also sexually, vertically and via blood products (Pica 2008). In some regions, particularly in Italy and Central Africa, HHV-8 can be found in up to 50% of the general population. The exact role of HHV-8 in the pathogenesis of KS is not clear. Infection with HHV-8 does not lead inevitably to KS. Interactions particularly with HIV-1 (Aoki 2004), possibly also with other viruses such as HHV-6 and HSV-1, changed signal transduction chains, an increased production of growth factors as well as cytokine dysregulation, all may play a role (McCormack 2005).

Among the HIV+ population, gay men are almost the only ones affected by KS; in HIV-infected women, children or hemophiliacs, KS is a rare disease. An immune defect and/or low CD4 T cells promote emergence and growth of KS. However, severe immunodeficiency is not a prerequisite for the development of KS which is one of the few AIDS illnesses occurring in patients with a relatively preserved immune status. Approximately 29% of all patients who participated in the US in the years 1996–
In one study, the activation of the CD8 T cells correlated more strongly with the progression than the number of CD4 T cells (Stebbing 2006).

### Signs, symptoms and diagnosis

HIV-associated KS does not have a preferential pattern of localization. It can begin on any area of the skin, but may also appear on oral, genital, or ocular mucous membranes. Typical findings at manifestation are a few asymptomatic purple macules or nodules. These lesions have a predilection for distribution along relaxed skin tension lines. As mentioned above, the disease progression is very variable: the tumors can remain unchanged for months to years, or grow rapidly within a few weeks and disseminate. Rapid growth can lead to localized pain and a yellow-green discoloration of the area around the tumor as a result of hemorrhage. Further progression of the tumor can lead to central necrosis and ulceration. The tumors may bleed easily. Plaque-like and nodular KS lesions often become confluent and can be accompanied by massive lymphoedema. In the oral cavity, the hard palate is frequently affected. Lesions begin with purplish erythema and progress to plaques and nodules that ulcerate easily. KS lesions may also involve the external genitalia including the foreskin and glans penis.

Regression of KS during treatment is not only indicated by reduction of the size of the lesions but also by change in color from dark to bright red. However, some lesions may persist lifelong. These often dirty-grey-brown to light brown hyperpigmentations are caused by hemosiderin deposits and, possibly, increased stimulation of melanocytes due to inflammation. Lymphoedema can also persist for years.

### Diagnosis

Diagnosis of cutaneous KS is usually made based on clinical findings. However, in all inconclusive or questionable cases a histologic diagnosis (excision or incision) is recommended. Differential diagnosis includes other neoplasia such as cutaneous lymphomas or angiosarcoma, but also infectious diseases such as syphilis and bacillary angiomatosis. Histological findings include spindle-shaped cells with vascular channels lined by abnormal endothelial cells. Extravasated erythrocytes, hemosiderin, and fibrosis can often be seen.

In all cases of KS, clinical staging procedures are recommended, including:
- Complete inspection (oral and genital mucous membranes!)
- Abdominal ultrasound
- Gastroduodenoscopy and colposcopy (both procedures obligatory when mucous membranes are involved)
- Chest radiography (exclusion of a pulmonary KS)

### Treatment

If KS is newly diagnosed in an HIV-infected patient naïve to antiretroviral therapy, ART should be initiated: in early KS, additional chemotherapy is only required in 20% of cases (Bower 2009). In patients on ART without complete suppression of HIV plasma viremia, ART should be optimized. Treatment interruptions should be avoided (Silverberg 2007). With decreasing HIV plasma viremia and immune reconstitution, many KS lesions stabilize or even resolve completely without any specific treatment. In one Italian study on 22 ART-naïve KS patients, the overall clinical response rate
to ART alone was 91%: 18 complete and 2 partial responses were achieved, and only two patients experienced disease progression. Complete remission was sustained in all 18 patients (Cattelan 2005).

Animal and in vitro experiments have suggested a direct anti-proliferative effect of PIs (Sgadari 2002, Gantt 2011). However, there is no ART combination of choice for KS patients. PIs are not required necessarily as NNRTI-based regimens are also effective with regard to KS (Grabar 2006, Martinez 2006). With ART, there is also an improvement of the humoral response against HHV-8 (Sullivan 2010) and HHV-8 viremia rapidly decreases (Cattamanchi 2011). ART interruptions should be avoided in patients with current or previous KS. In the SMART study, KS was among the most frequent AIDS-defining illnesses during treatment interruptions, in particular among patients with a history of KS (Silverberg 2007).

ART as the only therapy is not recommended in all cases. In patients with rapidly progressive disease (especially in the setting of IRIS), with KS-related symptoms, or with visceral disease or lymphoedema, ART should be combined with cytotoxic chemotherapy (Grabar 2006). There are different options:

Chemotherapy: Pegylated liposomal doxorubicin hydrochloride (Caelyx® or Doxil®) at a dosage of 20 mg/m² body surface is the treatment of choice (Di Trolio 2006). It has replaced older therapies such as the ABV regimen, a combination of adriamycin, bleomycin and vincristine. With Caelyx® complete remission rates of up to 80% are possible (Lichterfeld 2005). The infusions for 30–60 min. every 2–3 weeks are feasible on an outpatient basis and usually well tolerated. An antiemetic therapy is not necessary. Usually 6–8 cycles are required to achieve a good clinical response. Relapses during Caelyx® therapy occur rarely and particularly during the first year (Martin-Carbonero 2008). During treatment, myelotoxicity and cardiotoxicity of doxorubicin should be considered. Although the latter is rare and occurs only above cumulative doses of 450 mg, echocardiography (ejection fraction?) is recommend at the beginning of therapy as well as controls after six cycles. Another important side effect of Caelyx® is palmo-plantar erythrodysesthesia (PPE, “hand-foot-syndrome”), which becomes apparent as painful erythemas at hands and feet (Lorusso 2007). The incidence of PPE is increased in patients receiving Caelyx® compared with conventional doxorubicin.

In August 2011, Janssen-Cilag reported a shortage of Caelyx® (Doxil®) due to production delays at a contract manufacturer. Intermittent capacity constraints were seen during the following months. In the setting of this shortage, liposomal daunorubicine (DaunoXome®) is an alternative. However, DaunoXome® appears to be less effective than Caelyx® (Cooley 2007). Of note, non-liposomal and non-pegylated forms of doxorubicin are not bioequivalent.

Beside doxorubicine and daunorubicine, paclitaxel (Taxol®) is also effective in KS (Tulpule 2002, Dhillon 2005, Stebbing 2006, Cianfrocca 2010). However, paclitaxel is more myelotoxic and leads almost always to complete alopecia, often during the very first cycle (patient must be informed!). Paclitaxel should be used only if KS lesions show progression during therapy with Caelyx® or when Caelyx® or DaunoXome® are not available. Docetaxel (Taxotere®) is also effective according to uncontrolled studies (Autier 2005, Lim 2005). It should be mentioned that significant interactions may exist between the taxanes and ART (Bundow 2004). Paclitaxel levels may increase significantly when combined with PIs (Cianfrocca 2011). For the treatment of doxorubicin refractory cases, beside taxanes, oral etoposide (Evans 2002), irinotecan (Vaccher 2005) and the ABV regimen may be considered. According to a retrospective study from Kenya, even gemcitabine has promising activity in KS (Strother 2010).
**Immunotherapy:** With interferons (IFN) acceptable remission rates are reached. However, CR rates seem to be lower than with pegylated liposomal doxorubicin (Kreuter 2005). The effect mechanism of IFN on KS is not fully clarified. Apart from an immune modulating effect, IFN probably induces the apoptosis in KS cells. It is important to note that the effectiveness depends on the immune status. In patients with more than 400 CD4 T cells/µl, remission rates during IFN are at least 45%, compared with only 7% in patients with less than 200 CD4 T cells/µl. There may be other factors to predict response to IFN such as endogenous IFN levels, which are increased in the advanced stages of HIV infection.

There are currently no standardized IFN treatment regimens. Due to the considerable side effects, a high dose treatment (up to 30 million IU/day) is not commonly administered. Daily doses of 3–6 million IU subcutaneously are usually given. After remission (tumour growth stopped, tumours flattened, loss of purple color, change to brownish color), interferon dosing can be reduced to 3x/week. Remission can be expected after 6–8 weeks of treatment (often significantly later). There is no sufficient data on the use of the pegylated IFN for HIV-associated KS. However, there are some promising case report in AIDS patients (Van der Ende 2007, Ueno 2007) and in patients with classical KS (Di Lorenzo 2008).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated liposomal doxorubicine (Caelyx™ or Doxil™)</td>
<td>20 mg/m² IV every 2 weeks</td>
<td>Treatment of choice, beware of myelotoxicity, cardiotoxicity, hand-foot syndrome</td>
</tr>
<tr>
<td>Liposomal daunorubicin (DaunoXone™)</td>
<td>40 mg/m² IV every 2-3 weeks</td>
<td>Slightly less effective than Caelyx™, seldom used during the past decade. However, as capacity constraints for Caelyx™ are expected for 2012, an important alternative</td>
</tr>
<tr>
<td>Interferon-α 2a (Roferon™)</td>
<td>3-6 x 10⁶ I.E. SC or IM 3x/week</td>
<td>Considerable side effects, less efficacy than with doxorubicin. Use only when CD4 T cells are &gt;200/µl and limited disease</td>
</tr>
<tr>
<td>Pegylated Interferon-α 2b (Pegintron™)</td>
<td>50 μg SC weekly</td>
<td>Tolerability improved compared to conventional IFN-α (2a,b), but lack of data in AIDS KS, off-label use!</td>
</tr>
<tr>
<td>Paclitaxel (Taxol™)</td>
<td>100 mg/m² IV every 2 weeks or 135 mg/m² IV every 3 weeks</td>
<td>Beware of neutropenia, peripheral neuropathy, allergic reactions, alopecia</td>
</tr>
</tbody>
</table>

**Local therapy:** is well-tolerated and less costly. Many different methods are used depending on the size and location of tumors: cosmetic camouflage, cryosurgery, intralésional injections of Vinca alkaloids or interferons, soft x-ray radiation, electron beam therapy, cobalt radiation (fractionated) or Imiquimod (Celestin Schartz 2008). Compressive therapy with elastic stockings is an important strategy for the treatment of KS associated lymphoedema (Brambilla 2006). KS is a strikingly radiosensitive tumor (Becker 2006). Superficial macular or plaque-like KS lesions respond well to daily doses of 4–5 Gy (total dose 20–30 Gy, fractionated 3x/week) of soft x-ray radiation. In the case of large KS lesions with edema, radiation with fast electron beams (5 x 2 Gy per week, total dose 40 Gy) is recommended.
As KS is a multifocal systemic disease, surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically disturbing areas. Since tumors often extend further into the surroundings than is clinically visible and local trauma can lead to new tumors (Koebner phenomenon), local and regional recurrences can be expected. These can be prevented by radiation therapy: in order to reach the tumor cells spreading along the vascular channels, the field of radiation should be extended 0.5–1.0 cm beyond the edges of the tumor.

**New therapeutic approaches:** With regards to the KS pathogenesis, several new therapies have been suggested such as virustatic agents, cytokines and inhibitors of angiogenesis. They are described here briefly:

- **Valgancyclovir** – is a promising approach as this antiviral agent significantly reduces the frequency and quantity of HHV-8 replication. This was recently shown by a randomized trial (Casper 2008). Antiviral efficacy of valgancyclovir is higher than with valacyclovir or famcyclovir (Cattamanchi 2011). However, there are no data on clinical efficacy in AIDS-related KS published to date. As HHV-8 is involved in the early steps of KS pathogenesis, it is questionable if valgancyclovir has any effect on manifest lesions. In patients with classical KS, the drug remained inefficient (Krown 2011).
- **Interleukin-12** – high response rates in a Phase II study, in which this cytokine was combined with liposomal doxorubicin (Little 2007). No randomized studies.
- **Sirolimus (and everolimus)** – new immunosuppressive agents used in the transplant and rare diseases (tuberous sclerosis, LAM) settings. Good response rates in uncontrolled studies on HIV-negative renal transplant recipients with KS (Stallone 2005, Campistol 2007). It is postulated that these drugs inhibit tumour angiogenesis through impaired vascular endothelium growth factor production.
- **Bevacizumab** – an early study of this VEGF antibody showed moderate response rates in 31% of 17 HIV-infected patients with KS progression on ART (Uldrick 2010). A study of combination with liposomal doxorubicine is ongoing.
- **Imatinib (Glivec®)** – activation of the platelet-derived growth factor (PDGF) and c-Kit receptors has been proposed as important in mediating the growth of AIDS-related KS. Treatment with the PDGF receptor/c-kit inhibitor, imatinib mesylate, resulted in clinical and histologic regression of cutaneous KS lesions in 5/10 patients within 4 weeks (Koon 2005).
- **Sorafenib (Nexavar®)** – is an oral Raf kinase inhibitor, approved for the treatment of advanced renal cancer. Case reports on KS (Ardavanis 2008). Phase I studies are underway.
- **Matrix metalloproteinases (MMPs)** – are involved in tumour metastasis and are over-expressed in Kaposi’s sarcoma cells. MMP inhibitors such as COL-3 have shown activity in a Phase II study on patients with advanced KS (Dezube 2006). However, clinical response rates were at best moderate at 41%. The most common adverse events were photosensitivity and rash. Encouraging Phase II study with topical halofuginone (Koon 2011).
- **Retinoid compounds** (tretinoin, isotretinoin, acitretin) – may inhibit the proliferation of KS cells. Many studies on different formulations have been conducted (Duvic 2000, Bodsworth 2001, Bernstein 2002, Aboulafia 2003). However, efficacy is only moderate. Retinoids will probably face a difficult path in attaining approval for KS.
References


Aoki Y, Tosato G. HIV-1 Tat enhances KSHV infectivity. Blood 2004; 104: 810-4


Malignant lymphomas are neoplastic diseases of the lymphatic system that grow rapidly and aggressively, and lead to death within a few weeks or months if left untreated. Hodgkin’s disease (HD) is distinguished from the large group of non-Hodgkin’s lymphomas (NHL). In comparison to the general population, HIV-infected patients are affected significantly more frequently by all types of lymphoma (see Table 1). Aggressive non-Hodgkin’s lymphomas of B cell origin are particularly frequent. The incidence of lymphomas has been markedly reduced by the introduction of antiretroviral therapy. However, there is evidence that this reduction overall was not as impressive as with KS or most other opportunistic infections (COHERE 2009, Franceschi 2010). Thus, the relative proportion of lymphoma among all AIDS-associated illnesses is increasing. The decline of incidence seems to be greater for lymphoma subtypes that mainly occur in severe immunodeficiency (Kirk 2001, Polesel 2008).

In some HIV cohorts, malignant lymphomas have already overtaken KS as the most frequent malignancy. In the EuroSIDA study, the proportion of AIDS-defined illnesses that were malignant lymphomas increased from less than 4% in 1994 to 16% in 1998 (Mocroft 2000). Among the AIDS-related deaths, lymphoma is by far the most frequent disease involved. In France, lymphomas accounted for 24% of all AIDS-related deaths in HIV patients (Morlat 2012).

Table 1: Relative risk of different lymphomas in HIV+ patients in comparison to a non-HIV+ population (adapted from Goedert 2000)

<table>
<thead>
<tr>
<th>Malignant NHL total</th>
<th>165</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade malignancy NHL</td>
<td>348</td>
</tr>
<tr>
<td>Immunoblastic NHL</td>
<td>652</td>
</tr>
<tr>
<td>Burkitt’s NHL</td>
<td>261</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>580</td>
</tr>
<tr>
<td>Primary CNS lymphoma (PCNSL)</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Low-grade malignancy NHL</td>
<td>14</td>
</tr>
<tr>
<td>Plasmocytoma</td>
<td>5</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>8</td>
</tr>
</tbody>
</table>

Malignant lymphomas in HIV-infected patients are also biologically very heterogeneous and differ in several aspects. The frequency and extent of oncogenic mutations or cytokine dysregulation differ, as does the histogenetic origin of the malignant cells (Porcu 2000). In addition, the association with EBV and other oncogenic viruses such as HHV-8 or SV40 is very variable. The extent of immunodeficiency also varies significantly. Burkitt’s lymphoma and Hodgkin’s lymphoma (HL) frequently occur even when immune status is good. In contrast, immunoblastic and especially primary CNS lymphoma (PCNSL) are almost always associated with severe immunodeficiency. There is now some evidence that some subtypes of malignant lymphoma can be considered to be “opportunistic” as severe immunodeficiency is required for the development of these entities. For other lymphoma subtypes, chronic B cell activation, possibly induced by even low HIV viremia, is a prerequisite (Epeldegui 2007, Zoufaly 2009, Regidor 2011).

However, HIV-associated lymphomas – both NHL and HD – have numerous common clinical features. Characteristics include the usually aggressive growth, diagnosis in
the advanced stages with frequent extranodal manifestations, poorer response to treatment, high relapse rates and an overall poor prognosis (Levine 2000). Despite a better prognosis during recent years (see below), HIV-infected patients with NHL continue to endure substantially higher mortality compared with HIV-uninfected patients with NHL (Chao 2010).

The treatment of malignant lymphoma remains problematic. Although aggressive chemotherapy is possible in many patients with existing immunodeficiency, it is complicated and requires a close cooperation between HIV clinicians and physicians with experience in hematology/ oncology.

We discuss systemic NHL, PCNSL and HD separately; multicentric Castleman’s disease will also be mentioned as a distinct entity, although it is not considered a malignant lymphoma. Low-grade (indolent) NHLs are very rare in HIV+ patients, and will therefore not be discussed here. As there are no data or even recommendations available, the treatment of such cases should follow the recommendations for HIV-negative patients.

**Systemic non-Hodgkin lymphomas (NHL)**

A close association between systemic NHL and AIDS has been described for a long time – the first cases were published only about a year after the first description of AIDS and even before the discovery of HIV (Ziegler 1982). High-grade BNHLs have been AIDS-defining since 1985.

More than 90% of HIV-associated NHLs are of B cell origin. They are almost always of high-grade malignancy. Two main histological types dominate: according to the WHO classification, these are Burkitt’s lymphomas, which comprise 30–40% of cases, and diffuse large-cell B cell lymphomas, comprising 40–60%. However, a relatively large proportion of HIV-associated lymphomas (up to 30%) cannot be classified even by reference laboratories. A small proportion of NHLs (1–3%) are primary effusion or body cavity-based lymphomas and are considered a distinct entity (see below).

The prognosis of patients with NHL was poor in the pre-HAART era, being between 6 and 9 months (Levine 2000). Due to the introduction of combination that compared the variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy, NHL was the AIDS-defining event with the greatest mortality hazard ratio (ART-CC 2009). Whether the clinical and pathological spectrum of lymphoma subtypes is also changing remains unclear. A French study showed no differences in lymphoma features in antiretrovirally treated patients compared to treatment-naïve patients (Gérard 2009). However, it seems possible that, compared to HL or Burkitt’s lymphoma, the percentage of “opportunistic” NHL such as immunoblastic lymphoma will decrease.

**Prevention and early detection**

There is no data supporting specific therapies or diagnostic procedures (such as periodical ultrasound controls, etc) for prevention or for early detection of malignant lymphomas. Antiretroviral therapy seems to be the best protection against lymphoma. ART not only improves the immune status but it also reduces the chronic B cell stimulation, another risk factor for the development of lymphoma (Grulich 2008). HIV plasma viremia should be as low as possible as cumulative HIV viremia is an independent and strong predictor of AIDS-related lymphoma among patients receiving ART (Zoufaly 2009). Blood EBV DNA load also represents a risk factor (Leruez-Ville 2012). Besides ART, there have been numerous studies evaluating factors (so called “bio-
markers”) that may precede the development of AIDS-associated lymphoma. For example, it has been shown that the levels of serum globulins (Grulich 2000), interleukin-6 or -10 (Breen 2003), soluble CD33 (Pordue 2009, Breen 2012), activity of activation-induced cytidine deaminase (Epeldegui 2007) or circulating immunoglobulin-free light chains (Landgren 2009) may predict the risk of NHL. These activation markers were markedly elevated in those who developed AIDS-related NHL, when compared to AIDS patients and HIV-negative controls. These findings may help us understand the pathogenesis of lymphomas in HIV-infected patients. However, a routine diagnostics measure has not been found.

**Signs and symptoms**

The main symptom is lymph node enlargement. Lymphomas are firm, immobile or barely mobile and painless. A large proportion of patients have advanced-stage lymphoma at the time of diagnosis. Ann Arbor stages III-IV are almost always the rule, and B symptoms with fever, night sweats and/or weight loss are found in the majority of cases (60–80%). General asthenia, significant malaise and rapid physical deterioration are also frequently seen. Extra-nodal involvement is common, and may be to a grotesque extent. In our own cohort of 203 patients, 81% had at least one extranodal focus (Hoffmann 2003). Every conceivable region of the body can be affected—the orbital cavity, testes, heart, breasts, bladder, kidneys, muscles, bones, etc. The gastrointestinal tract, liver, and bone marrow are affected particularly frequently. Secondary CNS involvement can also occur. With extra-nodal disease, additional symptoms arise depending on the localization. These include, for example, abdominal pain from hepatosplenomegaly, hemorrhage or ileus symptoms due to intestinal involvement, bone pain with skeletal infiltration, or headache caused by brain disease.

**Diagnosis**

Rapid histological diagnosis is essential. If bone marrow biopsy cannot secure the diagnosis, then a lymph node (e.g., cervical, axillary or inguinal) should be extirpated. Mere puncture biopsy of a lymph node is often not sufficient to secure a representative specimen. It is imperative to send the material to a specialized pathology laboratory with extensive experience in lymph node morphology. Every case should be discussed with the pathologist and caution taken to avoid a misdiagnosis. A typical yet mostly wrong diagnosis is that of a high- or low-grade T cell lymphoma in an AIDS patient. T cell lymphomas are very rare in AIDS patients and in most cases, T cell infiltrates indicate several infectious diseases like malignant syphilis rather than lymphoma.

The basic pathological diagnosis should include information about the subtype of lymphoma (Burkitt?), the proliferation rate and the expression profile (definitely CD20, and probably CD10, CD138, MUM-1) as these can influence the therapy (see below).

All patients with suspected NHL should be staged according to the Ann Arbor classification (Tables 2a, b).

Basic diagnostic tests for staging include chest radiography; abdominal ultrasound; CT scans of the neck, thorax and abdomen; and bone marrow biopsy; aspiration alone is not enough. In addition to an updated immune status and viral load, the following should be determined at the very least: blood count, ESR, CRP, uric acid, LDH, liver and kidney parameters and electrolytes. ECG and echocardiography are also important right away. The possible cardiotoxicity of chemotherapy (anthracy-
clines) during the course of treatment can only be evaluated if these tests have been performed at the start. Pulmonary function should be tested before treatment with regimens containing bleomycin is initiated.

After two cycles of chemotherapy, a re-staging should be performed to evaluate treatment success. This restaging should be oriented according to the original localization of lymphoma. After completion of the protocol, a complete restaging with bone marrow biopsy (if there was initial involvement) and all CT scans are necessary. With a complete remission, restaging is recommended initially at three-monthly intervals. These intervals can be prolonged to six months after one year and to twelve months after two years. Relapses after more than three years are rare.

In advanced stages of the disease (Ann Arbor III-IV), and particularly with ENT involvement, a diagnostic lumbar puncture is necessary before initiating systemic chemotherapy to exclude meningeal involvement. In such cases, 15 mg of methotrexate can be administered intrathecally as prophylaxis. Whether this action, generally accepted by oncologists, actually has benefit or not, has never been shown in controlled studies. However, newer data suggest that there may be a benefit (Spina 2010).

Table 2a: Staging according to the updated Ann Arbor classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site plus its regional lymph nodes, with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III) can be accompanied by localized extralymphatic organ involvement (IIE) or spleen involvement (IIIS) or both (IIIE+S)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement; or isolated involvement of an extralymphatic organ with involvement of distal (non-regional) lymph nodes.</td>
</tr>
</tbody>
</table>

Table 2b: Every stage is divided into categories A and B

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>
| B        | General symptoms:  
  a) unexplained weight loss of more than 10% in the last six months, and/or  
  b) unexplained persistent or recurring fever with temperatures above 38°C, and/or  
  c) drenching night sweats |

**Therapy**

Due to extremely rapid generalization, even “early stages” move quickly. Every aggressive HIV-associated lymphoma should not be underestimated and should be treated with systemic chemotherapy with a curative intent. Surgery or radiation therapy alone are not sufficient. Treatment should be started rapidly due to the aggressive nature of these lymphomas. In particular, time should not be wasted on staging. The necessary tests should be completed within a week.

In Europe, diffuse large cell NHLs have been treated for many years with CHOP-based regimens (usually 4–6 cycles, see Table 3). CHOP is the abbreviation for the
combination chemotherapy of the cytostatics cyclophosphamide, Adriamycin (hydroxydoxorubicin), vincristine (Oncovin®) and prednisolone. To date, no other chemotherapy regimen has been shown to have better efficacy. There are no randomized controlled trials comparing CHOP with other regimens such as CDE or EPOCH which have been proposed by several working groups.

In contrast to CDE or EPOCH, CHOP can be administered in ambulatory care and is fairly well tolerated. At least 4–6 cycles should be administered, and – as far as possible – 2 cycles after reaching complete remission (CR).

The standard three-week CHOP regimen (CHOP-21) is shown in Table 3. Following the success of CHOP-14 (one cycle every two weeks) in older HIV-negative patients (Pfreundschuh 2004), CHOP-21 can also be “intensified”. In CHOP-14 the use of the growth hormone G-CSF (e.g., Filgastrim 30–48 million units or Neupogen® 300/480 µg SC daily on days 4 to 13) reduces the duration of neutropenia. This approach not only decreases the phase of increased susceptibility to infections, but also increases the dose intensity of chemotherapy. However, there is no comparative data on this for HIV patients. So far, we have had fairly positive experiences – in most HIV patients, it is possible to shorten the interval.

Recently, a study from East Africa reported on a dose-modified oral chemotherapy, consisting of lomustine, etoposide and cyclophosphamide/procarbazine. This pragmatic approach had acceptable remission rates in 49 patients with AIDS-related NHL and could be considered an alternative in resource-poor countries (Mwanda 2009).

Table 3: CHOP regimen (4–6 cycles of 3 weeks each, repeat on day 22)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Endoxan® 750 mg/m² IV day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Doxo-Cell®, Adriblastin® 50 mg/m² IV day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Vincristin® 1.4 mg/m² (maximum 2 mg) IV day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Decortin H® 2 tab. at 50 mg QD, days 1–5</td>
</tr>
<tr>
<td>Mesna</td>
<td>Uromitexan® 20% of cyclophosphamide dose at hours 0, 4, 8 (with reference to cyclophosphamide IV given as a short infusion or orally)</td>
</tr>
</tbody>
</table>

*Standard CHOP regimen (“CHOP 21”)

We recommend the administration of co-trimoxazole as an adjuvant therapy, up until one month after completion of chemotherapy (960 mg three times weekly), independent of CD4 T cell count. Oral mucous membranes should be treated with mouthwashes and topical amphotericin. Good compliance from the patients is an important factor. During chemotherapy, at least twice weekly monitoring of the patient’s condition, blood count, liver and kidney parameters is necessary. Treatment is usually continued with the full dose according to protocol if leukocytes are above 3000/mm³ and platelets above 80,000/mm³ on the planned day of treatment. Patients should be advised to carry out daily temperature monitoring and be told to present immediately in case of fever.

Rituximab in HIV-infected patients

The introduction of the monoclonal CD20 antibody rituximab (MabThera® or Rituxan®) was one of the biggest advances in oncology in recent years. In numerous lymphomas, this antibody, which binds highly specifically to CD20-positive B cells (CD20 is expressed by most lymphoma cells), has markedly improved the effectiveness and length of response of conventional chemotherapy. A combination of CHOP
and rituximab (R-CHOP) is now standard in many lymphomas. Rituximab is usually well tolerated, but often leads to a longer lasting B cell depletion, and occasionally to severe neutropenia (Voog 2003). It is not clear whether rituximab has a similarly large clinical benefit for HIV-infected patients as it has for HIV-negative patients with B cell lymphoma. The results from AMC 010, a multicenter prospective and randomized US study, have at least raised doubts (Kaplan 2005). In this study, 143 patients with CD20-positive AIDS-related NHL were randomized (1:2) to CHOP or R-CHOP (rituximab in the usual dose of 375 mg/m² on day 1 with a monthly maintenance therapy for 3 months following chemotherapy). In addition to the chemotherapy, all patients also received G-CSF, a co-trimoxazole prophylaxis and an AZT-free ART. Both groups were well matched. The planned CHOP cycles were carried out at the same intensity in both groups, and in both groups only slight dose reductions were necessary. The main results were disappointing. There was only a trend towards a better response in the R-CHOP arm (complete response rate 58% versus 47%, p=0.15). No differences were found with respect to the length of response, disease-free or total survival. However, neutropenia and incidence of (especially severe) infection were significantly higher in the rituximab group. Out of a total of 15 patients who died from an infection during the study, 14 had received rituximab (14% versus 2%, p=0.035). The cause of death was usually septicemia from various bacteria – both gram-negative and gram-positive were identified. Death occurred in the majority (8/15) during the first two cycles, although six cases happened during the rituximab treatment at the end of the chemotherapy. Fatalities occurred in all centers and were therefore not due to a possible lack of expertise in any one location. A further risk factor for “death from infection” was a low baseline CD4 count – 8/13 patients had less than 50 CD4 T cells/µl. The cause of the high rate of severe infections is still unclear. Pathophysiologically, it is at least possible that in pre-existing T cell defects present in HIV patients, a long-lasting rituximab-induced B cell depletion or hypoglobulinemia has particularly negative effects (Miles 2005). There are also some reports on an elevated risk for PML in patients receiving rituximab (Carson 2009). The reason for this association remains unclear. In contrast to the results of AMC 010, there are numerous mostly uncontrolled studies which did not find an elevated risk for serious infection with the use of rituximab (Spina 2005, Boue 2006, Ribera 2008, Sparano 2009). In our own prospective cohort study of 164 patients with NHL since 2005, treatment with rituximab was beneficial even in severely immunosuppressed patients (Wyen 2012). Moreover, we did not find evidence for a high incidence of PML (Hoffmann 2012). A recent meta-analysis of 15 prospective trials showed a moderate benefit. HIV patients treated with rituximab and chemotherapy had higher odds for complete remission and 2-year overall survival when compared to chemotherapy alone but also had a higher proportion of ART usage (Castillo 2012).

Following the current data, the use of rituximab can be considered in all HIV-infected patients with CD20-positive NHL. Even a severe immune deficiency (less than 200 CD4 T cells/µl) is not a contraindication. However, intensive monitoring and the prophylactic use of co-trimoxazole (and possibly quinolones) may be advisable. In addition, it is imperative that more data is obtained.

**More intensive chemotherapy as standard CHOP**

After earlier studies showed that intensive chemotherapy led to a disproportionately high risk of infection and toxic complications (Kaplan 1997), the tendency for a long time was to withhold HIV+ patients from therapy and often to treat them with
reduced-dose regimens. This seems to be changing in the age of combination ART. Several prospective studies have shown that the tolerability of chemotherapy is improved through ART (Powles 2002, Sparano 2004, Bower 2008).

In the past few years, small pilot studies have been repeatedly published in which HIV+ patients have been treated with CHOP. There are also studies in which doxorubicin has been given as liposomal Caelyx® (Levine 2004) or where the dose of cyclophosphamide was increased (Costello 2004). In addition, CDE, a regimen which, when given for several days as infusion is supposed to overcome the potential chemotherapy resistance of lymphoma cells, is propagated again and again (Sparano 2004, Spina 2005). This is also the case for the EPOCH regimen (Little 2003, Barta 2012). The CR rates in these studies were between 50 and 75%. In our experience, CR rates up to 70% are also possible with ART and standard CHOP. Whether these new attempts, which always cause a stir, are really better than CHOP, remains speculative. In our view, they are not ready for use outside of trials.

Even stem cell transplantations are now possible in HIV patients – a scenario that was unthinkable just a few years ago. Very high doses of myeloablative chemotherapy in combination with ART are well tolerated (see below). In HIV-infected with Burkitt’s lymphoma, intensive protocols that were originally developed for HIV-negative patients are also being successfully employed (see below). Today, the decisive question regarding more intensive chemotherapy in HIV-infected patients is, therefore, not whether it can be used, but who actually needs it or will benefit from an increased dose.

**What ART when?**

In early studies, the effect of combination ART on the prognosis of HIV-associated NHL was only modest (Levine 2000, Matthews 2000). Over the last years, however, many studies clearly demonstrated that prognosis of patients with NHL is markedly improved with ART (Antinori 2001, Besson 2001, Ratner 2001, Hoffmann 2003). In addition to survival, some studies also showed improved disease-free survival, response rates and even improved tolerability of chemotherapy. Even cases in which ART alone led to a complete remission of lymphoma have been published (Amengual 2008, Baraboutis 2009, Teng 2011). There is no doubt that every patient with AIDS-associated lymphoma should start an antiretroviral therapy, even in the setting of a relatively preserved immune function.

In most cases, an already existing, virologically effective ART can be continued during chemotherapy. However, a switch from AZT (myelotoxic) and from d4T/ddI (high risk of polyneuropathy, in particular when given with vinca alkaloids) to other nucleoside analogs or to a nuke-free regimen should be considered. Before switching to abacavir, an HLA-B*5701 genetic screening is recommended. When switching to tenofovir, intensive monitoring of renal function parameters is required.

In naïve patients, the first one or two CHOP cycles can be completed before starting ART. Some clinicians prefer to complete all six cycles out of concern for interactions and cumulative toxicities (Little 2003). In our opinion, this is not necessary, even though data on possible interactions between ART and chemotherapy is limited (Review: Mounier 2008). For example, the effect of PIs and NNRTIs on doxorubicin levels seems to be only moderate (Toffoli 2004) and in many studies, the concomitant use of ART and chemotherapy was feasible and safe (Powles 2002, Weiss 2006, Simcock 2007, Bower 2008). However, there have been some reports of patients who experienced severe vinblastine-associated neurotoxicity during concomitant treatment with ritonavir-boosted PIs (Cheung 2010). If PI-containing combinations are used, TDM is recommended.
In ART-naïve patients without pre-existing renal damage, we would favor a combination of tenofovir, FTC and raltegravir. The integrase inhibitor raltegravir has a low risk for interactions and side effects. Moreover, many studies suggest a faster viral decay with this agent compared to other antiretrovirals. During tenofovir, renal function should be monitored carefully.

**Special entities of lymphoma**

**Burkitt’s or Burkitt-like lymphomas:** the particularly high proliferative capacity and aggressiveness of Burkitt’s or Burkitt-like lymphomas is a problem even in HIV-negative patients. In this case, the CHOP regimen is insufficient (Trümper 2001). Although it is still unclear whether this is also true for HIV-infected patients with Burkitt's lymphomas, many clinicians have in recent years tended to treat such patients more intensively. A modified dose-adapted protocol of the German multicenter study group for adult acute lymphoblastic leukemia (GMALL) is usually used for the treatment of HIV-negative cases of Burkitt-NHL/B-ALL, and consists of four to six short, intensive 5-day polychemotherapy cycles, alternating A and B cycles. A cytoreductive pretreatment with cyclophosphamide and prednisone, each for 5 days, was given before the first cycle. During cycle A, fractionated doses of ifosfamide for 5 days, intermediate- or high-dose methotrexate 500–3000 mg/m², VM26, cytarabine (ara-C), vincristine, and dexamethasone are given. During cycle B, ara-C, VM26 and ifosfamide are replaced by doxorubicin and cyclophosphamide (Hoelzer 1996). Preliminary data show better responses than with CHOP (Hoffmann 2006) and rates comparative to those of HIV-negative patients (Oriol 2008). However, the GMALL protocol is very intensive and cannot be administered on an outpatient basis. Strict monitoring of patients in hospital for several weeks is very important. Centers without experience should not administer it to HIV-infected patients. Other intensive therapies have been also reported (Cortes 2002, Wang 2003). A significant problem with most studies is that there is no control group. There is no randomized study. However, there is increasing evidence that conventionally treated patients with Burkitt’s lymphoma continue to have a worse prognosis even in the age of combination ART (Conti 2000, Lim 2005, Spina 2005). Although this has not been confirmed by all study teams (Bower 2005), intensive therapy should be considered for every patient with Burkitt’s lymphoma. A poor immune status or the existence of a concurrent opportunistic infection does not necessarily have to be an obstruction (Lehmann 2005).

**Plasmablastic lymphomas:** are a relatively “new” entity in HIV-infected patients. Plasmablastic lymphomas probably belong to the diffuse large cell NHLs, but display a completely characteristic immune phenotype, which usually correlates to a post-germinal center cell – markers for the B-cell antigen CD20 are negative, whereas the plasma-cell reactive antibodies VS38c and CD138 are positive (Brown 1998, Teruya-Feldstein 2004).

The oral cavity is the site of involvement (Gaidano 2002), although extra-oral manifestations do occur (Chetty 2003). There is a close association with an HHV-8 infection but also EBV (Castillo 2008, Riedel 2008). Like Burkitt's lymphoma, plasmablastic lymphomas have a very high rate of proliferation and are extremely aggressive. Prognosis remains poor (Castillo 2012). In a study on 89 people with NHL, we were able to show that a post-germinal center profile, as often occurs in plasmablastic lymphomas, is independently associated with a worse prognosis (Hoffmann 2005). This observation was confirmed by other groups (Dunleavy 2010). Intensive chemotherapy regimens do not seem to increase survival (Castillo 2012). New options
are urgently needed. These could include bortezomib, which is a selective potent proteasome inhibitor that has been approved for clinical treatment of multiple myeloma and mantle cell lymphoma. There exists at least one case report (Bibas 2010).

Primary effusion lymphoma (PEL): a further therapeutic problem is the relatively rare entity of the so-called primary effusion lymphoma which is also called body cavity lymphoma (Carbone 1997+2000). These lymphomas are often very difficult to diagnose histologically. A visible tumor mass is usually absent, so malignant cells can only be found in body cavities (e.g., pleural, pericardial, peritoneal). There are histological similarities to immunoblastic and anaplastic cells with a non-B-, non-T phenotype. Every pleural or pericardial effusion occurring in an HIV+ patient and containing malignant cells, is suspicious of PEL. The involved pathologist should always be informed about this suspicion. There is a characteristic close association with the herpes virus HHV-8, which can be detected in malignant cells, and which provides a relatively typical gene expression profile (Simonelli 2005, Fan 2005). Recently, a solitary variant has been reported, which is neither morphologically nor immunophenotypically distinguishable from the classical PEL types (Chadburn 2004).

The response to the CHOP regimen is usually poor and poorer than that of centroblastic NHL (Simonelli 2003). Case studies with complete remission on ART alone have been described (Boulanger 2001, Hocqueloux 2001). We have, however, seen two PEL patients who have also died of progression despite CHOP and ART after only a few months. A small study reported encouraging results with a combined chemotherapy with high-dose methotrexate. In at least 3/7 patients a lasting complete remission was achieved – a notable achievement in view of the otherwise poor prognosis, and an approach that should be followed up (Boulanger 2003). On the other hand, there are reports in which even intensive treatment regimens were unsuccessful (Waddington 2004). A new option may be bortezomib, which is a selective potent proteasome inhibitor. Xenograft models have shown that bortezomib induces PEL remission, providing a rational basis for clinical evaluation (Sarosiek 2010).

Relapse therapy, stem cell transplantation

At the moment, no general recommendations for relapse therapy of NHL can be given. The prognosis of NHL relapse is poor. A team from the US reported their positive experiences using the ESHAP protocol (etoposide, methylprednisolone, ara-C and cisplatin). DHAP appears to have no effect here (Bi 2001). The EPOCH regimen may also be effective. Other salvage monotherapies with mitoguazon or liposomal daunorubicin are well tolerated, but purely palliative (Levine 1997, Tulpule 2001). It should always be checked whether the affected patient with a relapse of lymphoma qualifies in principle for an autologous stem cell transplant (ASCT). In ASCT, the intensity of the chemotherapy can be markedly increased by the preceding gain of pluripotent stem cells (own cells: autologous; foreign cells: allogenic). Following the myeloablative chemotherapy, the patients are re-infused with the stem cells. Over 200 cases of SCT in HIV-infected patients have been described so far worldwide (Gabarre 2000+2004, Re 2003, Krishnan 2005, Serrano 2005, Spitzer 2008). They have clearly shown that efficacy is comparable to HIV-negative patients (Simonelli 2010, Krishnan 2010). Even a few allogenic SCT have been reported (Kang 2002, Bryant 2008, Gupta 2009, Oka 2010). In 2009, one of these cases attracted much intention. German researchers from Berlin transplanted stem cells from a donor who was homozygous for CCR5 delta32 in a
patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound for years after transplantation and discontinuation of ART (Huetter 2009, Allers 2011). There is no doubt that this case offers great hope for potential gene therapies. However, given the high mortality of patients undergoing allogenic SCT, this treatment is too risky to become a routine treatment for HIV and too difficult to find donors with the right genetic make-up.

The critical problem of autologous SCT in many hematological centers is above all a logistical one, namely the complicated storage of stem cells, which has to conform to strict safety regulations. The storage of potentially infectious HIV material together with stem cells from non-infected patients in normal cooling tanks is not allowed – an extra (expensive) tank is required.

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Primary CNS lymphoma

Primary CNS lymphomas (PCNSL) are a late complication of HIV infection and used to occur in up to 10% of AIDS patients. Large autopsy cohorts in the 1990s showed even higher prevalence rates. The incidence of PCNSL seems to have decreased significantly in the last years in comparison to systemic lymphomas (Polesel 2008). PCNSL are EBV-associated in almost 100% of cases (Camilleri-Broet 1997). Histologically, findings are almost always consistent with diffuse large cell non-Hodgkin’s lymphomas. In these patients, the CD4 T cells are almost always below 50/µl at the time of diagnosis. In the pre-HAART era, PCNSL had the poorest prognosis of all the AIDS-defining illnesses, with a median survival of less than three months (Fine 1993). In more recent years, this bleak picture, often characterized by therapeutic nihilism, has changed significantly. In the HAART era, survival may be several years and complete remission has become possible (Hoffmann 2001).

Signs and symptoms

Different neurological deficits occur depending on the localization. Epileptic seizures may be the first manifestation of disease. Personality changes, changes in awareness, headaches and focal deficits such as paresis are also frequent. Fever is usually absent. As patients are almost always severely immunocompromised, constitutional symptoms may mask the real problem.

Diagnosis

Cranial CT or (better) MRT scan should be performed rapidly. The most important differential diagnosis is cerebral toxoplasmosis. A solitary mass is usually more indicative of PCNSL. However, 2–4 lesions may be present, which are usually fairly large (more than 2 cm in diameter). More than four lesions of a PCNSL are rarely found. In addition to an updated toxoplasmosis serology, which – if negative – makes toxoplasmosis very unlikely, a recent CD4 T cell count should be available. The better the immune status, the less likely the diagnosis of PCNSL. In our own cohort, less than 20% of patients had more than 50 CD4 T cells/µl at the time of diagnosis. At over 100 CD4 T cells/µl, however, cerebral toxoplasmosis is also less likely. In addition to the physical examination, a minimal diagnostic program (chest radiography, abdominal ultrasound) should clarify whether the CNS involvement is secondary to systemic lymphoma. This should always include fundoscopy to exclude ocular involvement (up to 20%). Besides cerebral toxoplasmosis, differential diagnoses include abscesses, glioblastoma and cerebral metastasis of solid tumors. In the absence of increased intracranial pressure, lumbar puncture is advised. If steroids have already been administered, however, the probability of finding malignant cells is diminished. EBV DNA is commonly detected in the CSF of HIV-infected patients. Quantitative EBV PCR in the CSF improves the diagnostic specificity, although the predictive value remains too low for it to be used as an isolated marker for PCNSL (Corcoran 2008). In most cases, a treatment attempt for toxoplasmosis can be made initially. If this is unsuccessful, PCNSL is more likely. In such cases, stereotactic brain biopsy is essential to secure the diagnosis.

Treatment

For many years, cranial radiation therapy has been the only option for patients with PCNSL, independent of HIV status. In HIV-negative patients, using the combination of radiation therapy and steroids, a remission of 12–18 months duration is usually
achieved. In HIV+ patients in the pre-HAART era, radiation only improved survival from 0.9 to 3.0 months (Fine 1993). Survival of more than one year was rare. The prognosis for HIV-negative patients has improved in the last years due to the introduction of methotrexate-based (MTX) chemotherapies (Carraba 2010). Whether these results will be applicable in HIV+ patients is not clear. In addition, the incidence of PCNSL is now diminishing to such an extent that convincing data on therapy efficacy can hardly be expected in the near future. A clear recommendation for treatment can not be made at this time.

Some clinicians still favor cranial radiation therapy alone in HIV-infected patients (fractionated, 40 Gy total dose). In our experience, before radiation a treatment attempt with intravenous MTX is justified (3 g/m² every 14 days with leucovorin rescue) – also in order to avoid possible neurological damage from radiation. A small study in HIV patients has shown that this approach is practical (Jacomet 1997). However, the decisive factor in all cases – independent of the specific therapy chosen – is the best possible immune reconstitution. With ART, survival of several years has become realistic. Complete remissions have even been described after treatment with ART alone (McGowan 1998, Aboufila 2007, Travi 2012). In our own cohort of 29 patients with histologically diagnosed PCNSL, all four patients who experienced an increase in CD4 T cells survived longer than 18 months. Three out of four patients reached complete remission. One patient has now lived for over eight years without evidence of relapse (Hoffmann 2001). In a multivariate analysis, combination ART was shown to be the only factor associated with a prolonged survival in addition to cranial radiation therapy. Two of these patients, however, died after about three years of a progressive neurological syndrome, which was probably a long-term sequela of radiation therapy in both cases. In view of the better prognosis for patients today, radiation toxicity should be considered more than in the past. Three further studies from France, the US and Australia have since shown a survival of several years thanks to ART (Rigolet 2001, Skiest 2003, Newell 2004).

All patients with PCNSL should therefore be treated intensively with antiretroviral therapy, to achieve the best possible immune reconstitution. If only a moderate immune reconstitution is possible, additional immunomodulatory or antiviral therapies should be evaluated. The partially very positive reports about ganciclovir, foscarnet and interleukin-2 (Raez 1999, Aboulafia 2002, Marretta 2011) or hydroxyurea (Slobod 2000) should, however, be interpreted with caution. “Between the lines” of these publications, in which either individual or hardly more than 2–4 patients were described, combination ART was almost always a factor.

In all cases with signs of raised intracranial pressure, rapid administration of steroids (e.g., dexamethasone 8 mg TID, decreasing the dose rapidly after resolution of edema) is indicated, even if diagnostic testing is more difficult as a result.

References
Hodgkin’s disease (HD)

The incidence of HD is elevated in HIV-infected patients by a factor of 5–15 compared to the HIV-negative population. For particular subtypes, such as lymphocyte-depleted and mixed-cellularity HD, the relative risk is presumably much higher (Frisch 2001). Despite this and the growing realization that these subtypes at least are clearly associated with immunodeficiency, HIV-related HD is not included as an AIDS-defining illness. There is growing evidence that the incidence of HIV-related HD is increasing in the setting of improved immunity. Several studies reported on an increased incidence during the last years (Clifford 2005, Biggar 2006, Engels 2008, Bohlius 2011). In our own cohort we found significant differences between NHL and HD (Wyen 2008). Whereas the majority of NHL cases was diagnosed in ART-naïve patients, HD mainly occurred in subjects receiving a virologically effective ART. In 54% of the patients with HIV-related HD, plasma viremia was below the limit of detection at the time of HD diagnosis (NHL: 21%, p <0.001). The reason for this phenomenon is still under debate. As CD4 T cells usually predominate in the tumor microenvironment of HD, it is speculated that immune reconstitution induced by ART provides an appropriate micro-environment allowing adequate growth signals for proliferation and survival of the neoplastic Reed-Sternberg (RS) cells in HD (Gloghini 2007). In addition, CD40/CD40L interactions and EBV infection may contribute to constitutive activation of NFkB which is an antiapoptotic factor in RS cells. Interestingly, patients whose CD4 T cell counts decline despite suppression of HIV-1 replication, are at risk for HD (Bohlius 2011).

An advanced stage of disease at diagnosis is typical, as is frequent extranodal involvement and a trend towards prognostically poorer subtypes (Tirelli 1995, Rapezzi 2001, Thompson 2004). Mediastinal disease is significantly less frequent than in HIV-neg-
ative patients. A further difference to HD in seronegative patients is the predominance of cases with RS cells, as well as the clear association with EBV infection, which is 80–100%, depending on the study. EBV infection is therefore seen as an important etiologic factor for development of HIV-related HD.

In comparison to HIV-negative HD, which is a highly treatable tumor, the prognosis of HIV-related HD was poor in the pre-HAART era. In nearly all cohorts with more than 20 patients, the median survival was only between 15–20 months, respectively (Andrieu 1993, Tirelli 1995, Errante 1999, Levine 2000). The response to chemotherapy was also moderate compared to the normal population. Complete remission rates were between 40 and 80%, and hematological and infectious complications were frequent. This gloomy scenario has clearly changed since the introduction of combination ART. In our own multicenter cohort of 56 patients, the median survival was 40 months. In patients with adequate ART, the two-year survival rate was 84%, which was very encouraging (Hoffmann 2004). In the meantime, other groups have also reported better prognoses with ART (Ribera 2002, Gérard 2003, Berenguer 2008).

**Signs and symptoms**

B symptoms occur in the majority of cases. Extranodal and advanced stages are almost always the rule. Lymphomas are firm, immobile or hardly mobile and painless, and the distinction from HIV-related lymphadenopathy or tuberculous lymphadenitis is not always possible.

**Diagnosis**

Staging is necessary as for non-Hodgkin lymphomas (see NHL above). Diagnostic lymph node extirpation is even more important here than with NHL, as puncture only rarely allows diagnosis of Hodgkin’s disease. Single accurate diagnostics are better than half-heartedly bothering the patient with repeated punctures and losing time unnecessarily. Surgical extirpation is possible as an outpatient in many centers. As with NHL, specimens should be sent to reference laboratories if possible. Since bleomycin will be administered, a lung function test should always precede the first chemotherapy.

**Treatment**

Risk-adapted treatment strategy in patients with HIV-related HD in accordance with standard treatment procedures established for HIV-negative patients with HD is recommended. The achievement of complete remission (CR) is important. In one larger cohort, the only variable independently associated with overall survival was the achievement of CR (Berenguer 2008).

In limited (Ann Arbor I-II, no risk factors) and intermediate (I-II with risk factors) stages, many clinicians still favor the classical ABVD regimen (four double cycles, see Table 4) for HIV-infected patients. ABVD is the abbreviation for the combination chemotherapy with the cytostatics adriamycin, bleomycin, vinblastine and DTIC (dacarbazine). Ambulatory treatment is possible.

In HIV-negative patients in advanced stages (as is almost always the case for HIV-related HD) the BEACOPP regimen of the German Hodgkin Study Group has been used recently, mainly with escalated dosing. This has proven to be significantly more effective, both with regard to response rates and long-term survival. However, the BEACOPP regimen is more toxic. Whether these positive results can be seen in HIV-
related HD is still not clear. However, based on initial reports and our own experience, BEACOPP seems to be possible (Hartmann 2003, Hentrich 2012). There is also growing experience to date with the Stanford V protocol, for which there have recently been promising reports (Spina 2002).

Table 4: ABVD regimen (4 double cycles, repeat on day 29)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin (doxorubicin)</td>
<td>Doxo-Cell®, Adriblastin®</td>
<td>25 mg/m²</td>
<td>IV</td>
<td>days 1 + 15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Bleomycin Hexal®, Bleo-Cell®</td>
<td>10 mg/m²</td>
<td>IV</td>
<td>days 1 + 15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Velbe®, Vinblastin Hexal®</td>
<td>6 mg/m²</td>
<td>IV</td>
<td>days 1 + 15</td>
</tr>
<tr>
<td>Dacarbazine (DTIC)</td>
<td>Detimedac®</td>
<td>375 mg/m²</td>
<td>IV</td>
<td>days 1 + 15</td>
</tr>
</tbody>
</table>

*ABVD regimen. Due to strong emetogenicity of dacarbazine, 5HT3-receptor blocker anti-emetics should always be administered, e.g., granisetron, tropisetron or ondansetron.

References


Multicentric Castleman’s disease (MCD)

Although rare, multicentric Castleman’s disease is a highly problematic illness for patients – not only due to the poor prognosis in HIV infection, but also because many clinicians and pathologists are not very familiar with this entity. The usually severely ill patients are often subjected to diverse diagnostic and therapeutic procedures.

In comparison to the benign, localized hyperplasia of lymphatic tissue, first described by Castleman in 1956, HHV-8-associated multicentric Castleman’s disease, as it occurs in HIV infection, is a malignant lymphoproliferative disease (Oksenhendler 1996, Talat 2011). Although HIV-related MCD is not classified as a lymphoma or AIDS-defining illness, prognosis is poor. In a prospective study, the median survival was 14 months (Oksenhendler 1996). According to a review on 84 cases with HIV-related MCD, life expectancy of the patients seems to have significantly improved in the era of combination ART with a mortality rate of only 29% compared to 75% in the pre-HAART era (Mylona 2008). During recent years, prognosis further improved, mainly due to the increased use of the monoclonal antibody rituximab (Bower 2011, Hoffmann 2011, Gérard 2012).

Pathogenesis

The pathogenesis of the disease is not completely understood. There is a close association to HHV-8, and as a result about half of the patients also have KS. Lymph nodes involved in HIV-related MCD are often involved coincidentally with KS (Naresh 2008). HHV-8 viremia in patients with MCD is often higher than in patients with KS (Sayer 2011). HHV-8 encodes a homologue of IL-6 (viral IL-6) that has been shown to be biologically active in several assays and whose activities mirror those of its mammalian counterparts. In particular IL-6 and IL-10 are elevated with close association to the HHV-8 viral load (Oksenhendler 2000). Viral IL-6 mediates its effects through the gp130 signal transducer, but signaling is not dependent on the structurally related IL-6 receptor subunit of the receptor-signal transducer complex (Moore 1996, Li 2001, Suthaus 2010). It is thus postulated that viral IL-6 has a broader spectrum of potential target cells than human IL-6. This may be reflected by the clinically impressive “cytokine storms” which are observed periodically in patients suffering from HIV-related MCD. HHV8-infected plasmablasts localize to the mantle zones of the lymphoid follicles (El Daly 2010). Of note, there are reports of MCD cases negative for HHV-8 infection (Seo 2009) but also of an IL-6-related systemic inflammatory syndrome in HIV-infected patients with HHV-8 but without MMCD (Uldrick 2010). In these cases, the pathogenesis remains unclear.

It remains also unclear why only a small proportion of patients with active HIV/HHV-8 coinfection develops HIV-related MCD. It should be noted that the extent of immunodeficiency varies significantly in these patients. We and others have seen MCD patients with a normal immune status and low viral load (Powles 2009). Moreover, ART does not appear to protect against HIV-related MCD. In our own cohort of 52 patients, the majority of the patients with HIV-related MCD were already on ART and had a viral load of less than 400 copies/ml at the time of diagnosis (Hoffmann 2011). It is also of note that HIV-related MCD, unlike KS, is not associated with a lack of HHV-8-specific CD8 T cells or limitation of their functional profile (Guihot 2008). There is also evidence that the incidence of HIV-related MCD is increasing. It appears to occur more frequently in older HIV-positive individuals with well-preserved immune function (Powles 2009).

Progression to malignant lymphoma (often HHV-8-associated entities such as PEL
Signs and symptoms

The main signs are the often significant lymph node enlargements, which are almost always combined with considerable B symptoms including fever, night sweats and weight loss. Almost all patients complain of weakness and severe malaise. There is always massive splenomegaly. Hepatomegaly (70%), respiratory symptoms (65%) and edema with hypoalbuminemia (55%) are also seen in the majority of cases. Lymph nodes, which may be anything from very soft (as with tuberculosis) to rock hard (as with lymphoma) on palpation, can normalize or relapse within weeks without any intervention.

The extent of symptoms is very variable and may fluctuate considerably. Many patients report on “Castleman episodes”, lasting from a few days to one or two weeks. Between these episodes, most patients do again relatively well for weeks or even months. In most patients who leave HIV-related MC untreated, the frequency of the episodic flares increases over time.

Diagnosis

The diagnosis is made histologically after lymph node extirpation – providing that the pathologist knows what HIV-related MCD looks like. The germinal centers of affected lymph nodes have an onion-skin appearance with vascular proliferation. Hyaline-vascular and plasma cell types of Castleman’s disease can be distinguished. Clinicians should explicitly indicate their suspicion. It is possible that a significant proportion of cases are never correctly diagnosed. In every case of episodic flares of B-symptoms, splenomegaly, lymphadenopathy and elevated CRP, the diagnosis of HIV-related MCD must be considered. HIV alone rarely causes such severe illness! In the case of the symptoms described above, the pathological diagnosis of HIV-associated lymphadenopathy should not be accepted too easily.

Ultrasound reveals hepatosplenomegaly. Laboratory tests show hypoalbuminemia and hypergammaglobulinemia. There is often significant anemia which may be hemolytic, often reflecting pancytopenia or hemophagocytic syndrome (Stebbing 2009).

In our experience, CRP is a useful parameter for monitoring the activity of HIV-related MCD and observing the effectiveness of MCD treatment. During an episodic flare, CRP levels of more than 100 mg/l can be seen. Between the episodes, however, CRP is often within normal ranges. In some patients, clinical symptoms are preceded by elevated CRP levels. Treatment success is reflected by sustained decrease of CRP. Determining the HHV-8 DNA level may also be useful in diagnosis and for follow-up (Marcelin 2007, Sayer 2011, Stebbing 2011).

Treatment

At present, there is no widely accepted recommendation for a specific treatment for MCD. However, something has to be done quickly as the course of disease can be extremely fulminant. According to newer data, we believe that the use of rituximab is the treatment of choice in HIV-infected patients with MCD (see below). Some
experts advocate rituximab monotherapy for good performance in patients without organ involvement and rituximab with chemotherapy for more aggressive disease (Bower 2010). ART should always be given, although it does not always help (Dupin 1997, Lanzafame 2000, Aaron 2002, de Jong 2003, Sprinz 2004). Some cases have even been described to occur after starting ART, leading to the suspicion that the inflammatory component of MCD may be increased by immune reconstitution (Zietz 1999).

Apart from ART, there are numerous, very diverse forms of therapy. However, no option has been tested in randomized, controlled trials. Another problem lies within the countless case reports, where a probable positive “publication bias” has to be taken into account.

**Rituximab:** this monoclonal antibody against CD20-expressing cells is also used in B cell lymphomas (see above). It has been speculated that rituximab is effective in HIV-related MCD by eliminating or reducing the pool of HHV-8 infected B cells which are localized mainly in the mantle zone of lymph nodes. Rituximab has been tried with success in several patients with HIV-related MCD (Corbellino 2001, Marcelin 2003, Casquero 2006). More recently, at least two larger studies showed encouraging results. In a French study, 16/24 patients with HIV-related MCD reached a complete remission of clinical symptoms after four cycles of rituximab (Gérard 2006). The overall survival (OS) after one year was 92% and the disease-free survival (DFS) was 74%. In a British study, 20/21 patients achieved a clinical remission with rituximab, and 14/21 patients showed a radiological response (Bower 2007). After two years, OS and DFS were 95% and 79%, respectively. CRP, immunoglobulins, cytokines such as IL-5, IL-6 or IL-10 and HHV-8 viremia decreased after treatment (Bower 2009). In our cohort, rituximab markedly improved prognosis in HIV-infected patients with MCD, compared to patients receiving chemotherapy only (Hoffmann 2011). There is also evidence that rituximab decreases the risk of lymphoma (Bower 2011, Gérard 2012).

Rituximab is usually given at a dose of 375 mg/m² body surface, once weekly over four weeks. Attention should be paid to good hydration. Rituximab is usually well tolerated. The main adverse event seems to be a reactivation of KS, which is seen in up to a third of the cases (Bower 2007). Rituximab is also effective as retreatment for rituximab-pretreated HIV-related MCD (Powles 2007). Based on the data published to date and on our own experience, we would consider rituximab to be the first option in patients with HIV-related MCD. However, there also some case reports in which rituximab was not successful (Neuville 2005, Buchler 2008). For these cases, other therapeutical approaches are briefly discussed here.

**Valgancyclovir:** promising, as this antiviral agent may act against HHV-8. As shown by a randomized trial, valgancyclovir significantly reduces the frequency and quantity of HHV-8 replication (Casper 2008). More recently, preliminary data suggest that valgancyclovir (combined with high-dose AZT) is active in HIV-related MCD. Of 14 patients, 12 had “clinical improvement”, showing a decline of inflammatory markers such as CRP, IL-6 and HHV-8 viremia (Uldrick 2011). However, in our own cohort we were unable to confirm these findings (Hoffmann 2011). According to some experts, valgancyclovir may have a role as maintenance therapy in the future (Bower 2010). In contrast, antiviral therapy with foscarnet or cidofovir had no benefit (Coty 2003, Senanayake 2003, Berezne 2004).

**Chemotherapy:** well-tolerated chemotherapies such as vincristine (2 mg IV as a bolus at 14-day intervals) or oral etoposide (50 mg daily) have proven effective according to several reports as well as our own experience (Scott 2001, Koth 2006). CHOP standard chemotherapy can help, but does not seem to significantly prolong survival.
Splenectomy: may be appropriate in severe cases. It is speculated that IL-6 production is reduced and that a large reservoir of HHV-8 is removed through the splenectomy. In a series of 40 patients, the median survival following splenectomy was 28 versus 12 months (Oksenhendler 2002). According to a US study, the symptoms were improved in 10/10 patients following splenectomy (Coty 2003).

Anti-IL-6 receptor antibodies: In HIV-negative patients, very optimistic data from Japan have been published, in which patients were successfully treated with anti-IL-6 receptor antibodies such as tocilizumab (Nishimoto 2005, Matsuyama 2007). In Europe, tocilizumab was approved in 2009 for treatment of rheumatoid arthritis. However, there are no data in patients with HIV-related MCD. Data is also lacking for siltuximab, a new IL-6 antibody.

Thalidomide: This drug is believed to inhibit cytokine dysregulation as well as the inflammatory component of MCD. Case reports in HIV-related MCD exist (Lee 2003, Jung 2004). It should be noted that thalidomide has been associated with venous thrombo-embolic events, including deep venous thrombosis and pulmonary emboli. Anticoagulation during thalidomide administration is mandatory. We have seen two patients developing pulmonary emboli despite anticoagulation. Therefore we would not recommend the use of thalidomide in HIV-related MCD.

Other immune therapies: For interferon, there are positive as well as negative examples (Coty 2003, Nord 2003). Steroids have no effect on MCD.

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HIV-infected patients have an increased risk of cancer. This applies not only to the three AIDS-defining malignancies (ADMs), namely Kaposi’s sarcoma, non-Hodgkin lymphoma and cervix carcinoma, but also to different non-AIDS-defining malignancies (non-ADMs). The risk for non-ADMs is approximately two to three times higher in HIV-infected patients than in the non-infected population (Frisch 2001, Franceschi 2010).

Incidence of some diseases such as Hodgkin’s Disease (see Malignant lymphomas) and anal carcinoma in HIV-infected patients are so high that there is, according to many experts, a demand to classify them as ADM. In contrast, breast cancer incidence is either same or less in HIV-infected patients compared to the general population (Latif 2011).

One-third of all malignancies in HIV-infected patients today are non-ADMs. They are, therefore, as frequent as malignant lymphomas and Kaposi’s sarcoma (Engels 2006). The tendency is rising slightly (Simard 2011). As a result, non-ADMs are a significant mortality factor within the HIV-infected population. In industrial countries, more deaths are attributed to non-ADMs than to ADMs, hepatitis C or cardiovascular diseases (Lewden 2007, DAD 2010). In a French National Survey in 2010, deaths among HIV patients caused by non-ADMs were almost as frequent as AIDS-related deaths (Morlat 2012). The following diagram shows the percentage of malignant diseases relative to total causes of death in HIV-infected patients in France in 2000 and 2005 (Bonnet 2009).

Figure 1 clearly shows that the percentage of AIDS-defining tumors, NHL and KS, are slightly on the decline, whereas the proportion of non-ADM are rising slightly. Different reasons may explain this. In the D:A:D study, the main risks of non-ADMs resulting in death were advanced age and acute smoking, and interestingly also CD4
T cell counts. Risk of non-ADMs increased, the lower the CD4 T cell counts were. Patients with CD4 T cells <50/µl had a 15-fold higher risk than patients with >500 CD4 T cells/µl (Monforte 2008). The high risk persists if CD4 nadir was low (Worm 2012). This correlation between non-ADM and severe immune deficiency is from the EuroSIDA study (Reekie 2010). In a US databank analysis which included 300,000 AIDS patients (Frisch 2001), some malignomas cases were associated with immunodeficiency: Hodgkin’s lymphoma, lung cancer, penile carcinoma, soft tissue sarcomas, testical and lip cancer.

Apart from immunodeficiency, other factors certainly play a role, such as life-style (mainly smoking, but also alcohol, UV exposure) or coinfections (HPV, HBV, HCV). Given the fact that HIV-infected patients are aging, an increase of incidences of malignancies is to be expected (Shiels 2011). ART seems to have little influence on the occurrence of non-ADMs since therapy interruption does not increase the risk for non-ADMs, in contrast to ADMs (Silverberg 2007).

**Early diagnosis and prevention**

It remains unclear whether HIV-infected patients require cancer screening and preventive medical checkups more frequently than HIV-negative patients. There are some indications for a benefit regarding anal carcinomas (see below). Regarding colon carcinoma the situation is not clear; however, there is evidence that neoplastic changes are found more frequently in colorectal cancer screening with HIV-infected patients (Bini 2009, Boesecke 2012). This examination, however, is not so popular with HIV-infected patients or with treating physicians. Compared to the HIV-negative population, colorectal cancer screening is utilized to a lesser degree than with HIV-infected patients (Reinhold 2005). With respect to PSA screening, which is discussed controversially in general, there is no specific recommendation for HIV-infected patients. Gynaecological examinations are discussed in the chapter HIV and Gynaecology. In patients coinfected with HCV, bi-annual ultrasound sonographies can have a benefit, as a recent study with 70 patients showed: hepatocellular carcinomas were less progressed at diagnosis in regularly screened patients resulting in a slightly better survival (Nunez 2010).

Finally, physicians should inform patients about the advantages of not smoking and support smoking cessation. Smoking contributes to substantial morbidity and mortality in the HIV-infected population (Lifson 2010). Patients often request and even insist upon more medical checkups, but it is repeatedly forgotten that abstinence from smoking is still the most important preventive measure for malignant diseases. Avoidance of obesity and a healthy lifestyle are more helpful than expensive medical examinations.

**Treatment**

One problem in the therapy of non-ADMs is that too little is known about chemotherapeutic substances and their interactions with ART. Especially since the new targeted substances have mostly not been investigated in HIV-infected patients. There are no prospective studies and very little data on imatinib, erlotinib, sunitinib, bortezomib, sorafenib or temsirolimus (Review: Rudek 2011). Few case reports exist for many malignant diseases. In most cases patients are younger compared to the HIV-negative population which may be due to better monitoring (Shiels 2010). Publications over the last years on different entities such as glioblastoma (Hall 2009) or colon carcinoma (Chapman 2009, Alfa-Wali 2011), bladder cancer (Gaughan 2009), prostate cancer (Pantanowitz 2008) or esophageal cancer (Stebbing 2010) show that HIV-
infected patients prosper from the recent and amazing progress made in the onco-
logical field. There should be no difference in treatment of HIV-infected and non-
infected patients – however, oncologists often need to be properly informed in order
to avoid adhering to an outdated and pessimistic concept of HIV treatment.

**Anal carcinoma**

Infections with human papilloma virus (HPV) are among the most frequently sexu-
ally transmitted virus infections. HPV belongs to the family of papovaviridae and
infect the basal cells of the epithelium of skin and mucous membranes. HIV+ patients
have a 2- to 6-fold higher risk for anal HPV infection, independent of sex and sexual
practices (Palefsky 1998, Piketty 2003). Risk of persistent HPV infection is 7-fold and
inversely correlated with CD4 T cell counts (Piketty 2003). By now almost 100 dif-
ferent HPV types are known, among them 20 that are associated with anal or cervix
carcinomas. HPV-16 and -18 have an especially high oncogenic potential and carry
an increased risk for anal carcinoma. HIV-infected patients commonly have coin-
fecions with several HPV subtypes. In a German study (Kreuter 2005), anal HPV
infection was found in 86% of 103 male patients, among them especially HPV-16
(53%) and HPV-18 (27%), but also HPV-58 (22%) and HPV-83 (22%).

Persistent HPV infection may lead to precancerous preliminary stages, the anal
intraepithelial neoplasia (AIN). AIN is histologically graded depending on the degree
doysplasia in grade 1 (mild), grade 2 (moderate) or grade 3 (severe). In severe cases
of AIN the whole epidermis is affected and the risk of anal carcinoma is high (Berry
2009). Although there is a connection to the degree of immune deficiency (Melbye
1995), the influence of ART is not clear. In some studies prevalence of AIN remained
high, albeit with ART (Fox 2003, Gonzalez-Ruiz 2994, Palefsky 2005), another study
observed a protective effect (Wilkin 2004). In our own cohort of 121 patients with
anal carcinoma, the vast majority of patients were on ART, with a well suppressed
viremia and a median CD4 T cell count of 400/µl (Hoffmann 2011).

There is no doubt that anal cancer rates are substantially higher for HIV-infected
patients. In a large study, the adjusted rate ratios were 80 for HIV-infected MSM and
27 for other HIV-infected men compared with HIV-uninfected men (Silverberg 2012).
The risk is also elevated in HIV-infected women in whom high grade AINs are fre-
quently found (Hou 2012). Incidence of anal carcinoma increased after the early
antiretroviral therapy era and then plateaued (Bower 2005, Diamond 2005, Piketty
2008, Silverberg 2012). The routinely repeated thesis of a worldwide dramatic increase
of incidence over the last years has not been clearly verified.

The most common symptom in cases of anal carcinoma is rectal bleeding. A patient
reporting blood in stool absolutely must visit a proctologist! Patients usually attrib-
ute the bleeding to hemorrhoids; however, this self-made diagnosis should not be
trusted. Other symptoms are burning and pain during stool or pruritus. If an anal
carcinoma has already developed squamous cell carcinoma and more seldom tran-
sitory epithelial carcinoma are histologically present. Anal canal and sphincter can
already be infiltrated at an early stage. Regional lymph nodes are affected depend-
ing upon where the anal carcinoma is localized. Deep-seated anal carcinomas infil-
trate inguinal, central pelvic, high lying mesentery. Distant metastases are rare. In
addition to proctoscopy, if possible, an endosonography, a CT of the abdomen and
the pelvis should be done.

If anal carcinoma manifests and the lesion is smaller than 2 cm, a continence pre-
serving operation is preferable. In these cases, an adjuvant chemo- or radiotherapy
is not necessary. Larger lesions are treated with combined radio-chemotherapy (mit-
omycin 10 mg/m² on days 1 and 29 and 5-FU 1000 mg/m² on days 1–5 and days
29–33, with subsequent radiation therapy of up to 50 Gray in fractions). Other more intensive therapies are possible (Blazy 2005). Complications can occur under such regimens. If something can go wrong, it will: we have experienced a patient who had first developed severe paravasation under mitomycin, followed by myocardial infarction under 5-FU and then a perforating, feculent radiation colitis. Additionally patients should always be treated in oncological departments. Following radiotherapy, a proctoscopy should take place every six months. Although positive effects are not certain (Bowler 2005), HIV-infected patients with anal carcinoma should receive ART. Overall prognosis is not worse than with HIV-negative patients (Chiao 2008, Hoffmann 2011, Alfa-Wali 2012).

Early diagnosis, treatment of pre-stages, vaccines

Early treatment is important, since usually many years can pass between AIN and manifestation of the anal carcinoma. In case of AIN 1, a topical therapy with imiquimod (or podophyllotoxin) is adequate, AIN 2+3 should be removed either surgically (electrocaustic therapy) or via laser ablation. Infrared coagulation is also possible (Stier 2008). In a randomized study on 148 HIV-infected MSM with histologically confirmed AIN, three procedures were compared, including 16 weeks of imiquimod (3 times a week), 5-FU (twice a week), and monthly electrocautery for 4 months. This study showed that regarding both efficacy and side effects electrocautery is superior to imiquimod and 5-FU in treatment of AIN, but recurrence rates were substantial (Richel 2012).

Condyloma should also be dissected by a proctologist (electroagulation, cryotherapy). A topical therapy alone with the immune modulator imiquimod (Aldara® cream) is possible, however the effects are often less powerful than with non-infected patients. Still, imiquimod clearly reduces the risk of a relapse in follow-up treatment. The mechanism of imiquimod is not directly antiviral, instead it almost certainly destroys tumor cells via cytokine induction. The most significant side effect is a local erythema (which means it is working!), more seldom may be burning and pruritis. Severe skin irritations are rare.

Some experts insist that perianal and intra-anal smears be taken yearly. However, it seems to be too early to recommend preventive medical checkup to all HIV-infected patients (Palefsky 2009).

HPV vaccines have proven to be protective for intraepithelial neoplasia and persistent HPV infections in cases of cervix carcinoma (Harper 2006). In 2011, a large study confirmed that use of the qHPV vaccine also reduces the rates of anal intraepithelial neoplasia, including grade 2 or 3, among men who have sex with men (Palefsky 2011). The vaccine had a favorable safety profile and may help to reduce the risk of anal cancer. There is also some evidence for a therapeutic effect of the vaccine in HPV-infected patients (Anderson 2009, Wilkin 2010).

Testicular tumors

Testicular tumors are the most frequently occurring cancer in men between 20 and 35. The relative risk factor for HIV-infected patients compared to normal population in the same age group is 2.5-fold (Frisch 2001, Powles 2003). This especially applies to seminoma, yet not so much to non-seminoma (Goedert 2007). So far, the largest analysis report of 34 and 35 patients respectively (Powles 2003, Fizazi 2001). The median CD4 T cell counts were between 300 and 350/µl at time of diagnosis, although with great variation. Overall prognosis was good and a matched-pair analysis did not prove worse with HIV-infected patients (Powles 2004). Other studies confirm the
positive course (Fizazi 2001). HIV-infected patients should be treated with the standard regimens that are also recommended for negative patients. Depending on histology and stage of cancer, the regimen consists of orchiectomy, lymph node extirpation or radiation, and or a platinum-based chemotherapy. High dose therapies are also possible (Hentrich 2009). Treatment should be performed in cooperation with a urologist experienced in oncology and an HIV specialist.

Lung cancer

In the general population, lung cancer is the most frequent cancer disease that leads to death in male patients. This tendency is increasing in women and already ranks third. The risk seems to be rising with HIV-infected patients. More recent studies from France show that lung carcinoma accounts for 5% of all causes of death and leads more frequently to death than Kaposi’s sarcoma (Bonnet 2009). In a British cohort, the relative risk in the early years of the HIV epidemic was similar to that of the normal population and has now risen by a factor of 8 (Bower 2003). In other cohorts, relative risk remained constant between 3–10 (Engels 2006, Cadranel 2006, Dal Maso 2009). Overall risk seems to rise as immunodeficiency increases (Guiguet 2009, Reekie 2011). In our own retrospective study of 72 patients developing lung cancer during the last decade, most cases occurred in the setting of limited immune deficiency and a long-lasting sufficient viral suppression (Hoffmann 2011). This increase can partly be explained by simple reasons: first, HIV+ patients live longer and have more time to develop lung cancer and second, HIV-infected patients smoke more than non-infected patients. In some HIV outpatient clinics, up to 60–70% of the patients are smokers. Smoking remains the main risk factor for developing lung cancer (Hoffmann 2011, Clifford 2012). Thus, one should discuss the issue of smoking: “It’s time to quit” – there are possibilities to cease smoking (Niaura 2000). Apart from age and nicotine abuse, other factors also seem determine an increased risk (Kirk 2007, Chaturvedi 2007). This is underlined by the fact that the most frequent subtype found in HIV patients, adenocarcinoma, is the subtype that is least associated with nicotine consumption (Tirelli 2000, Cadranel 2006). Because often immune deficiency is not present, other factors, such as specific lung infections and a resulting scarring, are assumed, but also increased proinflammatory cytokines in the lungs or reduced glutathione levels are found frequently in HIV-infected individuals. These factors can worsen the damage caused by smoking. Generally, HIV-infected patients seem to be more sensitive towards carcinogenesis (Engels 2006, Kirk 2007, Chaturvedi 2007). In the US veterans cohort, an increased risk for HIV-infected patients remained significant, even after adjusting for smoking, age, ethnicity and COPD (Sigel 2010). There is also some evidence for a genetic predisposition (Engsig 2011).

From a diagnostic-therapeutic view, patients always stand a better chance when the lung cancer has been diagnosed early. Symptoms are unspecific and when they present, it is often too late. In the case of HIV-infected patients, diagnosis is seldom early enough (Brock 2006). In our own cohort of 72 cases of lung cancer diagnosed 2000–2010, only 34% of the patients were in stages I-IIIA which are considered to be curable (Hoffmann 2011). Patients in early tumor stages should undergo surgery with curative intention since chemotherapy only suspends further progression for a few months. In most cohorts, survival is 4–8 months in the median (Tirelli 2000, Spano 2004, Powles 2003, Cadranel 2006, Lavolé 2006+2009). In our own cohort, median estimated overall survival (OS) was 1.12 years with a total 2-year OS of 23.7%. Clinical stage was highly predictive and long-term OS could only be achieved in very limited disease stages (Hoffmann 2011).
If chemotherapy is indicated, HIV-infected patients with non-small cell lung carcinoma (NSCLC) in otherwise good condition should receive standard therapy beginning with cis- or carboplatin plus either taxane (paclitaxel), gemcitabine or navelbine. These combinations have similar response in HIV-infected patients. Studies with HIV-infected patients are almost non-existent. Carboplatin/gemcitabine seem to be tolerated well (Bridges 2008). A second choice is pemetrexed or erlotinib, an inhibitor of EGFR-tyrosine kinase. HIV doctors should talk with and convince the oncologist not to expect the worst just because HIV-infection is involved and that HIV is not a contraindication for any drug. At times when even stem cell transplantations (with AIDS-NHL) do not comprise a principle problem, treatment should be orientated to the recommendations for HIV-negative patients. If general condition is poor, a well-tolerated combination of gemcitabine and navelbine can be given, which has been known to stop progression for a short time.

References


PART 4

Women and Children
HIV-positive women have a higher risk of cervical dysplasia and cervical cancer, genital ulcers, vaginal infections and genital condyloma than HIV-negative women. A gynecological examination including a Papanicolaou (Pap) smear and screening for sexually transmitted infections are therefore part of the routine evaluation of female HIV+ patients at the time of first diagnosis as well as during the further course of the disease.

**Prophylaxis**

Guidelines on Pap smear and breast cancer screening for the general population vary from country to country. In general, Pap smear screening starts at age 20 or 25 and continues until about age 50 or 60. Breast cancer screening starts in Germany at age 35. Regular gynecological checkups, including Pap smears, are especially important for HIV-positive women because of their higher risk of cervical dysplasia. In contrast, the risk of breast cancer in HIV-positive women is not elevated, it seems to be even lower than in HIV-negative women (Goedert 2006).

Physicians working with HIV-positive women should stress the importance of gynecological evaluations. It cannot be taken for granted that all women will visit the gynecologist regularly even when it is covered by health insurance. In Germany for example only 50% of women take advantage of regular Pap smear and breast cancer screening. Therefore it is crucial to talk about the necessity and the reasons for prophylactic gynecological screening.

The frequency of screening HIV-positive women depends on the clinical scenario. If the initial Pap smear after HIV diagnosis is normal, then a second screening should be done approximately 6 months later. If both results are normal, then an annual Pap smear is sufficient. Consider more frequent screening in women with a higher risk of cervical dysplasia, e.g., with abnormal Pap smear results, HPV infection, symptomatic HIV infection, CD4 T cell count <200/µl or after treatment for cervical dysplasia.

<table>
<thead>
<tr>
<th>Screening frequency</th>
<th>Clinical scenario</th>
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<tr>
<td>Every year</td>
<td>Routine control</td>
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<tr>
<td>6 months</td>
<td>First year of HIV diagnosis, then every year</td>
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<tr>
<td>&lt;6 months</td>
<td>Abnormal Pap smear</td>
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<td>HPV infection</td>
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<td>After therapy for cervical dysplasia</td>
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<td>Symptomatic HIV infection</td>
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<td>CD4 T cells &lt;200/µl</td>
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**Basic gynecological evaluation**

A full gynecological examination consists of inspection of the external genital and perianal region, bimanual examination of the inner genital area, rectal examination, colposcopy, microscopic examination of vaginal secretions and a Pap smear. In HIV-positive women palpation of inguinal and axillary lymph nodes is important, since enlarged lymph nodes are often present and may need a rapid mammographic/ultrasound evaluation. At age 35 a basic mammogram should be performed.
Menstrual cycle/menopause

Data about the influence of HIV on the menstrual cycle are conflicting. Older studies demonstrate a cycle prolongation (Shah 1994), whereas the WIHS study shows at the most a slight increase of very short cycles (Harlow 2000). It is also unknown whether or not HIV accelerates the beginning of menopause. There is only limited data on small populations (Clark 2000, Greenblatt 2000). In contrast, it is clear that post-menopause as well as HIV infection and antiretroviral treatment have adverse effects on bone, lipid and glucose metabolism and may contribute to osteoporosis and cardiovascular disease.

Contraception

When choosing a contraceptive method be aware of the expectations of the woman. Condoms are the most common form of contraception (and they protect sexual partners from HIV). Nevertheless their contraceptive effectiveness is comparatively limited. Condoms have a Pearl Index (number of pregnancies per 100 patient years) of 1–12. Contraceptive pills however have a Pearl Index of 0.1–0.9.

Other contraceptive methods are contraceptive pills containing varying hormone combinations and dosages, depot and transdermal formulations as well as intrauterine devices (IUD). Hormon-containing contraception has no influence on the course of HIV-infection, but this method may increase the risk of transmitting or acquiring HIV (Stringer 2009, Heffron 2012). Oral contraceptives interact with PIs and NNRTIs with almost unpredictable consequences. There are limited reliable studies of such interactions, and these interactions are agent-specific (El-Ibiary 2008). The same is true of new parenteral oral contraceptives like the hormone-containing vaginal ring (NuvaRing®), the etonogestrel implant (Implanon®), transdermal hormone patches and emergency contraception and abortion pills. Oral contraceptives are not a reliable contraceptive method for HIV-positive females taking a PI or NNRTI (Heikinheimo 2008). It is essential to inform patients about this situation when starting antiretroviral therapy. Exceptions are unboosted atazanavir and indinavir, etravirine, maraviroc and raltegravir in combinations without ritonavir.

Intrauterine devices made of copper as well as the levonogestrel-containing device (Mirena®), which increases cervical mucus viscosity, have proved to be safe and effective in HIV-positive women (Stringer 2007, Heikinheimo 2006). In an ACTG study depot formulations containing 150 mg medroxyprogesterone acetate (e.g., Depo Provera®) proved equally safe and reliable with patients on efavirenz, nevirapine or nelfinavir (Watts 2008).

Infections

In the pre-HAART era genital infections, especially genital herpes, vulvovaginal candidiasis and bacterial vaginosis, were more common in HIV-positive than in HIV-negative women. The prevalence and severity of these infections correlate with the CD4 T cell count and HIV viral load. Today only vaginal candidiasis seems to be more common, which may be a consequence of a higher rate of antibiotic treatment of HIV patients (Watts 2006). Sexually transmitted infections (STI) are more common as well, though this depends on the sexual activity of the patient.

Bacterial Vaginosis

Bacterial vaginosis (BV) results from replacement of the normal lactobacillus-dominant vaginal flora by mixed flora, including anaerobic bacteria. This increases HIV expression in the genital tract and may promote HIV transmission (Olinger 1999,
Persistence and severity of bacterial vaginosis increases with the progression of immune deficiency and antiretroviral treatment lowers the risk of vaginosis (Warren 2001). Most prevalent symptoms of bacterial vaginosis are a thin discharge and a “fishy” odour. In clinical practice BV is diagnosed when three of the following four criteria are present:

- thin, homogeneous discharge
- pH of vaginal fluid >4.5
- Fishy odour on adding Alkali-10% potassium hydroxide solution
- Clue cells on microscopy.

Treatments of choice are metronidazole or clindamycin, and a topical application is preferred because of better compliance (DGGG 2008). Clindamycin is contraindicated in pregnant women. Oil-containing clindamycin vaginal cream may erode latex condoms.

Table 2: Therapy of bacterial vaginosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy of choice</td>
<td></td>
</tr>
<tr>
<td>Metronidazole orally</td>
<td>500 mg 2 x daily for 7 days</td>
</tr>
<tr>
<td>Metronidazole gel 0.75%</td>
<td>5 g vaginally 1 x daily for 5 days</td>
</tr>
<tr>
<td>Clindamycin cream* 2%</td>
<td>5 g vaginally 1 x daily for 7 days</td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
</tr>
<tr>
<td>Clindamycin orally</td>
<td>300 mg 2 x daily for 7 days</td>
</tr>
<tr>
<td>Clindamycin vaginal tablets</td>
<td>100 mg 1 x daily for 3 days</td>
</tr>
</tbody>
</table>

*may erode latex condoms, CDC 2010

Genital herpes

In most cases, genital herpes is caused by the human herpes virus type 2 (HSV-2). The virus remains latent in the body after the first infection. Genital herpes increases the risk of HIV infection and HIV transmission (Heng 1994). Antiretroviral treatment lowers the frequency and severity of symptomatic episodes although there may be asymptomatic viral shedding (CDC 2010).

According to more recent studies reactivation of HSV-2 is associated with higher HIV replication (Rebbaprada 2007) while suppression of HSV-2 lowers HIV viral load in genital secretions, in breast milk and has positive impact on HIV-progression (Nagot 2008, Drake 2011, Reynolds 2011). Whether this lowers the risk of HIV transmission is a matter that continues to be investigated. However, the suppressive treatment of HSV-2 does not influence the susceptibility to HIV-infection in HSV-2-infected individuals (Celum 2008, Watson-Jones 2008).

Table 3: Therapy of genital herpes in persons infected with HIV (CDC 2010).

<table>
<thead>
<tr>
<th>Medicament</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infection</td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>400–800 mg orally 2–3 times a day</td>
</tr>
<tr>
<td>Famcyclovir</td>
<td>500 mg orally twice a day</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500 mg twice a day</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>400 mg orally 3 times a day for 5–10 days</td>
</tr>
<tr>
<td>Famcyclovir</td>
<td>500 mg orally twice a day for 5–10 days</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1.0 g orally twice a day for 5–10 days</td>
</tr>
<tr>
<td>Severe infection</td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>5–10 mg/kg IV every 8 hours</td>
</tr>
<tr>
<td>Acyclovir resistance</td>
<td></td>
</tr>
<tr>
<td>Foscarnet</td>
<td>40 mg/kg IV every 8 hours</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Topical Cidofovir gel 1%* over 5 days</td>
</tr>
</tbody>
</table>

* not available commercially, must be made up by pharmacist
HSV-2 infections are more common in HIV-positive women and episodes are more severe and atypical. Typical lesions present as painful vesicles in groups on red skin, which ulcerate and heal without scarring. Primary infection may also be associated with signs of systemic viral infection like fever, headache, etc. Diagnosis by clinical signs alone has low specificity and sensitivity (Sen 2007). Therefore, a clinical diagnosis should be confirmed by virologic and serologic tests, preferably by type-specific assays. Diagnosis should distinguish between syphilis and a ‘chancroid’ condition (Haemophilus ducreyi).

Vulvovaginal Candidiasis

Vulvovaginal candidiasis is more common and more persistent but not more severe in HIV-infected patients (Watts 2006). Low CD4 T cell count promotes the disease, though the more prevalent use of antibiotics in immunodeficient patients may play an important role. Causative organisms are Candida strains in most cases, with Candida albicans being the most prevalent strain, but the incidence of non-albicans strains is rising. 26–27% of C. non-albicans infections are caused by C. glabrata (Schuman 1998). Typical clinical symptoms are pruritus, vulvar burning, vaginal soreness and thick white-yellow discharge. Dyspareunia and external dysuria may also be present.

Diagnosis can generally be made on the basis of physical examination and colposcopy. Thrush patches are usually found loosely adhering to the vulva and/or vagina. Bimanual examination is not painful. Budding yeast or pseudohyphae are documented on a wet mount or KOH preparation or gram stain of vaginal discharge. In case of recurrent disease yeast culture is mandatory. In case of dysuria a urine test is recommended.

The treatment of choice for uncomplicated acute vulvovaginal candidiasis is a short course of an -azole drug for 1–3 days. Alternatives are triazoles orally, e.g., 150 mg single dose or itraconazole 2 x 200 mg. In patients with advanced immunodeficiency topical treatment may be extended to 7 days. Treatment of the partner is only necessary in case of suspected sexual transmission.

Table 4: Therapy of acute uncomplicated vulvovaginal candidiasis (CDC 2006).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butoconazole 2% cream</td>
<td>5 g intravaginally 1 x daily for 3 days</td>
</tr>
<tr>
<td>Butoconazole 2% cream</td>
<td>5 g (Sustained Release) single application</td>
</tr>
<tr>
<td>Clotrimazole 1% cream</td>
<td>5 g intravaginally 1 x daily for 7-14 days</td>
</tr>
<tr>
<td>Clotrimazole 2% cream</td>
<td>5 g intravaginally 1 x daily for 3 days</td>
</tr>
<tr>
<td>Miconazole 2% cream</td>
<td>5 g intravaginally 1 x daily for 7 days</td>
</tr>
<tr>
<td>Miconazole 4 % cream</td>
<td>5 g intravaginally 1 x daily for 3 days</td>
</tr>
<tr>
<td>Miconazole vaginal suppository</td>
<td>100 mg 1 x daily for 7 days</td>
</tr>
<tr>
<td>Miconazole vaginal suppository</td>
<td>200 mg 1 x daily for 3 days</td>
</tr>
<tr>
<td>Nystatin vaginal tablet</td>
<td>1200 mg single application</td>
</tr>
<tr>
<td>Nystatin vaginal tablet</td>
<td>100,000 units 1 x daily for 14 days</td>
</tr>
<tr>
<td>Tioconazole 6.5% ointment</td>
<td>5 g intravaginally single application</td>
</tr>
<tr>
<td>Terconazole 0.4% cream</td>
<td>5 g intravaginally 1 x daily for 7 days</td>
</tr>
<tr>
<td>Terconazole 0.8% cream</td>
<td>5 g intravaginally 1 x daily for 3 days</td>
</tr>
<tr>
<td>Terconazole vaginal tablet</td>
<td>80 mg 1 x daily for 3 days</td>
</tr>
<tr>
<td>Alternative</td>
<td></td>
</tr>
<tr>
<td>Fluconazole orally</td>
<td>150 mg single application</td>
</tr>
</tbody>
</table>

Warning: oil-based intravaginal products may erode latex condoms.
In recurrent vulvovaginal candidiasis prophylactic treatment with fluconazole 1 x 200 mg/week may be considered (Schuman 1997). Development of resistance against fluconazole either in its single application or given prophylactically once a week is rare (Sobel 2001, Vazquez 2001). In contrast, resistance is more common in non-albicans strains. In this case itraconazole and ketoconazole are a good alternative.

**HPV-associated diseases**

Human papillomavirus (HPV) infections are very common. More than 50% of sexually active individuals get infected by one or more of the more than 100 HPV-subtypes. Normally the infection resolves within a few months (Evander 1995, Ho 1998). Chronic HPV infection may lead to condylomata acuminata as well as intraepithelial and invasive cancer in the lower female genital tract. Genital warts are caused mostly by the low-risk subtypes 6 and 11. The high-risk subtypes 16 and 18 play an important role in the development of cervical cancer.

In comparison with their HIV-negative counterparts, HIV-positive women have a higher prevalence and incidence of HPV (Ahdieh 2001, Branca 2003), a higher HPV viral load (Jamieson 2002), a longer persistence of HPV (Sun 1997, Ahdieh 2000) and more frequent infections involving multiple subtypes (Levi 2004) and oncogenic subtypes (Minkoff 1998, Uberti-Foppa 1998, McKenzie 2009). Prevalence and persistence of HPV correlate with HIV viral load and immune status (Palefsky 1999). In women with advanced HIV disease, oncogenic subtypes are more common (Luque 1999) and HPV reactivation is possible (Strickler 2005). HPV viral load correlates with persistence and is higher in patients with low CD4 T cell counts (Ahdieh 2001). Testing for HPV is useful in patients over the age of 30 with a normal Pap smear since it allows detection of persistent high-risk subtypes for higher grade dysplasia (Ronco 2010). Specificity of the Hybrid Capture 2 Assay (HC 2) is generally higher than that of the HPV PCR, while the sensitivity is comparable.

**Condylomata acuminata**

HPV-associated genital warts are more prevalent in HIV-positive women, and the manifestation correlates with immune deficiency (Conley 2002, Silverberg 2002). Diagnosis is possible in most cases by inspection. A biopsy is only necessary if:
- diagnosis is uncertain
- warts do not respond to treatment
- warts progress in spite of therapy
- warts are pigmented, indurated, fixed, or ulcerated.

For treatment of condylomata acuminata, see section on STIs.

**Cervical dysplasia and cervical cancer**

The risk of development of HPV-associated cancer is significantly higher in HIV-infected women. Most common is cervical dysplasia, but other regions like the vulva and the perianal area are also affected (Maiman 1998, Massad 1999). In the pre-ART era 20% of HIV-positive women developed cervical dysplasia within three years (Ellerbrock 2000). Manifestation and severity correlate with advanced immunodeficiency and high viral load (Davis 2001, Massad 2001, Schuman 2003). Reasons for the correlation are the higher prevalence of oncogenic subtypes and the higher HPV viral load (especially HPV-16) in patients with advanced HIV disease (Weissenborn 2003, Fontaine 2005, Harris 2005). HIV-positive women have a nine times higher risk of invasive cervical carcinoma than HIV-negative women (Mbulaiteye 2003).
Cervical cancer is an AIDS-defining illness. The incidence of cervical cancer in WIHS and HERS was 1.2 per 1000 person years (Phelps 2001, Massad 2004). Interestingly there seems to be no correlation with CD4 T cell count. More recent studies demonstrate no decline of cervical cancer as a result of ART treatment (Dorrucci 2001, Moore 2002, Clifford 2005).

**Anal dysplasia**

Multifocal lesions of HPV infection are more common in HIV patients (Abercombe 1995). Therefore the risk of anal dysplasia in addition to cervical dysplasia is higher. The prevalence of dysplastic cells in cytological samples is up to 26% (Rabkin 1992, Holly 2001). Thorough inspection of the anal region plus cytologic/HPV diagnosis in selected cases is recommended.

**Diagnostic evaluation**

Gynecological/cytological screening is indicated every six months in the first year after HIV diagnosis. In patients with no abnormalities, evaluations should be performed annually. A higher frequency of screening is indicated if:

- last Pap smear was abnormal
- HPV infection is present
- cervical dysplasia has been previously treated
- symptomatic HIV infection is present or CD4 T cell count is <200 cells/µl.

**Therapy**

Treatment of cervical dysplasia (cervical intraepithelial neoplasia/CIN) and cervical cancer is the same in HIV-positive and HIV-negative women. However, HIV-positive women have a higher risk of recurrent disease and should be monitored closely (Fruchter 1996, Heard 2005). Surgical treatment of cervical dysplasia aims at complete removal of the transformational zone including all neoplastic lesions.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Management</th>
<th>Surgical Method</th>
<th>Non-invasive/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
<td>Colposcopic-cytological evaluation every 6 months</td>
<td>Loop conisation, laser (in case of persistence)</td>
<td>Up to 24 months watch and wait</td>
</tr>
<tr>
<td>CIN II</td>
<td>Colposcopic-cytological evaluation every 6 months</td>
<td>Loop conisation, laser</td>
<td>Up to 12 months watch and wait</td>
</tr>
<tr>
<td>CIN III</td>
<td>Therapy</td>
<td>Conisation (loop, laser, needle, knife)</td>
<td>Treat always, watch and wait only in pregnancy (conisation increases risk of premature delivery)</td>
</tr>
<tr>
<td>Lesion extends into deep endocervix</td>
<td>Colposcopic-cytological evaluation</td>
<td>Conisation (loop, laser or knife)</td>
<td>Possible in CIN I</td>
</tr>
</tbody>
</table>

Source: Interdisciplinary guidelines by German Cancer Association and German Gynecologic and Obstetric Association, 8/2008

CIN I: If lesion is restricted to ectocervix (documented by colposcopy), repeat evaluation in 6 months. In persistent and ectocervical lesions perform CO₂ – laser vaporisation. In endocervical lesions, broad indication for conisation.
CIN II: Repeat cytological and colposcopic evaluation in 6 months. Lesions persistent for more than 12 months should be treated like CIN III.

CIN III: Surgical removal by loop excision or conisation, ectocervical lesions where applicable by laser vapourisation, endocervical curettage. In case of R1 resection discuss further resection depending on individual situation (e.g., future pregnancy). In CIN I documented by histology, perform regular screening only. This also applies to CIN II and III in pregnancy. With CIN II or III that is persistent more than 12 months in patients not pregnant, surgery is indicated.

HPV vaccination: Public health officials in Australia, Canada, Europe and United States recommend prophylactic vaccination of young women against HPV to prevent cervical cancer and genital warts. Vaccination of HIV-positive or HPV-infected women is not recommended. Studies in these populations are still ongoing.


Moore AL, Sabin CA, Madge S, Mocroft A, Reid W, Johnson MA. Highly active antiretroviral therapy and cervical intraepithelial neoplasia. AIDS 2002, 16: 927-929.


16. HIV and Pregnancy
Therapy for mothers and prophylaxis for neonates

MECHTHILD VOCKS-HAUCK

Perinatal (vertical) HIV infection has become rare since the introduction of anti-retrovirals as transmission prophylaxis and elective cesarean section. While vertical HIV transmission rates hovered around 15% in Europe at the beginning of the nineties, it now reaches less than 2% (Connor 1994, European Collaborative Study 2005, Jasseron 2008, Townsend 2008). Postpartum HIV infections are avoidable provided HIV-infected mothers do not breastfeed without prophylaxis. At the same time as transmission prophylaxis was introduced, the treatment of HIV infection changed. Nowadays, pregnancy is no longer a general contraindication for ART (Agangi 2005, CDC 2011). The following chapter summarizes the German-Austrian guidelines for HIV therapy in pregnancy (DAIG 2011). Reference is made to the US (CDC 2011) and European (EACS 2011) Guidelines. Continuously updated recommendations can be found at www.AIDSinfo.nih.gov or www.europeanaidsclinicalsociety.org/guidelines.asp.

HIV therapy in pregnancy
Starting HIV therapy during pregnancy

It is important to distinguish between women with and without a therapy indication of their own. In the case of a maternal indication, treatment is generally begun in week 13+0 of pregnancy; if there is no maternal indication, i.e., solely transmission prophylaxis and low viral load, as of week 28+0 of pregnancy, and with a higher viral load (of more than 100,000 copies/ml) or high-risk pregnancy as of week 24+0 (DAIG 2011).

According to the US and/or European Guidelines transmission prophylaxis should be started at the beginning of the second trimester. The assessment of indications for therapy and drug selection is similar to that in non-pregnant patients (see chapter on ART 2012). Since the CD4 T count decreases physiologically by approximately 10–20% in pregnant patients, the threshold values should be adjusted upwards accordingly before treatment is started. Following the recommendations of the German-Austrian guidelines, antiretroviral therapy in symptom-free patients should begin when CD4 T cell count falls below 350/µl (15–20% relative). Before initiating therapy, a resistance test, and if necessary, subtyping, should be carried out (see chapter on Resistance).

When setting up a treatment plan, it is important that:

- AZT (Retrovir®) is part of the combination, but despite lack of approval in pregnancy, other nucleosides are also acceptable – if the result of the resistance test and the expected toxicity are favorable; and
- Efavirenz (Sustiva®, Stocrin®) is avoided because of possible teratogenic effects in the first trimester; and
- The combination of ddI+d4T is avoided.

A maximum suppression of viral activity (to <50 copies/ml) makes HIV transmission unlikely. In this case the intrapartum intravenous transmission prophylaxis with AZT could be waived (EACS 2011, see below).
Continuation of ART during pregnancy

Most pregnant HIV-infected women in the North have been pretreated with antiretroviral agents. As a rule, if pregnancy is diagnosed after the first trimester, the existent ART should be continued. Women in whom pregnancy is diagnosed during the first trimester should be informed about the benefits and risks of treatment in this period. In cases of reduced immune status in particular, ART could be continued in the first trimester under careful laboratory and ultrasonic controls. Embryonic toxicity seems to be low overall (Joao 2010, Antiretroviral Pregnancy Registry 2011, Watts 2011). However, agents with a toxic effect on the embryo should not be administered during early pregnancy (Table 1).

Table 1: Special features of anti-HIV therapy in pregnancy

| Explanation of risk: Only AZT is approved for perinatal transmission prophylaxis |
| No efavirenz (Sustiva®) in the first trimester (teratogenicity) |
| No d4T+ddi (Zerit®+Videx®) because of mitochondriopathies |
| Nevirapine-related hepatotoxicity in women with CD4 T cell counts >250/μl |
| Raised toxicity with combination therapy, therefore monthly controls of lactate, hepatic transaminase levels, viral load, CD4 T cell count |
| Therapeutic plasma drug level measurement (TDM) and possible dose adaptation |

Interruption of treatment in the first trimester

Women who have to discontinue ART during pregnancy, e.g., because of hyperemesis, should only restart ART when good HIV tolerance is expected. In this case, as in all others, the rule is to withdraw all drugs (NRTIs and PIs) simultaneously and re-administer them simultaneously, with the exception of NNRTIs. Due to their long half-lives, NNRTIs should be withdrawn up to three weeks before NRTIs in order to prevent development of resistance. Alternatively, the NNRTI can be replaced by a boosted PI. In other cases – especially if pregnancy is diagnosed very early – the fear of possible embryotoxic effects may also lead to an ART interruption until the end of the first trimester. Neural tube defects due to efavirenz can occur in the first 6 weeks. However, there are reports that after interruption of treatment in pregnancy, return of complete viral suppression may be much more difficult (Liuzzi 2006) and the risk of transmission is higher (Galli 2009). As it is usually not possible to determine pregnancy duration exactly, restarting is mostly initiated at the gestational point of 13+0 weeks. A continuously updated summary of the current state of knowledge about antiretroviral drugs in pregnancy can be found at www.AIDSinfo.nih.gov.

Combination therapy for the duration of pregnancy

HIV therapy and/or perinatal prevention is recommended to be based on a boosted PI. The prolonged half-life of NNRTIs makes them less suitable for a short course of treatment for prevention only. The prevention of mother-to-child transmission starts from the second trimester (CDC 2011) onward or 24–28+0 weeks of gestation. In pregnant women with a very low viral load a late start of HIV prevention from 32 weeks onwards may be acceptable (DAIG 2011). Before the decision of therapy the risk of teratogenicity has to be weighed carefully against the risk of HIV transmission. The approach of an earlier start of HIV prevention is based on the assumption that any timely decrease in viral load translates into a lowering of the transmission risk (Read 2010, Tubiana 2010). With a viral load of less than 1000 HIV RNA
copies/ml, the advantage of cesarean section compared with vaginal delivery can no longer be verified (Townsend 2008). For this reason, in the US as well as in most European countries vaginal delivery is considered an option for women on ART whose HIV status at the time of delivery is less than 1,000 copies/ml and/or undetectable (under 50 copies/ml) and in whom no obstetric complications are expected. These cases are increasing in Western Europe, and the rates have now reached about 40% (Rodrigues 2006, Townsend 2008, Boer 2010).

**Treatment monitoring**

In addition to measuring the hemoglobin concentration to exclude an AZT-associated anemia, transaminases for potential hepatic toxicity, especially in HIV and hepatitis virus coinfections, and lactate level to detect lactic acidosis early, the CD4 T cell number and viral load should be monitored at least bimonthly. If PIs are given, it is of particular importance to monitor the blood glucose level closely (El Betuine 2006, Snijdewind 2011). Resistance and plasma level are determined at the beginning and, if appropriate, at the point of failure of treatment.

**Special aspects of HIV prophylaxis/therapy in pregnancy**

Because embryotoxicity cannot be excluded and hepatic metabolism is altered in pregnancy, and in some cases plasma levels are reduced, some basic rules must be taken into consideration (CDC 2011) (Table 1).

It is important to understand that a detectable plasma viral load always necessitates a resistance test. AZT resistance was verified in approximately 17% of women who received AZT monoprophylaxis between 1991 and 1997 (Palumbo 2001). In the year 2006, resistance mutations were diagnosed in up to 23% of perinatally HIV-infected children, mutations which limited future therapeutic options and thus potentially worsened their prognosis (Vignoles 2007).

**HIV and hepatitis virus coinfections**

In chronic hepatitis B (HBV) coinfection and pregnancy, tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC) is recommended as NRTI backbone in HIV therapy (Shi 2010). The newborn of a mother with hepatitis B should receive hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours of birth.

A hepatitis C coinfection should not be treated during pregnancy, because interferon is contraindicated during pregnancy and ribavirin is known to be embryo- and fetotoxic (pregnancy category X).

Hepatitis virus coinfections could enhance liver toxicity in HIV therapy (Snijdewind 2011), therefore liver toxicity should be monitored monthly (CDC 2011, DAIG 2011). Mode of delivery in HIV/hepatitis coinfection is managed following HIV criteria.

**Antiretroviral agents in pregnancy**

**NRTIs**

NRTIs cross the placenta and can cause toxic damage not only to the mother but also the child. According to experience to date, the main problems are anemia and, when using combination therapy, lactic acidosis.

On the basis of pregnancies observed to date, it can be maintained that frequently used NRTIs such as AZT, 3TC and d4T do not increase teratogenicity by more than two-fold (Antiretroviral Pregnancy Registry 2011). Most of our experience is with AZT. Follow-up of more than 20,000 children who received AZT prophylaxis did not
show any serious side effects. An analysis of the causes of death of 223 children who
died within the first five years of life ruled out drug-related causes (The Perinatal
Safety Review Working Group 2011). In other studies no damage to mitochondrial
DNA or neurological development dysfunction in HIV-exposed children after ART
was detected (Alimenti 2006, Brogły 2010, Williams 2010).
In contrast to these findings, in a prospective study by Barret (2003) with 2644 ART-
exposed non-infected children, neurological symptoms with persistent mitochon-
drial dysfunction were reported in 0.26%. Retardation of auditory evoked potentials
(Poblano 2004), as well as nonspecific changes in cerebral MRTs in children perina-
tally exposed to AZT plus 3TC (Tardieu 2005) have been interpreted as a sign of neu-
rotoxicity. 24 months after combined nucleoside exposure, raised lactate values as
well as impairment of hematopoiesis can still be demonstrated in children, even
years after NRTI-exposure (ECS 2004, Vigano 2010, Brogły 2011). Severe mitochon-
driopathies have been observed during combination therapy of d4T+ddI. Tenofovir
and FTC proved to cross the placenta easily (Bonora 2007, Hirt 2009a+b). Fetotoxicity
has been demonstrated in animal studies but not in prenatally tenofovir-exposed

Table 2: Antiretroviral agents in pregnancy

<table>
<thead>
<tr>
<th>Preferred NRTIs (full placental transfer)</th>
<th>AZT + 3TC</th>
<th>AZT is metabolized in the placenta; mitochondriopathy risk: ddI&gt;d4T&gt;AZT&gt;3TC&gt;ABC&gt;TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + ddI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative NRTIs (full placental transfer)</td>
<td>d4T + 3TC</td>
<td>No side effects, PACTG 332</td>
</tr>
<tr>
<td>Abacavir</td>
<td></td>
<td>Some experience (HLA B*5701 Test)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>No published data in humans</td>
</tr>
<tr>
<td>FTC*</td>
<td></td>
<td>Alternative to 3TC, barely any experience</td>
</tr>
<tr>
<td>NNRTIs (full placental transfer)</td>
<td>Etravirine</td>
<td>Case reports</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>General use in perinatal prophylaxis; Hepatotoxicity ↑ especially in mothers with &gt;250 CD4 T cells; enzyme induction, rapid resistance</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td>No published data</td>
</tr>
<tr>
<td>Pls (minimal placental transfer)</td>
<td>Nelfinavir</td>
<td>Once frequent use; unboosted</td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td>Hyperbilirubinemia, nephrotoxicity</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>Only as booster</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td></td>
<td>Increasing experience, plasma level low ↓</td>
</tr>
<tr>
<td>Saquinavir SGC</td>
<td></td>
<td>Low plasma levels, only boosted</td>
</tr>
<tr>
<td>Amprenavir</td>
<td></td>
<td>Some experience, solution contraindicated</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
<td>Little experience</td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td>Limited experience; indir. hyperbilirubinemia, also with neonates</td>
</tr>
<tr>
<td>Tipranavir</td>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td>Entry and fusion inhibitors</td>
<td>T-20</td>
<td>Some experience</td>
</tr>
<tr>
<td>Maraviroc</td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>Raltegravir</td>
<td>Case reports</td>
</tr>
</tbody>
</table>

**NNRTIs**

In perinatal prevention, nevirapine has been employed successfully, particularly in
combination with AZT. Because of enhanced risk of liver toxicity during the first 18
weeks of treatment in women with CD4 T cell counts of more than 250/µl, treat-
ment should be monitored closely and frequently, especially during the dose escalation period (Boehringer 2004). Nevirapine in pregnant women with over 250 CD4 T cells/µl is only recommended following very careful assessment of the benefit-risk ratio (CDC 2011). In a retrospective study of 197 pregnant women, toxic side effects were observed in 5.6%, leading to treatment discontinuation in 3.6% (Joao 2006). However, a recent study did not find higher liver toxicity with nevirapine during pregnancy than with other compounds (Quyang 2010).

Perinatal single- and two-dose nevirapine prophylaxis resulted in the development of resistance mutations in more than 20% of cases (Flys 2005). This can be reduced by 50% or more by the additional administration of, for example, tenofovir and FTC (Chi 2007, Lehman 2009) but the intrapartum single-dose administration of nevirapine to pregnant women receiving ART is NOT recommended by the CDC (2011) or EACS (2011). If a mother gives birth less than two hours following nevirapine administration, or has not received any prior nevirapine at all, the newborn should receive a dose of nevirapine immediately after birth and a further dose 48–72 hours later (Stringer 2003). Because of embryonic toxicity in the rhesus monkey and also in humans (neural tube impairment) (Bristol-Myers Squibb 2004) efavirenz is not used during the first trimester of pregnancy and only after the second in those who have no alternative treatment option, providing reliable contraception is practiced after delivery (CDC 2011). The occurrence of isolated cases of neural tube defects caused the FDA to allocate efavirenz to category D. There are, unfortunately, only case experiences with etravirine and rilpivirine.

**PIs**

The use of PIs must be monitored carefully, especially in the later stages of pregnancy (monthly in the third trimester), due to possible diabetogenic effects (Beitune 2005) and hepatic toxicity. In other studies, however, no increased rate of gestational diabetes was seen (Hitti 2007, Azria 2009). Hyperlipidemia occurred more frequently in another study (Floridia 2006).

Presently, most experience relates to nelfinavir (Timmermans 2005). Since nelfinavir is less potent than boosted PIs, it is seldom used today. Indinavir can lead to hyperbilirubinemia and nephrolithiasis; the plasma levels can be lowered (Kosel 2003). As with indinavir, saquinavir should also be boosted with ritonavir in pregnancy (Zorilla 2007). A single dose of saquinavir is useful (Lopez-Cortez 2007). Lopinavir/r plasma levels are also lowered during pregnancy, especially in the third trimester (Manawi 2007, Aweeka 2010). Therefore the pharmacokinetics of increased doses have been investigated (Best 2010). With atazanavir/r, mild hyperbilirubinemia in neonates with low placental transfer of about 20% has been described (Ripamonti 2007, Ivanovic 2009, Mandelbrot 2011). Tipranavir reached higher concentration in umbilical cord blood compared to other PIs (Weizsäcker 2011). Darunavir does not cross the placenta (Ripamonti 2009). Fosamprenavir/r has been described as safe and effective (Martorelli 2010).

Monotherapy with lopinavir/r in pregnant women with an initial viral load under 30,000 copies/ml and CD4 cell count over 350 cells/ml reduced the viral load in more than 88% to less than 200 copies/ml. Side effects were less vs. triple ART (Tubiana 2011).

Previous speculation on increased rates of deformity when using PIs has been refuted, especially as PIs can barely cross the placenta due to their molecular size. An increase in premature births when using ART with a PI (EACS 2006, Cotter 2006, Grosch-Wörner 2008, Machado 2009, Townsend 2010, Powis 2011, Sibiude 2011) has also failed to be confirmed in other studies (Tuomala 2005, Kourtis 2007, Baroncelli 2009, Carceller 2009, Patel 2010, Dola 2011, Lopez 2012).
Alpha-fetoprotein levels are thought to be reduced on a PI regimen (Brossard 2006) although not the serum level of unconjugated estriol and human chorionic gonadotropin (Einstein 2004, Le Meaux 2008). Despite data of increased preterm deliveries, especially in European studies, PIs are still recommended for treatment and transmission prevention in pregnancy (CDC 2011).

**Entry, fusion and integrase inhibitors**

Enfurvitide (T-20) was administered with some success to women with multiresistant viruses, also in combination with tipranavir (Wensing 2006). Therapy failures with perinatal HIV transmission have been described. In T-20 there is no placental transfer (Brennan-Benson 2006). Like T-20, maraviroc is assigned to FDA category B (see below), in macaques there is no placental transfer. The integrase inhibitor raltegravir (FDA category C) seems to pass the placenta (Jaworsky 2010, McKeown 2010).

**FDA pregnancy classification for drugs**

The FDA has classified the potential toxicity during pregnancy into the categories A-D. All HIV agents belong to categories B-D, since “harmlessness through studies on the human being” (category A) has not been shown for any HIV drug.

**FDA category B** is defined as “Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women”. FDA category B includes ddi, FTC, tenofovir, etravirine, nevirapine, rilpivirine, atazanavir, saquinavir, ritonavir, nelfinavir, T-20 and maraviroc.

**FDA category C** is defined as “Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Use in pregnancy should occur only after careful benefit/risk appraisal.” All drugs not mentioned in category B fall into the FDA category C.

**FDA category D** is defined as “Adequate well-controlled or observational studies in pregnant women have demonstrated a risk for the fetus. Nevertheless, the benefits of therapy may outweigh the potential risk.” For example, the drug may be acceptable if it is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective. Efavirenz falls into category D because of neural tube defects in humans after first trimester exposure.

**FDA category X** is defined as “Studies in animals or humans have demonstrated fetal abnormalities and/or there is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risk involved in use of the drug in pregnant women clearly outweigh potential benefits.”

**Prevention of perinatal HIV infection**

In approximately 75% of cases, HIV is transmitted prior to, or during the last weeks prior to birth. About 10% of vertical HIV infections occur before the third trimester, and 10–15% are caused by breastfeeding. The probability of HIV transmission to a neonate correlates with the viral load (Warszawski 2008). This also applies to women receiving ART (Table 3). If the viral load is undetectable using currently available tests, the probability of transmission is extremely low (Tubiana 2011). Likewise, premature births and premature rupture of membranes are associated with an increased risk of HIV for the child in absent or insufficient HIV suppression.

For this reason, reduction in the level of plasma viremia and improvement in the immune status of pregnant women are vital prophylactic measures. If a mother is treated with antiretrovirals, these drugs should continue to be taken, if possible,
during delivery at the usual scheduled intervals in order to achieve the maximum effect and to minimize the risk of resistance. About 20% of perinatal HIV transmissions (less than 2% total) are due to resistance (Parker 2003). For the general prevention of vertical transmission of HIV, pregnant women should be warned not to use intravenous drugs or to have unprotected sex (Birkhead 2010).

Table 3: Known risk factors for perinatal HIV transmission

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High maternal viral load</td>
</tr>
<tr>
<td>Low CD4 T cell count, AIDS-defining illness of the mother</td>
</tr>
<tr>
<td>Vaginal delivery at a viral load &gt;1000 copies without ART</td>
</tr>
<tr>
<td>Premature rupture of membranes of &gt;4 h, pre-term infants (&lt;37 weeks of gestation)</td>
</tr>
<tr>
<td>Breastfeeding</td>
</tr>
</tbody>
</table>

In addition to the indicated or optional antiretroviral therapy of the mother, the following rules should be observed regarding chemoprophylaxis:

- Antiretroviral prophylaxis before and during delivery
- Elective cesarean section before onset of labor, because vaginal delivery with a viral load of >1000 HIV RNA copies/ml increases the transmission risk
- Post-natal chemoprophylaxis of the infants (post-exposure prophylaxis)
- No breastfeeding

**Antiretroviral transmission prophylaxis**

**Combination prophylaxis**

If the mother-to-be is not already on treatment and if the viral load is far below 100,000 copies/ml, then combination therapy should be started at 28+0 weeks gestation (32+0 at the latest in very low viral loads) until shortly after birth (Table 4). In the case of high-risk pregnancies (e.g., multiples) prophylaxis is begun at week 24+0. A monoprophylaxis with AZT or the combination of AZT+3TC is problematic because of the possible development of resistance (Mandelbrot 2001). Therefore, it is not usually recommended. A triple combination with a boosted PI is increasingly being used as prophylaxis. Due to elevated hepatotoxicity with a CD4 T cell count above 250/µl, combinations containing nevirapine are only implemented after careful assessment of the benefit-risk ratio.

Table 4: Combination prophylaxis with combination therapy containing AZT in cases with a viral load >50,000 RNA copies/ml, but otherwise only standard risk

<table>
<thead>
<tr>
<th>After resistance testing starting at 28 + 0 weeks gestation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two NRTI + PI/r (alternative NNRTI)</td>
</tr>
<tr>
<td>During delivery (elective cesarean section earliest from 37+0 weeks gestation to week 37+6 or vaginal delivery at VL &lt;50 copies/ml and ART): IV infusions of AZT as standard prophylaxis* (if viral load &gt;50 copies/ml):</td>
</tr>
<tr>
<td>2 mg/kg IV as a loading dose for 1 h to approximately 3 h preoperatively (prepartum)</td>
</tr>
<tr>
<td>1 mg/kg IV intraoperatively until delivery of the infant</td>
</tr>
<tr>
<td>In neonates AZT monoprophylaxis within 6 hours postpartum:</td>
</tr>
<tr>
<td>2 (4) mg/kg orally every 6 (12) hours for 2–4** weeks or</td>
</tr>
<tr>
<td>1.5 mg/kg IV every 6 hours for 10 days</td>
</tr>
</tbody>
</table>

* The advantage of intravenous AZT in a combination therapy and viral load <50 copies/ml is not certain (EACS 2011, DAIG 2011) ** 4–6 weeks at VL of 1000–10,000 copies/ml
**Prophylaxis in ART-pretreated pregnant women**

More than half of all HIV-positive pregnant women in the Global North have received pretreatment with ART. In the case of efficient ART with fixed combinations, it is feasible to stay on the regimen and not replace any of the NRTIs with AZT (CDC 2011, Tariq 2011).

**Procedure in cases of additional pregnancy risks**

The pregnancy risks mentioned in Table 5 require an intensified prophylaxis. Here too, the risk of transmission drops in the case of sufficient HIV therapy. In premature births, for example, perinatal HIV transmission only occurred when the mother had received no prophylaxis or only AZT monoprophylaxis (Aagaard-Tillery 2006).

**Intrapartum prophylaxis without antepartum regimens**

If the diagnosis of HIV infection is only established at the time of delivery, mother and newborn receive a dual or triple combination prophylaxis with AZT (plus 3TC and/or nevirapine) in cases of highly increased risk (high viral load and/or medical complications during delivery). Due to rapid resistance, nevirapine should only be administered in combination with other drugs.

**Treatment during delivery**

**Elective cesarean section or vaginal delivery in cases of uncomplicated course of pregnancy**

Cesarean section is carried out swiftly by experienced obstetricians prior to the onset of labor at the earliest from 37+0 up to 37+6 weeks of gestation using the Misgav-Ladach technique, which reduces bleeding. Blunt preparation and the delivery of the child within the intact amniotic sac are considered ideal (Schäfer 2001). In the case of undetectable viral load along with long-term ART, the advantage of elective cesarean over vaginal delivery is no longer recommended. For this reason, it is becoming more common in Germany to dispense with a C-section in favor of a later vaginal delivery.

**High-risk pregnancy**

Cesarean section in cases of multi-gravidity should be carried out using the same technique as for a cesarean section in a single pregnancy. In this context, the skill and experience of the operating surgeon are especially important. Cesarean sections in cases of premature infants are also important to avoid hypoxia in the neonate; the special aspects of chemoprophylaxis have been described above.

In cases with a premature rupture of membranes of less than four hours duration, a section is expedient for prophylactic reasons, providing that the clinical situation at that stage of delivery still allows this. If the rupture of membranes has lasted more than four hours, there is no longer an advantage of cesarean section compared to vaginal delivery. Nevertheless, vaginal delivery should occur as swiftly as possible, since the HIV transmission risk increases by about 2% per hour. The extension of the prophylactic scheme (Tables 5 and 6) is important if viral load in a high HIV transmission risk is not under 50 copies/ml at the time of delivery or 12 weeks before delivery has not yet been under 50 copies/ml. On the other hand in pregnancies with an increased transmission risk with a viral load of <50 copies/ml at least 12 weeks before delivery a single prophylaxis with AZT for 4 – 6 weeks is sufficient for the newborn.
### Table 5: Prophylaxis in the case of increased transmission risk

<table>
<thead>
<tr>
<th>Increased risk</th>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigravidity</td>
<td>Combination, e.g., AZT + 3TC + PI/r from 24+0 weeks gestation</td>
<td>Within 6h postpartum AZT 4 x 2 (2x4)* mg orally for 4 weeks (if IV necessary, 10 days)</td>
</tr>
<tr>
<td>VL prepartal &gt;1000 &lt;10,000 cop./ml</td>
<td>Combination therapy, e.g., AZT + 3TC + PI/r from orally for 4 weeks</td>
<td>Within 6h postpartum AZT 4 x 2 (2x4)* mg orally for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td>from orally for 4 weeks (if IV necessary, 10 days)</td>
<td>AZT dosage with premature birth &lt;36 + 0 wks/gestation: 2x2 mg/kg orally or 2x1.5 mg/kg IV from day 15: 3x2 mg/kg orally (for premature &lt;30 + 0 wks/gestation from day 29)</td>
</tr>
<tr>
<td>Premature infants &gt;33+0 to 36+6 weeks</td>
<td>Combination therapy, e.g., AZT+3TC+PI/r</td>
<td>AZT 4x2 (2x4)* mg/kg orally 6 weeks</td>
</tr>
<tr>
<td>of gestation***</td>
<td></td>
<td>AZT dosage with premature birth as above</td>
</tr>
<tr>
<td>VL&gt;50 cop./ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature infants &lt;33 weeks and VL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 cop/ml &lt;12 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For neonates >36+0 wks/gestation due to better adherence, also 2 x 4 mg/kg AZT

** See chapter on NNRTIs

*** For prematures, also triple prophylaxis (see below): 3TC, but cautiously with prematures

### Unknown HIV status in cases of known risk

If, at the time of delivery, the HIV status is unknown and the existence of risk is known, an HIV test can be offered to the mother (Bulterys 2004). Although specificity is high, it is still considered inadequate. The combined use of two rapid tests from different manufacturers is ideal. If one of the two tests is negative, there is probably no infection.

### Table 6: Prophylaxis in the case of highly increased transmission risk and VL >50 copies/ml.

<table>
<thead>
<tr>
<th>Highly increased risk</th>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature infants &lt;33+0 weeks</td>
<td>In addition to AZT or combination therapy: nevirapine*</td>
<td>AZT (dosage, see above) over 4–6 weeks plus</td>
</tr>
<tr>
<td>of gestation and VL &gt;50 cop/ml (or VL &lt; 50 cop/ml &lt;12weeks)</td>
<td></td>
<td>3TC** 2 x 2 mg/kg over 4–6 weeks plus</td>
</tr>
<tr>
<td>Amniotic rupture of membranes</td>
<td></td>
<td>nevirapine* 2 mg/kg within 2–48 h + 2nd dose 48–72 h postpartum (if no NVP prepartum or &lt;2h between ingestion and delivery) (If prepartum nevirapine, then only 1x after 48–72 h)</td>
</tr>
<tr>
<td>&gt;4 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amniotic infection syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise of viral load towards the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>end of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incision injury of the child</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td>Ingestion of hemorrhagic amniotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluid HIV diagnosed only post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>partum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See chapter NNRTIs.

** Premature babies: use 3TC cautiously.
Therapy of neonates

Standard postnatal prophylaxis

The postnatal transmission prophylaxis should begin, if possible, within the first 6 hours following birth with oral or – in the case of gastrointestinal symptoms – intravenous AZT prophylaxis. In Germany, the duration of the oral standard prophylaxis has been shortened from six to two (or four) weeks (Vocks-Hauck 2001).

Increased transmission risk (multiple neonates, premature infants)

In multiple-birth neonates without further risk, a two- to four-week AZT prophylaxis is recommended (without nevirapine). Premature infants (>33+0 weeks and VL >50 copies/ml and <33 weeks and VL <50 copies/ml) receive AZT monoprophylaxis for 6 weeks, if VL is <50 copies/ml at least 12 weeks before delivery.

Highly increased transmission risk

An additional transmission risk exists, e.g., in preterm babies <33 weeks and a viral load >50 copies/ml less than 12 weeks before delivery, a combination prophylaxis with AZT+3TC is recommended. A strongly increased risk exists, for example:

- after premature rupture of membranes,
- in cases of amniotic infection syndrome,
- when viral load >10,000 copies/ml prior to delivery,
- when there has been no transmission prophylaxis
- if an incision injury of the child during cesarean section,
- if the amniotic fluid sucked from the gastrointestinal or respiratory tract of the newborn is hemorrhagic,
- if maternal viral load has been more than 50 copies/ml

In the case of children with additional transmission risks, a combination prophylaxis of AZT+3TC, as well as two doses of nevirapine are recommended. Nevirapine is given either once to the mother before delivery and once to the infant, or twice postnataally. If maternal nevirapine administration occurs less than an hour before delivery, then the newborn receives its first dose within the first 48 hours (Stringer 2003). If nevirapine was a part of the combination therapy for the mother, the dose is doubled to 4 mg/kg in newborns because of possible enzyme induction. In addition, newborns receive an AZT+3TC prophylaxis for six weeks (CDC 2011). The pharmacokinetic data on ART in neonates are, however, extremely limited. According to the CDC guidelines (2011) the prenatal nevirapine dose to the mother is not applicable. Therefore the newborn receives nevirapine three times in the first week: immediately after birth and then after 48 and 96 hours. In addition, to lower toxicity only AZT is recommended as post-exposition prophylaxis for six weeks (two-drug regime, CDC 2011).

According to an FDA Safety communication (2011), lopinavir/r should not be administered to (premature) newborns during the first two weeks due to cardiotoxicity (McArthur 2009). Furthermore, transient adrenal insufficiency has been reported in newborns who have been exposed to lopinavir/r prenatally and for 30 days postnata tally (Siman 2011). As such, lopinavir/r is no longer given to newborns in the first two weeks.
<table>
<thead>
<tr>
<th>Abbreviated name</th>
<th>Average daily dose</th>
<th>Most frequent side effects</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT, Retrovir® 4 x 2 mg/kg, 2 x 2 mg/kg in PI* &lt;35 GW, from 15th day: 3 x 2 mg/kg*, in PI &lt;30 GW from 29th day</td>
<td>GI, anemia, neutropenia Mitochondriopathy in combination with 3TC</td>
<td>(P)ACTG 076, 316, 321, 353, 354, 358; HIVNET 012 III PACTG 331(PI)</td>
<td></td>
</tr>
<tr>
<td>3TC, Epivir® 2 x 2mg/kg in neonates (&lt;30 days)</td>
<td>GI, vomiting, mitochondriopathy in combination, incompatibility in premature infants</td>
<td>PACTG 358</td>
<td></td>
</tr>
<tr>
<td>FTC, Emtriva® 1 mg/kg postnatally (p.n.) or 2 mg/kg 12h p.n.; 3 mg/kg in neonates &lt; 3 months</td>
<td>GI Mitochondriopathy</td>
<td>ANRS 12109 Gilead PK study</td>
<td></td>
</tr>
<tr>
<td>ddl, Videx® 2 x 50mg/m² from 14th day</td>
<td>Diarrhea, pancreatitis, mitochondriopathy in combination</td>
<td>PACTG 239, 249; HIV-NAT</td>
<td></td>
</tr>
<tr>
<td>d4T, Zerit® 2 x 0.5mg/kg (&lt;30 days)</td>
<td>Mitochondriopathy in combination</td>
<td>PACTG 332, 356; HIV-NAT</td>
<td></td>
</tr>
<tr>
<td>ABC, Ziagen® 1 x 2–4 mg/kg &gt;1 month 2 x 8 mg/kg</td>
<td>HRS, mitochondriopathy, lactic acidosis</td>
<td>PACTG 321</td>
<td></td>
</tr>
<tr>
<td>TDF, Viread® 4 mg/kg p.n. and on days 3 and 5 13 mg/kg p.n.</td>
<td>Osteopenia, nephrotoxicity</td>
<td>NCT00120471, HPTN 057; ANRS 12109</td>
<td></td>
</tr>
<tr>
<td>NVP, Viramune® 1 x 2–4 mg/kg (or 1 x 120 mg/m²) for 14 days then 2 x 3.5–4 mg/kg (2 x 120 mg/m²)</td>
<td>Rash, hepatotoxicity, hyperbilirubinemia</td>
<td>PACTG 316, 356, HIVNET 012</td>
<td></td>
</tr>
<tr>
<td>NFV, Viracept® 2 x 40-60 mg/kg in infants &lt;6 weeks (NFV powder no longer available, 250 mg tablets can be dispersed in water)</td>
<td>GI, particularly diarrhea</td>
<td>PACTG 353, 356, PENTA 7</td>
<td></td>
</tr>
<tr>
<td>RTV, Norvir® Ritonavir 2x350–450 mg/m² in NN &lt;4 weeks</td>
<td>Hyperbilirubinemia, GI, especially nausea</td>
<td>PACTG 345, 354</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r, Kaletra® 2x300/75 mg/m² in infants &lt;6 weeks (avoid in newborns &lt; 2 weeks)</td>
<td>GI, especially diarrhea, cardiotoxicity, adrenal insufficiency in new-borns</td>
<td>PACTG P 1030, IMPAACTG P1060</td>
<td></td>
</tr>
</tbody>
</table>

I=infant; PI = premature infant; MI = mature born infant; NN = neonates; SD = single dose; (P)ACTG = (Pediatric) AIDS Clinical Trials Group; HIV-NAT = HIV-Netherlands Australia Thailand Research Collaboration; GI = Gastrointestinal side effect; GW = gestation week

Reference: Except for AZT in mature newborn infants, the dosage is from the studies. Antiretroviral agents that are not approved should be used in neonates; only in the context of studies, if possible.
Procedure in cases of no pre- or intranatal prophylaxis

Combination prophylaxis of AZT+3TC should start within the first 6 to 12 hours after delivery. In addition, a perinatal nevirapine prophylaxis is recommended. If HIV infection is discovered only after birth, a combination prophylaxis, begun within 48 hours, seems to be far more effective than a monoprophylaxis which is initiated only after 3 days (transmission rates 9.2% vs. 18.4%) (Wade 1998). However, even then, a certain positive effect of AZT prophylaxis as opposed to no prophylaxis can still be verified (18.4% vs. 26.6%) (Table 6). Even a late initiation of postnatal prophylaxis (>3 days) can still make sense.

Further studies for HIV prevention in neonates

A survey of studies of the pharmacokinetics in pregnancy and neonates is listed in Table 7 (Ronkavilit 2001+2002, Mirochnik 2005, Blum 2006, Chadwick 2008, Hirt 2009a+b). In order to continuously improve ART during pregnancy and the prophylaxis of perinatal HIV infection, a thorough documentation of clinical data is necessary. In the US, the Antiretroviral Pregnancy Registry is an extensive therapy register that helps to evaluate the potential teratogenicity of antiretrovirals on the basis of case reports of HIV-exposed neonates:

Antiretroviral Pregnancy Registry, Research Park, 1011 Ashes Drive, Wilmington NC 28405. Phone 1-800-258-4263, Fax 1-800-800-1052. For UK, Germany, France 0800-5913-1359, Fax 00800-5812-1658. Contact: www.apregistry.com/contact.htm


References


**Introduction**

For a growing number of men and women living with HIV/AIDS the perspective of parenthood is an important part in their planning of the future. Procreation without risk, or at very low risk of infection for the uninfected partner or prospective child, is achievable for couples in which one or both partners are HIV-infected. In an increasing number of countries reproductive counselling and/or support is provided to couples affected by HIV.

Procreative options for HIV-affected couples vary from unprotected intercourse to several techniques of assisted reproduction, donor insemination or adoption. Until recently, most couples have been advised against natural conception, as the priority is to prevent infection in the uninfected partner or child. In view of the strongly decreased risk of transmission with undetectable viral load, conception via intercourse without condoms is now being discussed as a possible option under certain circumstances. This has been greatly influenced by the “EKAF Statement” (Vernazza 2008, see also ART chapter) regarding the unlikeliness of HIV transmission while on effective ART.

In January 2008, the EKAF (Swiss Commission on AIDS-related issues) stated that physicians could inform their patients about a negligible sexual transmission risk if three conditions are met:

- The HIV-infected patient is on a physician-monitored ART and is adherent
- Plasma viral load has consistently been undetectable for more than 6 months
- No sexually transmitted diseases are present in either of the partners

The statement also emphasized that only the HIV-negative partners can decide for themselves whether they want to stop using condoms with their seropositive partner. The background of the statement includes some longitudinal studies on serodiscordant couples. No infection occurred when the partners were on ART or the viral load in untreated partners was below 1,000 copies/ml (see chapter on Prevention). A retrospective Spanish study (Barreiro 2006) saw no infections in a cohort of 74 HIV discordant couples (76 pregnancies) who conceived via timed intercourse. All HIV-infected partners had a viral load below detection. However, data from couples who did not conceive were not available. This option was discussed prior to the Swiss Statement (Barreiro 2007).

With a view to reproductive aspects the Swiss Statement puts on record that insemination with processed sperm is no longer indicated for prevention of HIV transmission if the viral load is below detection.

Studies on the association between viral load in sperm and blood show a high correlation, but data there are limited (Kalichman 2008). HIV can sometimes be detected in semen or genital secretions even when viral load in blood plasma is below the limit of detection. Viral load in semen or genital secretions does not always correlate with plasma viral load (Pasquier 2009).

Recently, the publication of the HPTN 052 Study data (Cohen 2011) has added support to the Swiss Statement, showing a 96% reduction of HIV transmission in the study group with immediate use of ART.

The British fertility guidelines recommend in the current draft version to advise couples where the man is HIV-positive on the negligible risk of transmission to the female partner through unprotected sexual intercourse when the criteria as described in the Swiss Statement are met (National Collaborating Centre for Women’s and Children’s Health 2012).
In France, the current guidelines consider natural conception as a reasonable option for serodiscordant couples with no detectable viral load, recommending self-insemination when the woman is HIV-positive and timed unprotected intercourse in case of the male partner's infection as the safest option (Madelbrot 2012). The current US guidelines (NIH 2012) recommend self-insemination or sperm preparation techniques coupled with insemination or other reproductive procedures as the safest methods. Infected partners are advised to start treatment before starting conception procedures. For couples with no access to reproductive services natural conception at ovulation is seen as a choice, when the infected partner has no detectable viral load. Pre-exposure prophylaxis (PrEP) is seen as an additional option. In view of the increasing worldwide access to ART, natural conception is increasingly discussed as a safe option for couples even in resource-limited regions (Ong’ech 2012). For HIV-infected women with an uninfected partner, self-insemination is a safe and affordable procedure also in these countries (Mmeje 2012).

Natural conception now has become an important issue for many HIV-discordant couples seeking reproductive counselling. The EKAF Statement and current data and the resulting reproductive options should be discussed with couples seeking counselling and support. Usually, there are significant differences in individual risk estimation and the need for safety between couples. In any case, couples who want to exclude even a minimal risk or who are facing fertility disorders are those who seek counselling. Furthermore it has to be considered that in some seropositive partners the viral load is not effectively suppressed, or that they have not started treatment because of a low viral load and an intact immune system. In these cases insemination with processed sperm – in case of unimpaired fertility – can be the method of choice. Recently, the start of ART in patients with low viral load in order to open the option for natural conception has also been increasingly discussed.

The German-Austrian guidelines for diagnostics and treatment of HIV-affected couples (DAIG 2011) suggest the following options:

Fertile HIV-discordant couples, ART, viral load below detectability, no other STIs:
- Intercourse without condom at ovulation time
- Intercourse without condom plus PrEP
- Self-insemination in case of infection of the female partner
- Intrauterine insemination and sperm processing in case of infection of the male partner

HIV-discordant couples, fertility impaired, detectable viral load or no ART:
- Depending on medical indication, several methods of assisted reproduction. In case of infection of the male partner sperm processing and cryopreservation are advised.
- Fertile HIV-concordant couples, undetectable viral load:
- Intercourse without condom
- HIV-concordant couples, fertility impaired, detectable viral load or no ART:
  - Depending on medical indication, several methods of assisted reproduction

Other options: Donor insemination is an alternative safe option for a small number of couples, but due to legal restrictions it is only offered in a minority of centers. In the UK, for example, there are no restrictions on donor insemination, whereas in Germany access is limited. In addition, most couples wish for a child that is the biological offspring of both parents. Adoption often is only a theoretical option: HIV infection of a partner often renders this procedure very difficult or even impossible (e.g., in Germany). Egg cell donation might be an option for a small number of women facing severe fertility disorders, but is offered only in a limited number of countries (i.e., Spain).
Equal access for HIV-positive women and men is granted in most, but not all of the countries that have established reproductive support for couples affected by HIV.

**Pre-conception counselling**

The counseling of the couple should not only consider extensive information on all reproductive options available, but also the psychosocial situation of the couple. Important issues to discuss can be any current psychosocial problems, the importance of a network of social support from family or friends, and planning and perspectives about the future as a family (Nakhuda 2005). A supporting, empathic and accepting mode of counseling is advisable, as many couples feel distressed if their motives for, or entitlement to, parenthood are questioned. The drastically reduced risk of transmission through unprotected intercourse if the viral load is undetectable should be discussed as well as the individual risk perception and risk management strategies of the couple. In cases where professional psychosocial services are not integrated, cooperation with community organizations or self-help groups is advisable. If reproductive assistance is planned, financial aspects and possible stress occurring during the work-up and treatment of the couple should be discussed as well as doubts or fears. Even with the very low risk of infection, anxieties regarding HIV transmission to the partner might occur (van Leeuwen 2008). The fear of results that might challenge their chance to become parents can also be a burden for couples.

Serodifferent couples need to know that the risk of HIV infection can be minimized, but not excluded completely. HIV-positive women have to be informed about the risks of vertical transmission and the necessary steps to avoid it. In any case, couples should know that even using state-of-the-art reproductive techniques, achieving a pregnancy cannot be guaranteed.

Table 1 shows the investigations as provided in the current German-Austrian guidelines (DAIG 2011).

<table>
<thead>
<tr>
<th>General</th>
<th>Comprehensive medical and psycho-social history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female exams</td>
<td>Gynecological examination, sonography, tubal patency test (hysterocontrast sonography, if necessary laparoscopy)</td>
</tr>
<tr>
<td></td>
<td>Endocrinological diagnostics (E2, LH, P, DHEAS, FSH, testosterone, SHBG, TSH, AMH)</td>
</tr>
<tr>
<td></td>
<td>Cervical smear [PAP, chlamydia PCR])</td>
</tr>
<tr>
<td></td>
<td>(UK: 2-5 FSH/LH and mid-luteal progesterone to evaluate female fertility)</td>
</tr>
<tr>
<td></td>
<td>Serology (rubella, varicella, TPHA, CMV, HBV, HCV)</td>
</tr>
<tr>
<td>HIV-specific</td>
<td>Blood glucose, creatinine, GOT, GPT, GGT, complete blood count</td>
</tr>
<tr>
<td>assessments</td>
<td>Ultrasensitive HIV PCR, CD4/CD8 T cell counts and, if necessary, resistance testing</td>
</tr>
<tr>
<td></td>
<td>HIV antibody test of the seronegative partner</td>
</tr>
<tr>
<td>Male exams</td>
<td>2 spermiograms, in case of pathologic results: semen culture, if necessary, sonography</td>
</tr>
<tr>
<td></td>
<td>Serology (HBV, HCV, TPHA), urethral smear (GO), chlamydia PCR (urine)</td>
</tr>
</tbody>
</table>

**Male HIV infection and reproductive assistance**

Following the decision to conceive with reproductive assistance, the couple should undergo a thorough sexual health and infection screen, including information about the male partner’s HIV status. The possibility of HIV infection in the female partner also has to be excluded. In some cases, it might be necessary to treat genital infec-
tions before starting reproductive treatment. Studies have indicated a frequent impairment of the sperm quality of HIV-infected men compared to that of HIV-negative men (Dulioost 2002, Pena 2003, Nicopoullos 2004, Bujan 2008). A prospective study of HIV-infected men during the first 48 weeks of ART revealed a significant impairment of sperm motility, even with therapies that were not regarded as particularly mitochondriotoxic (van Leeuwen 2008). Data on the effect of these changes on fertility are limited (Prisant 2010).

After sperm washing and testing for HIV, spermatozoa can be utilized in three different reproductive techniques depending on whether the couples have any additional fertility issues: intra-uterine insemination (IUI), extracorporal fertilization by conventional in vitro fertilization (IVF) and intracytoplasmic sperm injection followed by embryonic transfer. According to the German recommendations, the choice of method depends on the results of gynecological and andrological investigations and the couple’s preference. The success rate using IUI has been shown to be reduced if the sperm is washed and then cryopreserved before use. This is necessary in some centers where PCR testing of the washed sample for HIV cannot be done on the day of insemination. This, together with the possible impairment of semen quality results in a number of couples being advised to have IVF or ICSI.

Couples should be informed about further important aspects:

- Sperm washing and testing greatly reduce the risk of infection, but cannot exclude it completely. Following recent studies, this risk seems to be only theoretical.
- During treatment, consistent condom use is important, especially when the partner’s viral load is not effectively suppressed. HIV infection of the woman in the early stages of pregnancy can increase the risk of transmission to the child.
- Most couples attending European centers have to pay for treatment costs themselves. These are dependent on the technique applied and range from about €500 to €5,000 per cycle. An exception is France, where couples have cost-free access to treatment.
- Even the most sophisticated techniques cannot guarantee successful treatment.
- Following successful reproductive treatment, couples are usually monitored for HIV status for 6–12 months after childbirth, depending on the center.

The safety of sperm washing

The technique of processing sperm from HIV-positive men prior to the insemination of their HIV-negative partners was first published by Semprini in 1992. The first inseminations with sperm washed free of HIV were carried out in Italy and Germany as early as 1989 and 1991, respectively. Up to mid-2003, more than 1800 couples had been treated in about 4500 cycles, applying various techniques of assisted reproduction. More than 500 children have been born with no seroconversion reported in the centers closely following the protocol of washing and testing the sperm prior to assisted reproductive techniques (Bujan 2007).

Native ejaculate mainly consists of three fractions: spermatozoa, seminal plasma and nuclear concomitant cells. The HIV progenome and virus have so far been detected in the seminal plasma, the concomitant cells, and occasionally in immobile spermatozoa. Several studies have indicated that viable, motile spermatozoa are not likely to be a target for HIV infection (Pena 2003, Gilling-Smith 2003).

Motile spermatozoa can be isolated by standardized preparation techniques. After separation of the spermatozoa from plasma fractions and NSC (non-spermatozoa cells), the spermatozoa are washed twice with culture medium and re-suspended in fresh culture medium. Incubation for 20–60 minutes allows motile sperm to “swim up” to the supernatant. To be more certain that it is not contaminated with viral
particles, an aliquot of the sample should be tested for HIV nucleic acid using highly sensitive detection methods (Weigel 2001, Gilling-Smith 2003, Pasquier 2006). Depending on the method, the limit of detection is 10 copies/ml. After having studied the effectiveness of several methods of sperm processing, Anderson (2005) concluded that the combination of gradient density centrifugation and swim-up allows a 10,000-fold decrease of HIV-1 concentration in sperm. Since HIV could theoretically remain undetected, sperm washing is currently regarded as a very effective risk reduction, although not risk-free.

Most of the European centers that offer assisted reproduction to HIV-discordant couples are part of the CREATHE-network, which aims to optimize treatment and safety of the methods as well as to compile an extensive database. Compiled data from several centers hint on the safety and reliability of sperm washing (Bujan 2007).

**Pre-Exposure Prophylaxis (PrEP)**

Even before the FDA approval of Truvada® as the first antiretroviral substance for the prevention of HIV transmission through sexual intercourse, PrEP before periovulatory unprotected intercourse was an option for serodiscordant couples in some countries. Couples abstain from condom use only during the woman’s fertile days. Preconditions are an effectively suppressed viral load, the exclusion of sexually transmitted diseases, and unimpaired fertility status of both partners. Data from Switzerland and Germany shows high acceptance in couples. No case of HIV transmission has been reported in 53 couples, the pregnancy rate was 75% (Vernazza 2011). These data still have to be valued as preliminary. Up to now, there is no evidence that PrEP will further reduce the already negligible risk of infection when the viral load of the HIV positive partner is effectively suppressed. Nevertheless, some couples prefer this option because it increases their feeling of safety.

**Female HIV infection**

For many seropositive women having a child now is an important part of their planning for the future (Fiore 2008, Loutfy 2009). In France 32% of the seropositive women of reproductive age want to become mothers (Heard 2007). Treatment and care during pregnancy should be carried out according to the prevailing national or international guidelines (Fakoya 2008, DAIG 2011, Loutfy 2012). In some European countries reproductive options for women with unimpaired fertility include natural conception on the basis of the EKAF Statement and self-insemination, while self insemination is still seen as the safest procedure. Couples who decide for natural conception should undergo screening to exclude STDs. The transmission risk might be further reduced when the intercourse without condoms is limited to the time of ovulation. Women should be advised on the importance of adherence to medication and regular checks of the viral load (Fakoya 2008). If a woman is not taking ART, the viral load is not successfully suppressed, or concerns about the remaining risk are strong, self-insemination may be the method of choice. In some cases, ovarian stimulation may be advisable. This, however, requires highly qualified supervision to avoid multiple gestations. It is important to time ovulation accurately (i.e., by use of computer-based ovulation kits or urine sticks). A simple inexpensive way of determining whether the cycles are ovulatory, helpful in women who have regular cycles, is a basal temperature chart beginning about three months before the first self-insemination. At the time of ovulation, couples can either have protected intercourse with a spermicide-free condom and introduce the ejaculate into the vaginal cavity afterwards,
or the ejaculate can be vaginally injected using a syringe or applied with a diaphragm or portio cap. Thus the conception remains within the private sphere of the couple. After 6–12 months of unsuccessful self-insemination, the couple should have further fertility investigations with a view to assisted conception. Should the couple experience problems with self-insemination, intrauterine insemination (IUI) can be considered. HIV-specific and infective diagnostics are recommended. If no pregnancy has occurred over a period of 6–12 months (or earlier, if the couple so wishes) fertility diagnostics should be carried out (Table 1). If there are indicators of reduced fertility in one or both partners, fertility diagnostics might be carried out at an earlier stage in the counselling process.

**Fertility disorders**

In some cases, women will only be able to conceive by intercourse without condom or self-insemination. Dependent on the fertility status of both partners, IVF and ICSI can be considered as methods of choice. Fertility disorders in HIV-positive women seem to have a higher prevalence than in an age-matched HIV-negative population (Ohl 2005, Gingelmaier 2010) and might lead to a lower success rate of assisted reproduction (Coll 2006) although data show some conflicting results. Reasons might be infection of the upper genital tract (Sobel 2000), surgery due to cervical intraepithelial neoplasia (Gilles 2005) or a depletion of mitochondrial DNA in the oocytes (Garrabou 2006, Lopez 2008).

Data reported from a program in Strasbourg indicated infertility problems in most HIV-positive women. IVF and ICSI were far more effective than IUI (Ohl 2005). In the Barcelona program, Coll (2006) observed a decreased pregnancy rate in HIV-positive women after IVF compared to age-matched HIV-negative controls and HIV-infected women who received donated oocytes. Results indicated a decreased ovarian response to hyperstimulation in HIV-positive women. A slightly impaired ovarian response to stimulation during 66 ICSI cycles in 29 HIV-infected women was also described by Terriou (2005). Martinet (2006) found no difference in ovarian response between HIV-positive and HIV-negative women in Brussels.

Data concerning a possible association between ART and fertility disorders in women is limited (van Leeuwen 2006). Although assisted reproduction for seropositive women with fertility disorders is offered in centers in various European countries as well as the US, access to assisted reproduction often is still more limited for women than for men.

**HIV infection of both partners**

A growing number of HIV-concordant couples are now seeking reproductive counseling. In some centers, these couples are also accepted for reproductive treatment in case of fertility disorders. If both partners are on effective HAART and there are no fertility disorders present, timed unprotected intercourse can be the method of choice. The discussion pertaining to the transmission of mutated drug-resistant virus between partners is still ongoing. Up until now, only a very small number of superinfections have been published, and they have only occurred in individuals not on ART (Willberg 2008).

Couples should be offered the same range of fertility counseling and screening as HIV-discordant couples. The current health of each partner should be carefully evaluated with a full report from their HIV physician.
Psychosocial aspects

- Experiences from more than a decade of counselling show the importance of offering professional psychosocial support to couples planning to conceive, especially if reproductive assistance is necessary. Accepting the desire to become parents and dealing with the underlying motives as well as the psychosocial situation in an empathic way enables couples to see obstacles as well as to develop alternative perspectives if this wish cannot be realized.

- Frustration, strains and disappointment may accompany unsuccessful treatment cycles or premature termination of pregnancy. Psychiatric co-morbidities in one or both partners (i.e., substance abuse, psychoses) can be reasons to at least postpone treatment. Professional diagnosis and support is necessary in these cases.

- Often, the central importance of the wish for parenthood of many migrant couples is overlooked in the medical and psychosocial counselling system. Language or communication difficulties on both sides, ignorance of different cultural backgrounds and lack of acceptance of other life-styles can lead to feelings of discrimination, isolation, helplessness or despair in couples.

- Issues concerning the welfare of the child should be openly discussed during reproductive counselling (Frodsham 2004). Many couples are concerned about a potential negative effect of antiretroviral drugs on their offspring. Severe impairment of the health of the prospective parents might lead to concerns for the future well-being of the child.

The future

Healthcare professionals are encountering a growing number of couples or individuals who are contemplating parenthood. Having a child is an expression of a fulfilled partnership and an important perspective in life. This is no less true in couples with HIV/AIDS. In the medical and psychosocial care of patients, it is important to create an environment where reproductive aspects and parenting can be discussed on an open and non-judgemental basis. Worldwide, there is a growing demand to establish reproductive health services, to support sexual rights of people living with HIV/AIDS and to provide reproductive counselling and assistance.

The publication of the Swiss Statement and the HPTN 052 Study data as well as the increasing access to effective antiretroviral therapy have encouraged a growing number of health care professionals in many countries to discuss natural conception as an option for HIV positive men and women with suppressed viral load. In some centers, sperm washing, self insemination and assisted reproduction are only recommended in the presence of fertility disorders, or detectable viral load. In some centers, sperm washing, self insemination and assisted reproduction are only recommended in the presence of fertility disorders, or detectable viral load.

Future priorities include continued reporting of data pertaining to the applied methodologies as well as to the outcomes, reporting of adverse results and the follow-up of couples (Giles 2005). Steps towards optimizing semen-processing procedures, namely quality control of virus detection in processed sperm and laboratory safety, have already been taken (Politch 2004, Pasquier 2006, Gilling-Smith 2005, Vitorino 2011). Long-term outcomes in couples that receiving reproductive assistance, health outcomes among children, both in medical as well as in psychosocial terms, and consensus regarding best practice or surveillance of care provided by clinics have received little notice up till now.

Many couples cannot afford the high costs of treatment, or travel long distances, sometimes even to other countries, to reach specialized units. There is an urgent need to develop strategies for the counseling and financial support of these couples in cases where natural conception is not possible or not advisable.
The use of donated oocytes in reproductive services for HIV-positive women (Coll 2006) is limited in several countries due to legal and ethical considerations. It even enables treatment of women who have reached an age where reproductive assistance is not usually offered anymore due to the high risk of miscarriages and malformation and the low success rate of assisted reproduction techniques.

Medical and technical progress has opened a wider range of options, but aside from comparing higher or lower success rates, there is an urgent need to discuss psychological and psychosocial issues pertaining to the welfare of parents and child.

References


Characteristics of HIV infection in childhood

More than 95% of children are infected with the virus through perinatal transmission (vertical infection). In most cases (75–90%) HIV is transmitted peri- or intrapartum. Only a small proportion of children are infected in utero (10–25%). Transmission by breastfeeding is more common in resource-limited settings, but plays a minor role in developed countries, where breastfeeding by HIV-infected mothers is strongly discouraged. The increasing knowledge about how HIV is vertically transmitted has led to highly effective interventions to prevent transmission and a significant reduction of the transmission rate to less than 2%. However, new infections in HIV-exposed children still occur:

- if the HIV status of the mother is unknown;
- if prevention of transmission prophylaxis is incomplete;
- if the mother does not have access to transmission prophylaxis during pregnancy.

Without antiretroviral therapy there is a bimodal presentation of vertical HIV infection: in 10–25% of the children, rapid progression with AIDS-defining symptoms and potentially lethal complications is observed within the first year of life. In 75–90% there is a much slower disease course with a mean duration of more than 8 years until AIDS-defining symptoms occur. At present, disease progression is mainly influenced by the efficacy of antiretroviral therapy.

At birth, viral load is usually low (<10,000 copies/ml) and then rises rapidly within the first 2 weeks of life to values above 100,000 copies/ml and only slowly decreases after the age of 4–5 years. These viral dynamics are significantly different from the rapid increase and decrease of the viral load seen in untreated adults within a few months following acute HIV infection (Figure 1).

Figure 1: Differences in the natural course of HIV in the first months after infection/transmission of viral load and differences in HIV immunity between adults and infants/toddlers.
In children, the higher viral load is associated with the somatic growth of the lymphatic system and the inability of the immature immune system to mount an HIV-specific response. When assessing the immune system in infants and children, it is very important to compare the child’s CD4 count with the age-appropriate values (e.g., the mean CD4 T cell count for a 6-month-old baby is 3.0 \times 10^9/l). Lymphocyte counts are very high in infancy and decline to adult levels after the age of 6 (Table 1). In adults typical manifestations of the acute HIV seroconversion illness include fever, sore throat, lymphadenopathy and a mononucleosis-like disease. HIV seroconversion illness has not been described in perinatally-infected children. Symptomatic disease presenting in childhood has been classified according to severity of symptoms (Table 2) and at www.who.int/hiv/pub/guidelines/en/index.html.

If antiretroviral therapy in children is effective, opportunistic infections (OIs) become a rarity. However, in children who newly present with HIV (e.g., if HIV status in the mother is unknown and there was no transmission prophylaxis) opportunistic infections are observed.

### Table 1: 2006 WHO HIV Pediatric Classification System: Immune Categories Based on Age-Specific CD4 values. See also [http://www.womenchildrenhiv.org](http://www.womenchildrenhiv.org)

<table>
<thead>
<tr>
<th>Classification of HIV-associated immunodeficiency</th>
<th>Age-related CD4 Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>,11 months (absolute number/μl or % CD4)</td>
<td>12–35 months ( % CD4)</td>
</tr>
<tr>
<td>None or not significant</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Advanced</td>
<td>25–29</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

### Table 2: WHO clinical staging for children with confirmed HIV infection

#### Clinical stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy

#### Clinical stage 2
- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Fungal nail infection
- Angular cheilitis
- Lineal gingival erythema
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Herpes zoster
- Recurrent or chronic upper resp. tract infections (otitis, otorrhea, sinusitis or tonsillitis)
Table 2 (continued)

**Clinical stage 3**
- Unexplained moderate malnutrition or wasting not adequately responding to stand. therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6–8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anemia (<8 g/dl), neutropenia (<1000/μl) and or chronic thrombocytopenia (<50,000/μl)

**Clinical stage 4**
- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (or orolabial or cutaneous of more than one month’s duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Central nervous system toxoplasmosis (after one month of life)
- Extrapulmonary cryptococcosis (including meningitis)
- HIV encephalopathy
- Disseminated endemic mycosis (coccidiomycosis or histoplasmosis)
- Disseminated non-tuberculous mycobacterial infection
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

**Diagnosis of HIV infection in children**

The detection of HIV antibodies does not prove infection in infants. High titers of IgG are transferred transplacentally from mother to child. Maternal antibodies can be detected in children up to the age of 18 months. Therefore a direct method of detecting HIV is necessary. Identification by PCR is highly sensitive and specific. Cord blood is not useful for the diagnosis because maternal cells may be present and may cause a false positive test result. Within the first 48 hours after birth, 62% of all HIV infected infants are still HIV PCR negative. Even 4 weeks after birth 11% of the infections are still not detectable by PCR (Dunn 1995, Burgard, 2012). First PCR testing should be done within 14–21 days. Once a positive HIV PCR is found, a second
independent blood sample should be taken as soon as possible for repeat analysis. As diverse subtypes exist, it is advised to test paired samples from mother and infant by HIV PCR. If the mother’s virus is not amplified by the primer set used then another set or another test can be used to avoid a false negative result in the infant. The disappearance of maternal IgG antibodies to HIV needs to be documented before HIV infection can be definitely excluded in the child. Tests with an increased sensitivity to detect HIV antibodies are not useful as they may detect maternal antibodies up to 28 months of age leading to anxiety and confusion in the affected families (Nastouli 2007).

In children who present with symptoms of possible HIV infection, and whose mother’s HIV status is unknown, an HIV antibody test should be performed first, followed by a confirmatory PCR if this is positive. A negative HIV test in the mother early in pregnancy should not preclude testing the child, as the rate of mother to child transmission is high if the mother becomes infected later in pregnancy or during breastfeeding. In children older than 18 months, HIV infection is diagnosed in an analogous way to adults (see chapter on HIV Testing).

### When to initiate ART

Keep the following facts in mind before starting ART in children:

- Treatment of HIV-infected children is usually not an emergency
- Take as much time as needed to decide whether to start with ART or not.

A randomized study in 377 infants under the age of 3 in the South African CHER study (Children with HIV Early Antiretroviral therapy) examined whether to start directly after diagnosis (AZT+3TC plus lopinavir/r) or defer treatment until symptoms occur or CD4 T cells fall below 25% (Violari 2008). Deferred treatment is associated with a higher mortality (16% versus 4%). These data are of fundamental importance as clinical practice and guidelines before this study did not advise to treat all infants. In children who are diagnosed beyond infancy many experts defer treatment in asymptomatic children (i.e., with a low viral load and without immunodeficiency). Commencing antiretroviral therapy too early risks possible long-term side effects and early exhaustion of the limited supply of antiretroviral drugs that can be safely used in children. Therefore, the indication for treatment is based on CD4 T cell count, viral load and clinical criteria.

<table>
<thead>
<tr>
<th>0–11 months</th>
<th>Treat all children</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–35 months</td>
<td>Treat if CDC Stage is B or C/WHO Stage 3 or 4</td>
</tr>
<tr>
<td></td>
<td>Treat if CD4 T cells are &lt;20% or &lt;1,000 cells/μL</td>
</tr>
<tr>
<td></td>
<td>Consider treatment if viral load &gt;10,000 copies/mL</td>
</tr>
</tbody>
</table>

| 36–59 months | Treat if CDC Stage is B or C/WHO Stage 3 or 4 |
|             | Treat if CD4 T cells are <20% or <500 cells/μL |
|             | Consider treatment if viral load >10,000 copies/mL |

| 5 years + | Treat CDC Stage B or C/WHO Stage 3 or 4 |
|          | Treat if CD4 T cells are <350 cells/μL |
|          | Consider treatment if viral load >10,000 copies/mL |
Viral load and CD4 T cell counts are independent prognostic markers for end stage, AIDS or death. A computer program has been generated which can be used to give the risk of progression to AIDS or death within 6 or 12 months according to the age and either CD4 T cell count or viral load in the child (PENTA Calculator, http://www.hppmcs.org/). Some updated guidelines are listed here:

- European guidelines: www.pentatrials.org/guidelines.htm

**General considerations for treatment of HIV-infected children**

The treatment of children with antiretroviral drugs is complex. Successful treatment requires an interdisciplinary approach to the children and their families. Good adherence is key to treatment success. In the prospective PACTG 377 study, adherence was defined as having not missed a single medication dose over the previous 3 days. According to this definition, only 70% of children were found to be adherent (125 children within an observation period of 48 weeks) (Van Dyke 2002). The modalities of the daily intake of medication need to be discussed in detail and adjusted to the daily and weekly routines of the family. Clear treatment goals need to be set, e.g., 90% of the prescribed doses. Education of the patient and the family regarding the antiretroviral drugs is necessary. Sometimes a brief period of hospitalization at the start of antiretroviral therapy is useful to educate the child and family and gauge the tolerability of the regimen. Adherence is particularly problematic in adolescence, and successful reduction or control of viral load may only be achieved in 1/3rd of these patients (Ding 2009). In this age group, adherence often needs close follow up including other health care professions such as psychologists and social
workers. In a meta-analysis, peer support and home-based nursing were shown to improve ART adherence (Bain-Brickley, 2011). Sometimes (planned) periods off ART, despite the risk of ill health, have to be accepted in this group of patients. A promising approach to increasing adherence in children and adolescents is the availability of once-daily regimens: in PACTG Study P1021 a once-daily regimen with ddI+FTC and efavirenz was studied over ≥96 weeks in 37 treatment-naive children (age 3 to 21 years) (McKinney 2007). This regimen resulted in a relatively high percentage of children having VL below detection (70% after 2 years), but unfortunately the study lacked a comparator arm. Underdosing has been shown to be a problem in daily practice (Menson 2006). Dosing by weight instead of body surface area (given as an alternative in some older guidelines) may result in underdosing and ongoing growth may not be adjusted for. Particular genotypes are associated with hypermetabolism of NNRTIs and PIs. Plasma levels of NNRTIs and PIs can be measured (therapeutic drug monitoring, TDM) to detect interindividual differences in drug metabolism and lack of adherence, to check on dosages that may be too low or to prevent toxicities from too high a dosage (Fletcher 2009).

Before medication is initiated or changed, the decision should always be based on at least 2 independent blood samples. Infections and vaccinations may influence viral load and CD4 T cell count. Therefore, it is not recommended to base decisions on data that have been gathered within 14 days of an infection or vaccination.

**Treatment strategy**

At present, eradication of HIV cannot be achieved. In some children viral load remains below detection for years and subsequently there are no HIV-specific antibodies detectable. Ultra-sensitive assays can detect HIV (Persaud 2004). Children tend to show a poorer response to first line HAART than adults. Therefore risks and benefits of antiretroviral therapy have to be balanced in each child. Interruption or incomplete adherence may cause more harm than deferring therapy. The decision to start antiretroviral therapy has fundamental consequences for the children and families. From this point on it usually means that children will take the medication for life. A retrospective analysis of unplanned treatment interruptions in children demonstrated a significant decline of CD4 percentages by 6.6% per year (Gibb 2004). PENTA (Pediatric European Network for Treatment of AIDS) did a randomized pediatric study of CD4 guided, planned treatment interruptions (PTIs). There were no serious negative clinical outcomes. Younger children had better CD4 recovery after PTIs (PENTA 11). However, there are insufficient data on the long-term effects of treatment interruption to recommend this routinely, although it may be necessary when there is drug toxicity or poor adherence.

Table 5 shows the current treatment concept for choosing antiretroviral drug combinations. It appears useful to start with a combination that includes two classes (2NRTIs + PI or 2 NRTIs + NNRTI) in order to spare one or two classes for any future change of antiretroviral therapy and to minimize toxicity. If full viral suppression on treatment is not achieved development of resistance (and then cross-resistance) to NNRTIs and PIs is very likely. Therefore, sparing classes may be useful for long-term efficacy.

As there are only small numbers of children and adolescents with HIV in Europe it is highly recommended to include all children who receive antiretroviral therapy in multicenter clinical trials (e.g., PENTA (Pediatric European Network for Treatment of AIDS), http://www.pentatials.org, Dr. Diana Gibb, Phone: + 44 20 7670 4709; Lynda Harper Phone: + 44 20 7670 4791). The randomized PENPACT 1 study with participation both of the PENTA and the PACTG group has answered the question
of whether initial therapy in children is more effective with 2 NRTI+PI or with 2 NRTI+NNRTI (n=263). There was no significant difference concerning viral load reduction over the observation period of five years (Babiker 2011). LPV/r based regimens may be more effective than nevirapine-based regimens in children who received nevirapine as “single dose” transmission prophylaxis (common in African countries) (Palumbo 2010).

Table 4: Treatment in HIV-infected children

<table>
<thead>
<tr>
<th>Regime</th>
<th>Recommendation</th>
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<tr>
<td>2 NRTIs* + PI** or 2 NRTIs +NNRTI***</td>
<td>Include children in multicenter clinical trials</td>
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* AZT, ddl, 3TC, d4T, abacavir, FTC, tenofovir. Preferred combination: ABC+3TC, which has superior long-term efficacy to AZT+3TC and can be given QD to children over 3 years, and to younger children once viral suppression is achieved (PENTA 13 and PENTA 15; http://www.pentatrials.org/)

** Preferred PI: lopinavir/r. For teenagers, atazanavir/r may be preferable because it has the advantage of QD dosing. Unboosted PIs are no longer recommended. Atazanavir/r, fosamprenavir/r, darunavir/r and saquinavir/r have comparable efficacy with lopinavir/r in adults. Fosamprenavir/r is licensed for children from age 6 in Europe. Atazanavir/r and darunavir/r have pediatric licenses in the US, and may be licensed for children in Europe in 2009.

*** Preferred NNRTI: Efavirenz age ≥ 3 years, nevirapine in combination with 2 NRTIs at an age < 3 years.

Classes of antiretrovirals

The different antiretroviral classes that are currently used in children are outlined with emphasis on pediatric issues. All drugs can lead to nausea, vomiting, fever, headache, diarrhea, rash and anorexia. There is significant hyperlipidemia in a number of children and its long term consequences are unknown (Jacobson 2011). Some investigators found a high rate of coronary artery abnormalities in adolescents and young adults with long term ART exposure (Mikhail 2011). As with adults, dyslipidemia is associated with the use of PIs (Lainka 2002). This includes elevated total cholesterol, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c) and decreases in high density lipoprotein cholesterol (HDL-c). In lipodystrophy, there is a loss of subcutaneous fat (lipoatrophy) and/or a deposition of fat tissue subcutaneously or in visceral stores (lipohypertrophy). The exact prevalence of lipodystrophy in children is unknown and there are no clear diagnostic criteria. Lipodystrophy and dyslipidemia coexist, and their interconnection is unclear. Other classes such as NRTIs (e.g., d4T) and NNRTIs (efavirenz, not nevirapine) also play a role in the pathogenesis of lipodystrophy. Insulin resistance is another side effect that may present with or without fasting hyperglycemia, with new onset diabetes mellitus and exacerbations of pre-existing diabetes (Bitnun 2005). Moreover, PIs may influence bone mineral density and metabolism (Mora 2004). Taken together, the long-term consequences of PI-containing ART for growth and development of the child are currently not known. In the Swiss cohort, children exposed to PIs over a period of more than 10 years did not experience any major side effects (Rudin 2008).

NRTIs

The combination of 2 NRTIs as part of ART is effective and well-tolerated. Severe side effects are rare but potentially life-threatening, such as lactic acidosis and hepatic steatosis. Other side effects are neuromuscular dysfunction, cardiomyopathy, pancytopenia, pancreatitis and neuropathy. All of these effects are probably related to mitochondrial toxicity caused by NRTIs. Due to pharmacologic and antiviral antag-
onism as well as synergistic neurotoxicity, the following combinations are not recommended: AZT+d4T, ddI+TDF and FTC+3TC. The prevalence of lipoatrophy in children is unknown, as diagnostic criteria are not established. Whenever possible, d4T should be replaced by ABC or TDF.

Zidovudine (ZDV, AZT, Retrovir®) is available as syrup, capsules, tablets and concentrate for injection or intravenous infusion. Dosage is 180 mg/m² orally every 12 hours. Maximum dosage is 300 mg every 12 hours.

Lamivudine (3TC, Epivir®) is available as oral solution and tablets. Dosage is 4 mg/kg every 12 hours, or 8 mg/kg every 24 hours; maximum dosage is 150 mg every 12 hours or 300 mg every 24 hours. In older children and adolescents (>35 kg body weight) combination with AZT (Combivir®) or abacavir (Kivexa®/Epzicom®) can be used and daily pill burden reduced. In adults, 3TC has antiviral activity against hepatitis B virus (HBV). In HIV-negative children with chronic hepatitis B early initiation of 3TC appears to achieve a high HBe and HBs conversion rate (Choe 2007). There are no data in HBV-coinfected children, and there is concern that using 3TC as the only drug active against HBV in dually infected children may select for 3TC-resistant HBV. In the PENTA 15 study the pharmacokinetics, feasibility and acceptability of dosing ABC or ABC+3TC QD in children aged 3 months to <36 months was studied. The AUC for QD dosing of both ABC and 3TC was bioequivalent to BID.

Didanosine (ddl, Videx®) is available as oral solution and tablets. Dosage is 200 mg/m² once daily. Maximum dosage is 400 mg (body weight >60 kg) or 250 mg (body weight <60 kg). DdI is not recommended for use in combination with tenofovir. Powder for oral solution is reconstituted with water and Mylanta Extra Strength or MaaloxPlus antacid suspensions. It should be taken on an empty stomach (2 hours after and 1 hour before food or milk). Caps can be opened and sprinkled on a spoonful of food, e.g., yogurt, but there is a decrease in AUC (see Packet Information). ddl is not recommended for first-line therapy.

Abacavir (ABC, Ziagen®) is available as oral solution and tablets. Dosage is 8 mg/kg every 12 hours, or 16 mg/kg every 24 hours, maximum dosage is 300 mg twice daily or 600 mg once daily. A once-daily regimen in combination with 3TC has been shown to be as effective as twice daily (see PENTA 15 Trial above). In the PENTA 5 trial, the NRTI backbone of ABC+3TC showed better efficacy regarding viral load suppression than AZT+ABC and AZT+3TC. There is a potential risk of a hypersensitivity reaction (HSR). If ABC HSR occurs and the drug is stopped, it should never be restarted as, rarely, deaths have occurred in adults upon rechallenge. HLA B*5701 is associated with HSR, and should be tested for before prescribing ABC. An alternative NRTI can be used in HLA B*5701 positive children.

Emtricitabine (FTC, Emtriva®) is available as capsules and oral solution. Dosage is 6 mg/kg once daily. The administration of capsules results in a 20% higher plasma level. Maximum dosage is 200 mg QD, reduction in dosage is necessary in patients with renal impairment. There are no controlled trials regarding the efficacy in children.

Tenofovir (TDF, Viread®) is currently only available as tablets (300 mg). Dosage in children is 8 mg/kg once-daily; >8 yrs of age: 210 mg/m² once-daily. Maximum dose is 300 mg once-daily. It should be taken with meals. There are no controlled trials on the efficacy of tenofovir in children. Tenofovir has been shown to have metabolic renal and bone side effects that may be significant for children and should be monitored closely. Tenofovir is also effective for treatment against HBV. In HBV-coinfected children who require treatment for HIV, a backbone of TDF+FTC (Truvada®) should be considered as this will be effective against both viruses.
Stavudine (d4T, Zerit®) is available as oral solution and capsules. Dosage is 1 mg/kg every 12 hours. Maximum dosage is 40 mg every 12 hours. It should be taken on an empty stomach. d4T is not recommended for first-line therapy as it has a high risk of causing lipoatrophy.

NNRTIs

NNRTIs have a low genetic barrier to resistance. Suboptimal dosing or adherence can lead to cross-class resistance mutations within a few weeks, affecting all available NNRTIs. NNRTIs exist in palatable liquid preparations that are easier for children to tolerate than the liquid PI solutions. It has to be kept in mind that single dose nevirapine exposure as part of the perinatal transmission prophylaxis may affect subsequent treatment response, if NNRTIs are used in an initial regimen for infants (Lockman 2007).

Efavirenz (EFV, Sustiva®, Stocrin®) is available as capsules, tablets and oral solution. Dosage for capsules and tablets is 200 mg (body weight 10–15 kg), 250 mg (15–20 kg), 300 mg (20–25 kg), 350 mg (25–33 kg), 400 mg (33–40 kg), 600 mg (>40 kg) once daily. Maximum dosage is 600 mg once daily. It should be taken on an empty stomach. High fat meals should be avoided. When using the solution, a 20% higher dosage than for capsules or tablets is necessary. Upon standard dosage EFV serum levels vary considerably in African children due to polymorphisms in the CYP2B6 drug metabolizing enzyme (Fillikes, 2011). Central nervous system symptoms (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, lack of concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) appear to be more common in adults than in children. Skin rash is observed in <10%. It is rarely severe and usually disappears within days despite continuation of efavirenz. Efavirenz may cause raised lipids in some patients.

Nevirapine (NVP, Viramune®) is available as tablets and suspension. Dosage is 150 mg/m² once daily for 14 days, followed by 150 mg/m² every 12 hours, if liver function tests are normal. In a retrospective analysis, once-daily application – 300 mg/m² after week 2 – was as effective as twice-daily (Verweel 2003). The most common side effect of NVP is a skin rash. It occurs in up to 16% of children during the first weeks of treatment, may be quite severe (8%) and require hospitalization. Life-threatening complications (Stevens-Johnson Syndrome, toxic epidermal necrolysis) are rare. Hepatotoxicity may also occur, and fatal cases have been reported in adults, but this appears to be less common in children.

Etravirine (ETV, Intelence®) is available as 100 mg tablets and 25 mg tablets through compassionate use. The tablets are dispersed in water. ETR is taken with food. The AUC is decreased by 50% if it is taken on an empty stomach. Dosage is 5.2 mg/kg in children (currently under investigation), versus in adults at 200 mg BID. Side effects are pruritis and rash. The rash usually resolves in 1–2 weeks. Etravirine may be effective against HIV with some NNRTI resistance mutations, but is not used broadly due to the lack of a pediatric formulation, lack of pediatric pharmacokinetic data, lack of efficacy or safety data in children, and lack of data in antiretroviral-naïve patients.

PIs

All PIs can be used in combination with 2 NRTIs. PIs differ from each other in respect to their tolerability and side effects. All PIs should be boosted with ritonavir, which increases plasma concentrations of the therapeutic PI.
Lopinavir/r (LPV/r, Kaletra®) is a co-formulation of lopinavir and ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster). It is available as 200 mg LPV/50mg RTV tablets or 100 mg LPV/25mg RTV tablets or 133.3 mg LPV/33.3mg RTV capsules in some countries. There is a liquid preparation with an unpleasant taste (5ml = 400mg LPV/100mg RTV), which has to be kept in the fridge. In therapy-naive and -experienced children, the combination of LPV/r and NRTI or NNRTI shows a high efficacy (Saez-Llorens 2003, Fraaij 2004). The dosage in neonates/infants (14 days–6 months) is 300 mg/m² BID; in older children 230–300mg/m² (most centers use the higher dose) or 13 mg/kg lopinavir/3.25 mg/kg ritonavir twice daily (body-weight 7<15 kg), 11 mg/2.75 mg (15–50 kg), 533 mg/133 mg (>50 kg). It should be taken with meals. The dosage of LPV/r may need to be increased by up to 30% when combined with an NNRTI. Therapeutic drug monitoring is useful in this situation. Cautious use is advised in patients with hepatic insufficiency.

Fosamprenavir (FPV, Telzir®) is available as 700 mg tablets and 50 mg/ml liquid. Liquid is given with or after food to aid palatability. Tablets are taken without food. Dosage in a child is 30 mg/kg BID (2–5 years); >6 years (25–32 kg) is 18mg/kg BID with ritonavir 3mg/kg BID; in the weight range 33–38 kg, 18 mg/kg BID with 100 mg ritonavir BID with food; >39 kg: 700 mg fosamprenavir BID with 100 mg ritonavir BID. Maximum dose is 700 mg BID. Preliminary long-term study results (> 180 weeks) show a good reduction of viral load (Palladino 2010).

Ritonavir (RTV, Norvir®) is available as oral solution or capsules. Most children do not tolerate the taste of the oral solution. The dosage is 350–400 mg/m² every 12 hours, maximum dosage 600 mg every 12 hours. It should be taken with meals. Today, ritonavir should be exclusively used as a booster for other PIs. The dosage of this depends on whether the coadministered PI is given once or twice daily. A new tablet formulation of ritonavir has recently been approved by FDA (Meltrex®), and should be better tolerated than the capsule and not require refrigeration.

Saquinavir (SQV, Invirase®) is available as tablets. Dosage in children is unknown. There is very limited experience with 50 mg/kg every 12 hours. Saquinavir should only be used in combination with ritonavir because of poor bioavailability. It should be taken with meals.

Atazanavir (ATV, Reyataz®) is available as capsules. It should be taken with meals. Omeprazole and all other PPIs are contraindicated. Avoid indigestion remedies. ATV is interesting in children because of its once-daily application and lower incidence of dyslipidemia. Dosage for children is (15–25kg) 150 mg QD with RTV 80 mg QD; (25–32kg) 200 mg QD with RTV 100 mg QD; (32–39kg) 250 mg QD with RTV 100 mg QD; (>39 kg) 300 mg QD with RTV 100 mg QD. Some patients develop jaundice. Better levels of ATV are obtained with ritonavir boosting. Unboosted ATV is given at a dosage of 520 mg/m² (2–13 years) or 620 mg/m² (13–21 years). In children of ≤2 years of age, PK data were very variable (Kiser 2011).

Tipranavir (TPV, Aptivus®) is available as 250 mg soft gel capsules given with or after food. Dosage from 2 yrs on is 14mg/kg BID with RTV 6mg/kg BID or 375mg/m² BID with RTV 150mg/m² BID. In pre-treated children and adolescents a reduction of the viral load of 35% below 50 copies/ml has been achieved after 12 months (Salazar 2008). It has been associated with significant hepatotoxicity in adults. There are interactions with ABC and AZT leading to reduced TPV levels.

Darunavir (DRV, TMC114, Prezista®) is available as 75 mg, 300 mg, 400 mg and 600mg given with or after food. A liquid formulation is under investigation. Dosage in a child >6 years (20–30 kg) is 375 mg darunavir BID plus 50 mg ritonavir BID; in children 30–40 kg dosage is 450 mg darunavir BID plus 60 mg ritonavir BID; >40kg
it is 600 mg darunavir BID plus 100 mg ritonavir BID. In pre-treated children and adolescents darunavir/r achieves a reduction of viral load of 48% below 50 copies/ml in 12 months (Blanche 2009).

**Entry and integrase inhibitors**

*Enfuvirtide (T-20, Fuzeon®)* can be used in children older than 6 years of age. The drug is injected subcutaneously at a dosage of 2 mg/kg every 12 hours. A study with 14 children showed no severe side effects, but after a two-year treatment duration only 6 of 14 children stayed on this therapy (Church 2004). Reasons for treatment discontinuations were aversion to injections, local injection site reactions, inefficient viral load suppression, thrombocytopenia and edema. There are no controlled studies on the use of T-20 in children.

*Maraviroc (MVC, Celsentri®)* is available as 150 and 300 mg tablets. In adult patients, efficacy and safety have been proven. A tropism test is required prior to the use of CCR5 antagonists. There are no data on the use of maraviroc in children.

*Raltegravir (RAL, Isentress®)* is available as 400 mg tablets. Preliminary data of an open-label study with a chewable tablet at 2 x 6mg/kg/day show RAL to be well tolerated and safe (Nachman 2010). Long-term data on safety, pharmacokinetics and effectiveness are not available; a clinical trial is underway.

**Drug interactions**

There are a great number of interactions that may complicate antiretroviral therapy when it is co-administered with other drugs. In particular, tuberculosis and atypical mycobacterial treatment may interact with ART so close monitoring and expert advice should be sought.

**Monitoring efficacy and watching out for failure**

Not all children achieve complete viral suppression, and development of resistance is not uncommon due to the selection pressure of the HIV immune response to the suboptimal antiretroviral therapy. There is no commonly used definition of treatment failure in children treated with antiretroviral drugs. Therefore, it is also not well-defined when to change antiretroviral therapy. In the PENPACT 1 study, this important question is being addressed. Children are randomized to change a failing treatment at either low or high viral rebound (>1000 or >30,000 copies/ml). Alternatively, therapy failure can be defined by a decrease in CD4 T cell counts, e.g., a decrease by at least a third of the absolute CD4 cell number in less than 6 months. In children with relatively low CD4 T cell percentage (of less than 15%), a decrease of more than 5% may be significant enough to consider therapy failure. The use of clinical criteria such as toxicity of the drugs, progression within the CDC classification, an increased susceptibility to infections, encephalopathy and failure to thrive may all indicate treatment failure.

Many children with multi-disciplinary support and modern drug regimens now manage to maintain long-term (>5 years) viral suppression on first-line therapy, and the longer this can be maintained the better. Indeed over the last few years as more treatments have become available for children they have shown increasing success with treatment. The most common cause of treatment failure is insufficient adherence, which is found in up to 25–30% of children. Assessment of adherence may be
difficult as questionnaires may not be reliable. Determination of plasma levels and resistance tests (e.g., recurrence of wild type) are other options to assess adherence and monitor antiretroviral therapy more effectively.

Change of therapy

The PENPACT 1-Study (see above) investigated whether to switch to second-line ART at a viral load of 1,000 copies/ml versus 30,000 copies/ml (Babiker 2011). Interestingly, delayed switching at 30,000 was not associated with an inferior outcome. The suppression of viral load that can be reached on a second or third regimen depends on the preceding therapy, resistance status and ongoing adherence. The longer and more intensive treatment is, the lower the viral load reduction to be expected. When a new antiretroviral drug combination is introduced, the age of the child, the availability of appropriate formulations (e.g., solution for infants), side effects and interactions with other drugs all need to be taken into account. At present it is unclear whether dyslipidemia and lipodystrophy can be significantly influenced by a change from a PI-containing regimen to an NNRTI-containing one. In adults, randomized and prospective trials have shown that a change of antiretroviral therapy guided by resistance tests leads to better treatment response. In children there is a smaller prospective study (Englund 2004). Usually, the initial treatment regimen contains a double NRTI backbone (e.g., AZT+3TC or ABC+3TC). When changing therapy, it appears useful to introduce a backbone with two new NRTIs + a new class. A mega-ART therapy combining five to six antiretroviral drugs has not been systematically investigated in children. In single cases, it may be useful to introduce up to five drugs if treatment failure has occurred despite multiple drug regimens.

Supportive therapy and prophylaxis

OIs have become rare in perinatally infected children who experience immune reconstitution with ART. In most of these children respiratory and other infections are not much more common than in healthy children. The incidence of invasive pneumococcal disease among perinatally HIV-infected children has decreased since the introduction of HAART (Steenhoff 2008). HIV-infected children who are treated with ART and who are clinically stable can even be given live varicella virus vaccine and show a specific response, which is an impressive sign of successful immune reconstitution (Taweesith 2011). In the vast majority of stable treated children treatment with IV immunoglobulins and PCP prophylaxis is no longer required (Nachman 2005b). However, there are still life-threatening infections and deaths from HIV if perinatal HIV infection is unrecognized or ART has not led to immune reconstitution. A description of such infections in adults is given in other chapters of this book. An excellent and detailed guide for treatment of children with OIs can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5811a1.htm

Conclusion

In many aspects HIV infection in children is different from HIV infection in adults. The ongoing growth and development of children, their viral dynamics and immaturity of the immune system result in a different response to HIV compared to adults. This has important consequences for diagnosis and treatment of HIV in children. The aim of therapy is to achieve maximum efficacy while avoiding long-term side effects. Sustained success in the treatment of children with HIV infection depends on:
• a multidisciplinary approach;
• standardized treatment protocols;
• participation in multicenter trials;
• development of new drugs, appropriate formulations and treatment strategies for children.

In developed countries the clinical picture of HIV infection in children has now changed from an often fatal to a treatable chronic infection. This picture is entirely different in developing countries, where the majority of children do not have access to ART (Prendergast 2007). In the year 2006 according to WHO 380,000 children died from HIV infection or its sequelae, a disease that can be treated and more importantly prevented.

References


PART 5

Special Issues
19. HIV and HBV/HCV Coinfections

JAN-CHRISTIAN WASMUTH AND JÜRGEN ROCKSTROH

HIV and HCV Coinfection
Epidemiology and Transmission

Coinfection with HIV and HCV occurs frequently, due to the fact that they are transmitted via the same pathways (parenteral, sexual, vertical). In the US about 25% of HIV-infected individuals are estimated to be infected with both viruses. Several European countries have even higher rates of coinfection (Rockstroh 2005). In Russia, about 70% of the 940,000 HIV-infected patients are also HCV-positive as a result of the high incidence of IV drug users. Needle exchange programs have resulted in a marked decline in new infections of HCV in Western Europe. For example, in Barcelona the prevalence of HCV coinfection in persons with newly diagnosed HIV-infection has decreased from 24% during 2000–2002 to 10% in the years 2006–2008 (Trevino 2009).

As HCV is ten times more infectious than HIV via blood-to-blood contact, intravenous drug users and recipients of blood products are particularly susceptible to coinfection. Nevertheless, the probability of transmission from occupational needle-stick injuries after exposure to HCV contaminated blood is less than 2%, possibly even lower; i.e. 0.3% as after exposure to HIV-contaminated blood (Kubitschke 2007). In contrast, sexual transmission of HCV occurs significantly less frequently than HBV or HIV (risk of transmission via heterosexual intercourse is <1%). About 4–8% of all HIV-infected men who have sex with men are also infected with HCV. Clusters of cases of acute hepatitis C among homosexual HIV-infected men have been observed in London, Paris, Amsterdam, Berlin, and also in the United States, Australia and Taiwan. The risk of transmission depends on concomitant sexually transmitted diseases such as syphilis or lymphogranuloma venereum, performance of sexual practices that are prone to injuries of the mucosal membranes like fisting or intensive repetitive anal sex, and snorting drugs (Vogel 2005). Perinatal transmission of hepatitis C is rare in immunocompetent individuals (<1%). The transmission rate rises with increasing immunosuppression in HIV-infected mothers, and is estimated to be as high as 20%. On the other hand, HIV-infected mothers treated effectively with antiretroviral therapy do not appear to have an increased risk for materno-fetal transmission of the hepatitis C virus (<3% with cesarean section) (Pembrey 2005). Cesarean section did not reduce the risk of transmission to the newborn HCV monoinfected patients putting the role of cesarean section into question (Indolfi 2009).

Clinical course and pathogenesis

Course of hepatitis C in HIV/HCV-coinfected patients

The clinical course of hepatitis C and HIV coinfection is determined by HIV-associated immunosuppression. Progression of immunosuppression accelerates the course of hepatitis C. The latent period until development of liver failure or hepatocellular carcinoma in coinfected patients is estimated to be 10–20 years, whereas it is 30–40 years in HCV-monoinfected patients (Benhamou 1999). Improved treatment options for HIV infection have increased the likelihood of patients actually living to experience the development of liver failure. In some centers, liver failure is now the most frequent cause of death in HIV-infected patients (Rosenthal 2007). Conversely, there
is no significant influence of hepatitis C on the course of HIV infection (Rockstroh 2005). Antiretroviral therapy can improve the unfavorable course of hepatitis C and delay the development of liver failure. This is particularly true for patients who achieve good immune recovery (Pineda 2007). Therefore, early initiation of ART (CD4 <500/µl) is recommended in HCV-coinfected patients (EACS 2011).

On the other hand, hepatitis C infection can aggravate the potential hepatotoxicity of ART regimens. Up to 10% of patients have to discontinue ART due to severe hepatotoxicity. This risk is associated especially with the so-called “d drugs” (ddI, d4T). These agents should be avoided in coinfected patients. Nevirapine and tipranavir should be used with caution.

In some coinfected patients, a temporary increase in transaminases is observed after initiation of ART. This most likely corresponds to an increased inflammatory activity of hepatitis C as a result of improved immune status. Nevertheless, long-term follow-up has shown that ART improves the course of hepatitis C. Indications for ART, according to current treatment guidelines, should be carefully checked in all coinfected patients (Rockstroh 2009).

**Diagnosis**

Diagnostic tests used in coinfected patients are no different from those used in patients with HCV monoinfection (see Table 1). Detection of HCV antibodies (anti-HCV) confirms exposure to HCV, but does not distinguish between resolved and chronic hepatitis C. Chronic hepatitis C is diagnosed by the detection of HCV viremia (i.e., HCV RNA). It should be noted that HCV antibodies might be lost during the course of HIV infection as a result of the underlying immunosuppression, although nowadays this phenomenon has become rare, probably due to improved test kits. It may therefore be useful to determine HCV RNA levels, even if the anti-HCV test is negative, if there is clinical suspicion or advanced immunodeficiency (it can occur in patients undergoing chemotherapy also). Similarly, determination of HCV RNA levels is indicated in cases of suspected acute (primary) HCV infection, as HCV antibodies usually only become detectable one to five months after infection. HCV-specific antibodies were still lacking in 37% of patients 3 months after first detecting HCV RNA (Thomson 2009).

Patients with HIV/HCV co-infection have significantly higher levels of HCV viremia than patients with HCV monoinfection (about 1 log). Based on current knowledge the level of viremia does not have a prognostic value for the course of hepatitis C. Regular testing of HCV RNA as a routine clinical procedure is not necessary. However, it should be noted that some patients might lose HCV RNA in parallel with progression of immune deficiency, but experience a flare up of hepatitis C together with clinical symptoms following immune reconstitution while on ART (Kim 2006). Therefore, regular testing around the initiation of ART seems prudent.

It is possible to predict a response to treatment from the level of the HCV viremia: if the concentration of HCV RNA is below 400,000 – 500,000 IU/ml, the probability of treatment success is significantly higher than at levels above 400,000 IU/ml (400,000 IU/ml equals about 1 million copies/ml; depending on the test used the conversion factor varies from 1 to 5).

When considering the treatment of hepatitis C, genotyping is necessary before starting. Six genotypes with numerous subtypes are known, and are seen to have different regional distributions: genotypes 1 and 3 are predominantly found in Europe, whereas genotypes 4 and 5 are found in Africa, and genotype 6 in Asia. Genotypes 2 and 3 in particular are associated with significantly better responses to interferon therapy. Co-infection with several genotypes is possible.
Another marker associated with response to treatment is determination of IL28B genotype. This is a T/C dimorphism close to a region coding for human interleukin 28B. Likelihood of treatment response is about twofold higher upon existence of IL28B-CC genotype than with the TT variant (Nattermann 2011). Spontaneous clearance in case of acute infection is better in CC genotype patients as well.

Assessment of liver fibrosis is very important to guide treatment indication. Among several non-invasive methods available the Fibroscan® device is of special interest. This device measures liver stiffness directly correlated to the degree of fibrosis with a special technique (transient elastography). The role of the liver biopsy has to be newly defined: if a liver biopsy is not an option, current consensus recommendations suggest treatment of hepatitis in case of genotypes 2+3, or genotype 1 and low HCV viremia. If a liver biopsy has been performed that shows no significant fibrosis, immediate treatment is usually not required regardless of the underlying genotype. There are several histological classifications used. In Europe the METAVIR score is most often used. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = some septa, 3 = significant septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2-F4; it may be deferred for grades F0+F1 (see below). As fibrosis progression is accelerated in HIV-infected patients, monitoring of fibrosis in yearly intervals seems prudent. An increase of 2 or more stages in liver fibrosis after only 3 years was observed in 25% of all coinfected patients in one study (Sulkowski 2007).

If there is clinical suspicion requiring the detection or exclusion of extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia), appropriate investigations may be necessary (skin biopsy, urine tests, kidney biopsy, detection of serum cryoglobulins).

The recommendations for autoantibody testing to exclude autoimmune disease vary and test results are difficult to interpret: up to 60% of all patients with hepatitis C have autoantibodies such as ANA, RF, antecardiolipin, SMA, and LKM1 antibodies as an accompanying autoimmune phenomenon without any clinical relevance. If the titers of these autoantibodies increase or appear for the first time during interferon therapy, treatment does not usually have to be discontinued, so the need for routine testing of autoantibodies is arguable. In order to exclude autoimmune hepatitis, however, ANA, SMA, ANCA, and LKM1 antibodies should be determined before interferon therapy is initiated. Patients with positive results should be monitored closely for deterioration of liver function on interferon therapy as a sign of active autoimmune hepatitis. If liver function worsens, interferon should be discontinued. The need for immunosuppressive therapy can only be decided on a case-by-case basis.

Before treatment with interferon, TSH levels should always be determined to exclude thyroid disease. With normal thyroid function, it is sufficient to monitor TSH at quarterly intervals. In cases of hypothyroidism, substitution with levothyroxine is recommended, and thyreostatic treatment is similarly recommended for hyperthyroidism before initiation of interferon therapy. After adequate treatment, interferon therapy can usually be administered with close monitoring of TSH (every 4 weeks). Approximately 5% of patients develop thyroid dysfunction on interferon therapy. This generally manifests within the first 3 months of treatment. If hypothyroidism is induced, interferon therapy can usually be continued in combination with substituted levothyroxine. The first manifestation of hyperthyroidism is enough for most practitioners to discontinue treatment, although it may be possible to continue interferon therapy in certain cases. In the majority of patients, thyroid dysfunction
resolves after discontinuation of interferon. However, if it does persist, cases need to be considered individually.

Up to 12% of patients with hepatitis C have thyroid autoantibodies before treatment with interferon (antibodies against thyroid peroxidase = anti-TPO, anti-thyroglobulin antibodies and TSH receptor antibodies). In the setting of HIV/HCV-coinfection an even higher prevalence of up to 30% has been observed (Woitas 2005). In these patients, the risk of deterioration in thyroid function on interferon is significantly higher than in patients without these antibodies. If possible, autoantibodies should be determined in all patients before beginning treatment, but at the very least in those patients with abnormal TSH levels, in order to have a baseline value to allow subsequent monitoring.

If treatment is deferred alpha-fetoprotein (AFP) and sonography of the liver should be performed every 6–12 months in order to detect hepatocellular carcinoma (HCC). This is particularly relevant for patients with F3/F4 fibrosis. As the course is accelerated in HIV-coinfected patients and 10–30% of patients will develop HCC without preexisting cirrhosis, screening at regular intervals should be considered for patients with less advanced liver disease. Some experts recommend even shorter intervals that are not yet feasible in most circumstances.

Table 1: Diagnostic procedures for hepatitis C in HIV-coinfected patients (Rockstroh 2008).

<table>
<thead>
<tr>
<th>Diagnosis of hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Ab (positive 1–5 months after infection, may rarely be lost with immunosuppression)</td>
</tr>
<tr>
<td>HCV RNA levels (while not prognostic for progression, it is important for evaluating the possible response to treatment; see above)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment of liver status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading of fibrosis (e.g., Fibroscan, liver biopsy, serum markers)</td>
</tr>
<tr>
<td>Hepatic synthetic function (e.g., coagulation, protein, albumin, CHE)</td>
</tr>
<tr>
<td>Ultrasound and AFP every 6 months in cirrhotics</td>
</tr>
<tr>
<td>Gastroscopy upon diagnosis of cirrhosis (every 1–2 years thereafter)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype and serum HCV RNA</td>
</tr>
<tr>
<td>IL28B genotype</td>
</tr>
<tr>
<td>Auto-antibodies (ANA and LKM1)</td>
</tr>
<tr>
<td>TSH, thyroid autoantibodies if applicable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential blood count and liver enzymes every 2–4 weeks</td>
</tr>
<tr>
<td>HCV RNA at week 4 (to evaluate rapid virological response) at wks 12, 24, 48, (72 if applicable) and 24 weeks after stopping HCV therapy</td>
</tr>
<tr>
<td>CD4 T cell count every 12 weeks</td>
</tr>
<tr>
<td>TSH every 12 weeks</td>
</tr>
</tbody>
</table>

**Therapy**

**Treatment of acute hepatitis C**

Increasing numbers of acute hepatitis C have been observed in MSM. Mainly patients with high-risk sexual contacts are affected (such as unprotected anal intercourse, use of insertive sex toys, fisting). Diagnosis of acute hepatitis C is made according to anamnesis, elevated liver enzymes (usually 5fold-rise above the upper limit of normal; ideally to be documented as normal previously) and positive HCV RNA. HCV antibodies will be negative in many instances due to the long latency of the antibody
response. Infection may possibly be missed, as it will be asymptomatic in about one half up to 2/3 of patients. 

Up to 20% of patients with acute hepatitis C clear the virus spontaneously (up to 40% in HCV-monoinfection). Factors such as IL28B CC genotype, female sex, sexual transmission (vs. iv-drug abuse), or symptomatic course have been associated with a higher likelihood of clearance. However, exact impact of most factors has not been determined so far.

With early treatment response rates of about 70% (80% in genotype 2/3) can be achieved. These rates are higher compared to delayed treatment in chronic hepatitis C (Vogel 2005). Therefore, treatment should be initiated during the acute phase of infection. Treatment should be offered, when spontaneous clearance is unlikely (NEAT 2010):

- 4 weeks after identification of acute hepatitis C HCV RNA is monitored. If there is less than a 2 log reduction, treatment should be initiated. In case of more than a 2 log reduction further monitoring is advisable.
- If HCV RNA is detectable at week 12, it is unlikely that viral clearance will occur, and initiation of treatment should be considered.
- All genotypes should be treated with PEG-interferon plus weight-adapted ribavirin. Dose is chosen as for chronic hepatitis C. According to current consensus duration of treatment is adapted individually with respect to viral response (NEAT 2010):
  - If the viral load is negative at week 4, a treatment duration of 24 weeks seems to be sufficient.
  - If this goal is not reached, duration should be 48 weeks.
  - If the viral load has not decreased more than 2 log after 12 weeks, treatment can be stopped.

However, the optimal strategy is still unclear. If possible, patients should be treated within prospective clinical studies.

**Treatment of chronic hepatitis C**

The most important reasons for initiating HCV treatment are an unfavorable course of hepatitis C with HIV coinfection, improving life expectancy for HIV infection, increasing liver-related mortality, and increased risk of hepatotoxicity. Indeed, successful treatment of hepatitis C translates into better overall survival (Berenguer 2009). The goal of hepatitis C treatment is to achieve permanently negative HCV RNA levels. This is generally referred to as a “sustained virological response” (SVR). It is defined as a negative HCV RNA six months after completion of treatment. Negative HCV RNA at the end of the treatment period is described as “end of treatment response” (ETR). If transaminases have normalized, this is referred to as a biochemical response. However, the latter does not correlate with the further clinical course of hepatitis C. Failure to respond to treatment is referred to as a non-response. In the following text, response rates always refer to sustained responses. Only sustained responses have been clearly associated with resolution of liver fibrosis and extrahepatic manifestations, as well as with the prevention of further transmission. When HCV RNA becomes detectable again after having been negative, it is referred to as a relapse. The probability of a relapse is highest within the first months following completion of treatment and decreases steadily afterwards. Therefore, the success of therapy is usually determined and evaluated six months after the end of treatment.
**New options – the future has arrived**

The combination of pegylated interferon with ribavirin has been regarded as standard therapy for all genotypes in coinfected patients for the last decade. A sustained response can be achieved in about 50% of patients (Torriani 2004, Nuñez 2007). Genotypes 2 and 3 can be treated more effectively (about 80%) than genotypes 1 and 4 (about 35%).

Approval of first HCV-specific oral direct acting antivirals boceprevir and telaprevir in 2011 has improved treatment options for HCV monoinfected patients considerably (about 30% higher response rates). For HIV coinfection only data of small pilot studies are available so far. However, response rates were found to be raised to the same extent as in monoinfected patients.

Numerous studies with other specific HCV substances are underway. These substances are characterized by improved intake (QD instead of TID), tolerability (main problem: rash and anemia) and efficacy (main problem: rapid selection of resistant viral strains). HCV-treatment will be more personalized (and sophisticated) in the near future. In return, duration of treatment will be shorter (so far at least 48 weeks for genotype 1). In addition, interferon-free combinations and substances for non-1-genotypes are likely to become available within the next years.

At the moment current data on boceprevir and telaprevir (both protease inhibitors) can be summarized as follows:

- Both substances are very potent. Combined with PEG-IFN and ribavirin, high SVR rates are reached in both naïve (80%) as well as in pre-treated patients (50%).
- HCV is highly replicative. Monotherapy selects resistance within few days, eventually even hours. Therefore, combination of both PIs with interferon and ribavirin will remain the standard care for the next months.
- Both substances are active against genotype 1 only.
- Administration differs between individuals in HCV-monoinfected patients (e.g. “lead in” phase for boceprevir, but not telaprevir; variable duration of treatment according to treatment response).
- Optimal duration of treatment is not finally defined. It is anticipated that 24 weeks will be sufficient in most patients (even shorter in individual patients with very rapid response), whereas longer periods most likely do not add any benefit.
- Both substances may have distinct adverse events (e.g., rash with telaprevir; anemia with both substances). These add to toxicity of interferon and ribavirin.

With respect to HIV/HCV patients following aspects have to be considered at this time:

- Currently data from clinical trials are still very limited. Therefore, treatment should be performed within clinical trials if feasible.

Telaprevir:
- Telaprevir can be added to standard combination therapy for 12 weeks (750 mg every 8 hours).
- With low HCV viral load (HCV RNA < 1000 IU/ml at weeks 4 and 12; < 20 IU/ml at week 24), interferon+ribavirin is continued till week 48.
- Telaprevir can be combined with raltegravir, boosted atazanavir, rilpivirine, etravirine and efavirenz (adapt dose to 1,125 mg every 8 hours). Other PIs or NNRTIs should not be combined, whereas NRTIs have no clinically relevant interactions.

Boceprevir:
- Treatment begins with a lead-in phase of 4 weeks interferon+ribavirin.
- In case of >2 log reduction of HCV RNA, boceprevir can be added.
- Subsequent treatment duration is guided by treatment response. However, exact recommendations are lacking at the moment.
- Boceprevir should not be combined with ritonavir boosted protease inhibitors, as levels of HIV PIs or telaprevir levels can decline substantially.

Figure 1 shows a possible approach when new substances are used. This is derived from HCV-monoinfection as data are sparse for the setting of coinfection.

**Pegylated Interferon + Ribavirin – standard of care for non-1 GT**

Standard treatment for non-1 genotypes is a combination of pegylated interferon and ribavirin. In general, treatment duration is 48 weeks. This should be prolonged in patients with genotypes 1 and 4 if the viral response is delayed (HCV RNA detectable at week 4) (Nuñez 2007). If the viral load is undetectable by week 4, shorter treatment periods may be possible (at least in genotypes 2 and 3). Liver transplantation may be an option for patients who have cirrhosis and cannot be treated with interferon therapy.

Concerns that interferon treatment could have a negative effect on HIV infection have never been confirmed. In fact, detectable HIV viremia will be significantly suppressed in the majority of patients as a result of the antiviral effect of interferon. Absolute CD4 T cell counts may drop slightly due to temporary leukopenia, but percentage values usually remain stable or rise. No treatment study to date has shown a significant deterioration of HIV infection (Soriano 2007).

Treatment options remain inadequate for patients with a non-response or relapse. In patients treated previously with interferon monotherapy, an attempt can be made to use a combination of PEG-IFN and ribavirin. There are currently no standard recommendations for treatment of patients after failed PEG-IFN therapy. HCV-specific protease inhibitors and polymerase inhibitors will add new options for these patients also.

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**Figure 1: Possible algorithms for the use of telaprevir and boceprevir (only genotype 1)**
Practical tips for treatment management

Indications and contraindications

As HIV coinfection accelerates the course of hepatitis C and increases the risk of hepatotoxicity after initiation of ART, the indication for treatment should be determined in all patients with diagnosed HIV/HCV coinfection. In particular, treatment should be discussed for cases with a bioptically confirmed fibrosis of grade F2–F4 and for patients with a high likelihood of treatment response (genotypes 2 and 3; genotype 1 with low viremia; IL28B CC genotype). Probability of treatment response can be calculated on the basis of HCV RNA, HCV genotype, fibrosis grade and IL28B genotype (Prometheus index: http://www.fundacionies.com; Medrano 2010). Extrahepatic manifestations of hepatitis C are also an indication for treatment (vasculitis, glomerulonephritis, systemic cryoglobulinemia).

Most important contraindications for treatment with interferon-ribavirin are:
- Decompensated liver cirrhosis or history of decompensation (but not compensated cirrhosis, i.e., CHILD A cirrhosis!)
- Leucopenia (<1,500/µl)
- Thrombocytopenia (<50,000/µl)
- Anemia (<10 g/dl)
- Severe, as yet untreated, thyroid dysfunction
- CD4 T cell count <200/µl (relative contraindication, see below)
- Severe psychiatric illnesses, active drug or alcohol abuse
- Symptomatic cardiac disease
- Active opportunistic infections
- ART with ddl (AZT and d4T should be avoided also)

Methadone or polamidone substitution is not a contraindication if good monitoring is maintained during treatment. However, patients with active drug or alcohol abuse should first be introduced to the appropriate detoxification programs.

Timing of treatment

Initiation of ART should be considered in all patients not yet on HIV-treatment. The course of hepatitis C is accelerated, when HIV-replication is not suppressed. Therefore, ART is recommended for all patients with CD4 T cells <500/µl. In patients with CD4 T cells >500/µl, hepatitis treatment may be started immediately. An advantage of this approach is avoidance of hepatotoxicity and drug interactions of ART, as well as possibly better adherence. However, if hepatitis treatment is deferred, some experts recommend initiation of ART in all patients regardless of CD4 T cell count (i.e., in patients with more than >500 cells/µl also), in order to ensure inhibition of fibrosis progression. If necessary, antiretroviral treatment should ideally be modified several weeks before HCV therapy is initiated. Didanosine (ddl) is contraindicated with concurrent HCV therapy (as it can lead to pancreatitis, mitochondrial toxicity, and more cases of liver decompensation). AZT and d4T should also be avoided, in order to prevent additive toxicities (AZT, anemia and leucopenia; d4T, mitochondrial toxicity, lipoatrophy). Meanwhile the use of abacavir has been suspected to be associated with lower response rates. However, with currently recommended weight-adapted doses of ribavirin (1000–1200 mg/day) there was no difference in treatment response (Vispo 2008). Therefore, abacavir can be used without restriction.

Drug interactions have to be checked carefully with the new HCV-protease inhibitors. Before modifying ART, it should be insured that the treatment success of HIV therapy is not going to be compromised. HCV treatment should only be started if the overall clinical situation is stable, i.e., viral suppression has been achieved and side effects have been evaluated or treated.
Treatment schedule

The combination of PEG-IFN with ribavirin over a period of 48 weeks is recommended as the standard therapy. The duration of treatment needs to be adjusted according to genotype and the dynamic of treatment response (Soriano 2007, Rockstroh 2008).

Two interferons are currently available as PEG-IFN: PEG-Intron® and Pegasys®. PEG-Intron® is administered subcutaneously and the dose is based on body weight at 1.5 µg/kg. Pegasys® is injected subcutaneously at a fixed dose of 180 µg. Both agents are administered once a week, and must be kept refrigerated.

The dosage of ribavirin should be adapted to body weight: patients below 75 kg should receive 1000 mg daily, patients above 75 kg 1200 mg daily – regardless of genotype. Ribavirin is licensed for twice daily administration. However, due to the very long half life once daily administration is possible and has been investigated in several studies.

Patients must be made aware of the fact that both interferon and ribavirin are potentially teratogenic. A reliable method of contraception for at least six months after treatment is important.

All patients require regular clinical monitoring. This should initially take place every 2 weeks; later at least every 4 weeks. Laboratory monitoring should include (see Table 1):
- A complete blood count and transaminases every 2–4 weeks
- Thyroid function every 12 weeks (more frequently with pre-existing dysfunction)
- Immune status every 12 weeks
- Lactate levels every four weeks in patients on d4T comedication
- HCV RNA is the most important parameter for measuring the treatment response.

It is determined at weeks 4, 12, and 24 to decide on the duration of treatment. The duration of treatment is determined by the dynamic of treatment response. If a very early virologic response is achieved (HCV RNA negative at week 4), treatment can be shortened for genotypes 2 and 3 (with low baseline viral load and low grade fibrosis). If HCV RNA has not dropped more than 2 logs at week 12 in all other circumstances, treatment should be stopped. Successful treatment is not expected in this case (“2 log stopping rule”).

![Algorithm for treatment of hepatitis C in HIV infection (modified EACS guidelines October 2011).](image)
Management of adverse events

The management of possible side effects is often the decisive factor for the success of treatment (see Table 2). A high discontinuation rate in numerous (older) clinical studies of about 30% is likely also to have been due to a lack of experience with combination therapy. Proper management of side effects probably results in significantly better treatment success rates (about 15%).

Patients should be counseled extensively on the expected side effects before beginning treatment. It is often helpful to indicate to patients that side effects are reversible after stopping therapy. Three main aspects should be explicitly addressed:

Almost all patients experience influenza-like symptoms or malaise when beginning treatment. As the severity of symptoms cannot be predicted beforehand, treatment should be initiated at a time when there are no important private or professional events pending (e.g., before a weekend). The administering physician should be readily available during the first days of treatment. In addition, paracetamol should be prescribed (dosage has to be adjusted individually; single dose = 1000 mg). Symptoms usually improve within the first two to four weeks.

Most patients tolerate treatment quite well and can continue their daily activities normally. However, it is possible that particularly in the initial stages of treatment, they may be unable to work for several days. In rare cases, the side effects may be so grave that patients are unable to work for the entire duration of treatment. This also needs to be discussed with the patient in advance.

Ribavirin causes hemolytic anemia in up to 20% of patients. This can be overcome by dose reduction of ribavirin. However, ribavirin exposure is clearly associated with improved treatment response. Therefore, most physicians are reluctant to perform a dose reduction and try to maintain ribavirin dose as long as possible.

Special consideration should be given to patients with coronary disease, kidney disease or patients on AZT. In case of ongoing anemia despite dose reduction, interferon-induced autoimmune hemolytic anemia due to interferon should be considered.

Epoetin-alpha may be regarded as an alternative to dose modification of ribavirin, although there are no data that confirm an improvement in treatment response. Dose recommendations differ: usually approximately 100 IU/kg body weight are injected subcutaneously three times a week. 40,000 IU once a week also significantly improves ribavirin-induced anemia (Sulkowski 2005).

Treatment with granulocyte colony stimulation factor (G-CSF) may ameliorate an interferon-induced leukopenia. As with ribavirin, there are no firm data that would make this a better option as compared with dose reduction of interferon. However, so that the required dose of interferon can be maintained in selected cases of severe leukopenia (neutrophils below 500/µl), this recommendation seems to be justified.

Doses have to be adjusted individually. In most instances low doses are adequate, as hematopoiesis itself is not impaired (e.g., filgrastim 30 Mio IE once a week). The evaluation of psychological side effects is made at every clinic visit. Observations made by others, such as family members, may be very helpful. Mild depression while on interferon can be treated with well-tolerated antidepressants (e.g., paroxetine 20 mg daily). In certain cases, prophylactic administration of paroxetine can be considered. Therapy should be stopped immediately in cases of severe depression or on development of suicidal thoughts.

The frequent occurrence of weight loss can be lessened with dietary counseling. It is important to ensure a regular diet that is tailored to the patient’s wishes (e.g., inpatients with drug addiction). NRTIs with a lower risk for development of lipoatrophy (i.e., Truvada®) should be considered.
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon-associated</strong></td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>Paracetamol (acetaminophen)</td>
</tr>
<tr>
<td>Leukopenia, Thrombocytopenia</td>
<td>Dose reduction of IFN, possibly G-CSF</td>
</tr>
<tr>
<td>Psychiatric changes</td>
<td>Antidepressants, discontinuation of IFN</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Regular diet</td>
</tr>
<tr>
<td>Autoimmune phenomenons</td>
<td>Discontinuation of IFN</td>
</tr>
<tr>
<td><strong>Ribavirin-associated</strong></td>
<td></td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Dose reduction of ribavirin, possibly epoetin</td>
</tr>
</tbody>
</table>

Treatment discontinuation is not always necessary if thyroid dysfunction develops (see ‘diagnosis’ above). In most instances, hyperthyroidism is induced first that can turn into hypothyroidism if treatment is continued. Manifestation of hyperthyroidism is enough cause for most practitioners to discontinue treatment. In the majority of patients, thyroid dysfunction resolves after discontinuation of interferon. However, if treatment is continued, irreversible hypothyroidism requiring lifelong hormone replacement therapy may develop.

References


HIV and HBV coinfection

Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95% of all HIV-infected patients have been infected with hepatitis B, and approximately 10–15% have chronic hepatitis B, with considerable variation among geographical regions and risk groups (Alter 2006, Konopnicki 2005). It is estimated that around 100,000 HIV-infected patients in the US suffer from chronic hepatitis B. Due to implementation of vaccination programs in many countries transmission rates decrease, especially in the younger population. Hence, epidemiology will alter significantly over the next years.

Sexual transmission is the most frequent route of transmission. Transmission via the bloodstream is more likely than for HIV: following a needle stick injury contaminated with HBV-infected blood, the risk of infection is around 30% (HCV <2%; HIV approximately 0.3%).

Primary HBV infection leads to chronic hepatitis in 2–5% of immunocompetent adults, whereas HIV-infected patients experience chronification about five times more often. A possible reason for this is the HIV-associated immunodeficiency, whereas virus-specific factors such as the extent of HBV viremia and genotype do not contribute significantly (Bodsworth 1991).

Hepatitis B and HIV share several features, although hepatitis B is a circular DNA virus (“closed circular supercoiled” DNA (cccDNA)). Hepatitis B is one of a few known non-retroviral viruses which use reverse transcription as a part of its replication process. Therefore, replication can be inhibited with NRTIs. Although elimination can basically be achieved by cytotoxic T lymphocytes (CTL), it has to be assumed that the hepatitis B virus will persist lifelong in most patients. Therefore reactivation can occur after many years, e.g., due to immunosuppression in advanced HIV infection or following chemotherapy – regardless of the pattern of antibodies found.

HBV diagnosis methods in HIV patients do not differ from HIV-negative patients. Table 1 summarizes the interpretation of serological test results. Screening HIV-infected patients for HBV starts with HBsAg, anti-HBs, and anti-HBc. If a positive HBsAg is found, testing for HBeAg, anti-HBe, and HBV DNA should follow.

Table 1: Interpretation of serological test results for HBV.

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>HBsAg</th>
<th>anti-HBs</th>
<th>anti-HBc</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior contact with HBV</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
<td>–</td>
<td>+ (IgM)</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Past infection with immunity</td>
<td>–</td>
<td>+</td>
<td>+ (IgG)</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>+</td>
<td>–</td>
<td>+ (IgG)</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Latent/occult infection¹</td>
<td>–</td>
<td>–</td>
<td>+/– (IgG)</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Pre-core mutant</td>
<td>+</td>
<td>–</td>
<td>+ (IgG)</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inactive carrier state</td>
<td>+</td>
<td>–</td>
<td>+ (IgG)</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Immunity after vaccination</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

¹ Controversial. See text above.
The isolated presence of anti-HBc in the absence of HBsAg and anti-HBs (so called “anti-HBc only”) is found quite frequently in HIV-infected patients (less than 2% in healthy blood donors). Three situations should be considered: 1) early phase of an acute hepatitis B, 2) many years after recovery from acute hepatitis B when anti-HBs has fallen to undetectable levels, or 3) after many years of chronic HBV infection when the HBsAg titer has decreased to below the cutoff level for detection. Clinical significance of this state has not been clearly defined. In most instances, it will be a loss of anti-HBs without any clinical consequence.

A so-called occult infection means lack of HBsAg, but positive HBV DNA (with or without anti-HBc). Prevalence and clinical impact in coinfection is still unclear. In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months. Serum alpha fetoprotein and an ultrasound of the liver should be performed. This recommendation is independent of apparent cirrhosis, as 10 to 30% of patients who develop HCC do not have pre-existing cirrhosis. Patients with chronic hepatitis B should be tested for hepatitis D infection also.

Course of hepatitis B with concurrent HIV infection

The course of hepatitis B is negatively influenced by HIV infection. Liver-associated mortality is about 15 times higher than in HIV-negative patients and has increased significantly since the introduction of ART (Thio 2002, Konopnicki 2005). In addition, HIV coinfection accelerates the progression of hepatitis B and increases the risk of cirrhosis. Entanglement between the profibrogenic effect of HIV itself and the alteration by HIV of HBV innate and adaptive immune responses has been elucidated further during recent years (e.g. direct cytopathic effect on liver tissue by CCR5-mediated activation of hepatic stellate cells and hepatocytes; indirect upregulation of pro-inflammatory and apoptotic factors). Despite these unfavorable effects, the clinical course appears initially usually more benign in HIV-positive patients, although viral replication is increased. This seems contradictory at first, but can be explained by the impairment of cellular immunity, which may lead to an increase in viral replication, but at the same time also reduces hepatocyte damage. Therefore, transaminases in HBV/HIV-coinfected patients are frequently only mildly increased. In contrast, HBV DNA, as a marker for viral replication, is higher than in immunocompetent patients. Accordingly, despite less inflammatory activity, liver fibrosis and cirrhosis are more common. This phenomenon can be observed in other groups of patients with immunosuppression, e.g., organ transplant patients.

There is a direct correlation between the extent of immunosuppression and the control of viral replication of HBV. Patients with apparently resolved hepatitis B (anti-HBe positive, HBV DNA negative) and increasing deterioration of the immune system may result in a reactivation of the HBV infection (Soriano 2005). Notably, some cases of reactivation of hepatitis B have been described following immune reconstitution after initiation of ART.

HIV/HBV coinfection possibly has a negative impact on the course of HIV infection also. An increase of overall mortality and AIDS-defining events has been described in HIV/HBV-coinfected patients (Nikolopoulos 2009, Chun 2012). Moreover, the risk for ART-related hepatotoxicity is about three times higher. Whether or not the prognosis of HBV/HIV-infected patients is changed by effective therapies for ART and HBV remains to be seen. According to some studies, a reduction in HBV-associated mortality is associated with effective treatment of HBV (e.g., French GERMIVIC cohort) (Puoti 2007, Rosenthal 2009).
Prevention

All patients infected with HIV but with negative hepatitis B serology should be vaccinated. The vaccine may, however, be less effective due to immunosuppression. Approximately 30% of HIV-infected patients have a primary non-response (only 2.5% in immunocompetent individuals). The response to the vaccine is influenced by the CD4 T cell count and level of HIV RNA. Therefore, patients with CD4 T cell counts of less than 200/µl who are not on ART should receive ART first and HBV immunization thereafter. Vaccination is performed as recommended by the manufacturers (20 µg at months 0, 1, and 6). Re-vaccination can be considered in case of an insufficient response (anti-HBs <10 IU/ml 12 weeks after vaccination). Double dose re-vaccination (40 mg) at 3–4 vaccination time-points (months 0, 1, 6 and 12) may help to improve vaccination response rates (Fonseca 2005, Launay 2011).

Loss of protective immunity is seen in up to 30% of patients each year following seroconversion. Therefore, anti-HBs should be monitored once a year and consideration given to booster doses if anti-HBs-antibody levels are less than 100 IU/l. HIV patients, who are not adequately immunized against HBV should be screened yearly to look for newly acquired infection.

HIV/HBV-coinfected patients who are seronegative for hepatitis A should be vaccinated (months 0 and 6), as there is an increased rate of severe or fulminant hepatitis in case of acute hepatitis A. Patients who are susceptible to both hepatitis A and B can be vaccinated with a bivalent vaccine (months 0, 1, and 6).

Following immunization, patients should be counseled about common measures to prevent further transmission and transmission of other viruses such as hepatitis C (safer sex practices, avoidance of needle-sharing, etc). They should be educated about strategies to prevent progression of liver disease such as avoidance of alcohol consumption, tobacco use (controversial), or herbal supplements, many of which are hepatotoxic. The application of hepatotoxic drugs (e.g., anti-tuberculous agents) should be carried out cautiously.

Newborns of mothers with chronic hepatitis B should receive hepatitis B-immunoglobulin and active immunization.

Treatment

Treatment of chronic hepatitis B is problematic in coinfected patients because of impaired immune function. Loss of HBsAg with development of protective anti-HBs antibodies is difficult to achieve. Realistic treatment goals are seroconversion from HBeAg to anti-HBe, a complete suppression of HBV DNA, normalization of transaminases, improvement of liver histology, and prevention of hepatocellular carcinoma. Other benefits of HBV therapy include a reduction in the risk of transmission and possibly in the risk of ART-induced hepatotoxicity. As mentioned above, HBV-associated mortality is likely to improve also.

Drugs with HBV activity

Possible treatment options for hepatitis B are nucleoside analogues, nucleotide analogues and interferon (see Table 2). Tenofovir, active against HIV and HBV at the same time, is the most important drug right now. All other drugs play a less significant role today.

Like tenofovir, 3TC, FTC, and entecavir are active against both HBV and HIV. Drugs with activity against HBV only are adefovir and telbivudine. However, one case report raised the possibility that telbivudine might be active against HIV also (Low 2009). Clinical significance (selection of HIV resistance?) of this report is unclear, as in vitro studies could not confirm any HIV activity (Lin 2010). Interferon – occasionally used
in HBV monoinfection – does not play a relevant role in the setting of HIV/HBV coinfection.

Table 2: Current therapeutic options for chronic hepatitis B in HIV/HBV coinfection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>FTC</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 mg (3TC naïve) QD, 1.0 mg (3TC experienced) QD</td>
</tr>
<tr>
<td>3TC</td>
<td>300 mg QD</td>
</tr>
<tr>
<td>Telbivudin</td>
<td>600 mg QD</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg QD</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>5 MU per day or 10 MU 3 days per week</td>
</tr>
<tr>
<td>PEG-Interferon</td>
<td>Pegasys® 180 µg once a week</td>
</tr>
<tr>
<td></td>
<td>PEG-Intron® 1.5 µg/kg body weight once a week</td>
</tr>
</tbody>
</table>

Tenofovir is the drug with the best clinical activity. More than 95% of patients treated with tenofovir have viral suppression after 5 years. Accordingly, no distinct mutations have been described so far that are associated with phenotypic resistance (possibly A194T). In contrast to tenofovir, most other substances are afflicted with significant resistance: Monotherapy with 3TC selects a mutation in the YMDD motif in the HBV DNA polymerase gene (similar to a pre-core mutant, HBeAg production may stop in case of mutations in this motif). The frequency of resistance development has been reported to be at least 20% of patients per year. Cross-resistance exists between 3TC, FTC, entecavir, and telbivudine. This can be overcome only partially with an increase in dose (e.g., entecavir has to be administered with a higher dose following treatment with 3TC). Although the nucleotide analogue adefovir has a different mechanism of resistance development, selection of the A181T mutation with ongoing viral replication has been described.

It is reasonable to assume that combination of two drugs active against HBV will enhance antiviral activity and delay the selection of HBV resistance. No resistance mutation has been observed in small cohorts when a nucleoside and a nucleotide analogue are combined. However, up to now there is no formal proof that combination therapy is indeed more efficacious. In light of the lessons learned from HIV, combination therapy of at least two drugs is recommended by some experts.

Interferon might be the preferred treatment option in a select, not selected group of patients who are not taking ART and show prognostic markers for a favorable treatment response to interferon – they have a high CD4 T cell count, positive HBeAg, elevated ALT, and low HBV DNA. However, treatment with interferon is limited by its side effects. Interferon is contraindicated in patients with decompensated cirrhosis. It should only be used (and with caution) in patients with advanced liver disease. Finally, liver transplantation may be an option for selected patients who have cirrhosis and/or develop hepatocellular carcinoma.

**Treatment guidelines**

Due to accelerated progression and increased mortality in coinfection, treatment possibilities should be examined for every patient. According to current guidelines (EACS guidelines October 2011) treatment is recommended if:

- Cirrhosis or significant fibrosis (F2–F3)
- HBV DNA >2,000 IU/mL (1 IU/ml corresponds to approximately 5 copies/ml
depending on the assay used): there is a direct correlation between viral load and risk of progression to cirrhosis and HCC. Therefore, HBV viral load is the most important parameter for treatment decision.

- ALT is consistently >2-fold above the norm (high pre-treatment ALT values correlate with better treatment responses to interferon and 3TC).

Liver biopsy is not mandatory in most cases. It may provide additional information on differential diagnosis (e.g. hepatotoxicity) and inflammatory activity though. To assess liver fibrosis several non-invasive methods are available. Among these the Fibroscan®-system has an outstanding role. Liver stiffness is measured as a surrogate of liver fibrosis by transelastography. It has to be taken into account that cut-off values differ in HIV/HBV-coinfection from those in HBV-monoinfection or HIV/HCV coinfection (Lacombe 2012).

There are several histological classifications used. In Europe the META VIR score is most often used. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = some septa, 3 = significant septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2–F4, it may be deferred for grades F0 and F1. Current treatment guidelines are summarized in Figures 1 and 2.

In a first step indication for treatment of hepatitis B is checked (figure 1). Thereafter, treatment is chosen in accordance with the current HIV-situation (figure 2). An effective treatment of HIV infection must not be put at risk. Accordingly, lamivudine (3TC), emtricitabine (FTC), tenofovir, and entecavir effective against both HIV and HBV, have to be combined with other agents effective against HIV in order to ensure an adequate ART. On the other hand, adefovir (and telbivudine, see comment above) is not effective against HIV and must not be considered as part of the ART regimen. Even in patients with CD4 T cell counts >500/µl initiation of ART (including TDF+FTC) is the first choice, as high rates of seroconversion have been observed. If a patient is unwilling to start ART, or does not tolerate TDF, adefovir and telbivudine may be used as an alternative to control HBV alone.

A transient elevation of transaminases – which is usually moderate and soon resolves – may be observed after initiation of HBV therapy. It is caused by immunoreconstitution and subsequent increased inflammatory activity. In case of marked and/or ongoing elevation of transaminases, other explanations have to be considered (e.g., increasing HBV replication and resistance, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with hepatitis viruses other than hepatitis B).

Initial normalization of ALT and significant reduction of HBV DNA will be achieved in most cases by any anti-HBV agent. ALT levels do not correlate well with inflammatory activity and are influenced by many other factors such as hepatotoxicity of ART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their value for monitoring treatment is limited.

The optimal duration of HBV treatment is unclear. As eradication is most unlikely, continuous suppression of viral replication probably will be necessary as it is in HIV. Therefore, HBV-active drugs are integrated into the ART combination permanently. If drugs active against HBV are discontinued, an acute hepatitis may develop clinically. In rare cases even fatal liver failure may occur. Therefore any interruption of treatment has to be considered thoroughly in HBV/HIV-coinfected patients. In the setting of cirrhosis special consideration has to be given as hepatic decompensation may occur with interruption of HBV-active drugs. In case of resistance, treatment may be discontinued safely without any danger of clinical deterioration of hepatitis. All nucleos(t)side analogues have to be dose-adjusted in case of renal insufficiency.
Figure 1: Indication for treatment of hepatitis B in HIV/HBV coinfected patients (modified after EACS Guidelines 2011).
* 1 IU/ml corresponds to approximately 5 cop/ml, depending on the assay used.

Figure 2: Treatment recommendations for HIV/HBV coinfected patients (modified after EACS Guidelines October 2011).
* if compatible with treatment of HIV infection.
HBeAg seroconversion will occur in as many as 40% of patients treated with tenofovir, a loss of HBsAg in about 10% after 5 years.

As most cases of acute hepatitis B even in HIV-positive patients resolve spontaneously, only symptomatic treatment is recommended. In addition, data on this situation are sparse (e.g., danger of resistance in case of early therapy with no options afterwards).

References


Hippocrates (5th century BC) was the first to postulate that signs of inflammation represent both a symptom of disease and as well as a hint of its cure. Edward Jenner (18th century) demonstrated that an artificial infection with a harmless cowpox is able to prevent the dangerous smallpox. William Coley (19th century) prevented progress of malignancies by bacterial toxins (Coley 1893). In 1927 the Nobel Prize for Medicine was awarded to the Austrian neurologist Julius Wagner von Jauregg, who was able to obtain improvement in patients with late stage symptomatic neurosyphilis by infecting them with the malaria parasite. Thus, infectious diseases may result in harm reduction under certain conditions.

GB virus C (GBV-C) is a flavivirus closely related to hepatitis C virus. The name GB virus stems from early experiments on the transmission of acute hepatitis from humans to marmoset monkeys. One of the first source patients had the initials “G.B.” and was a 34-year old colleague of the author of the experiment (Deinhardt 1967). Later on, two hepatotropic viruses, GB virus A (GBV-A) and GB virus B (GBV-B), were isolated from these monkeys. Two independent research groups simultaneously discovered the related GB virus C in humans with hepatitis in the mid-1990s. Subsequently, GB virus C has promoted a discussion as to whether the natural course of HIV infection might be modulated in a favorable way by this particular coinfection. In addition, because GBV-C was first found in humans with hepatitis, and due to its close relationship to the hepatitis GBV-A and GBV-B viruses, GBV-C was also called “hepatitis G virus (HGV)” by one research group. This name should no longer be used, because it has since been shown that GBV-C neither causes hepatitis nor worsens preexisting hepatitis (Berenguer 1996, Tillmann 1998, Rambusch 1998, Stark 1999). In fact, GBV-C is not a hepatotropic but rather a lymphotropic virus. Despite intensive research, GBV-C has until yet not been shown to cause any known disease in humans. However, one case control study from Canada found persistant GBV-C viremia in the absence of HIV coinfection as a risk factor for Non-Hodgkin-Lymphoma (Krajden 2009).

<table>
<thead>
<tr>
<th>GBV-C-Viremia (RNA)</th>
<th>Anti-E2-Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR / b-DNA</td>
<td>ELISA</td>
</tr>
<tr>
<td>GBV-C negative</td>
<td>negative</td>
</tr>
<tr>
<td>Replicative GBV-C Infection</td>
<td>positive</td>
</tr>
<tr>
<td>Past GBV-C Infection</td>
<td>negative</td>
</tr>
</tbody>
</table>

* Anti-E2 antibodies may disappear over time

The virus is not uncommon in healthy individuals: Prevalence studies revealed GBV-C viremia within the general population ranging from less than 5% in industrialised countries up to more than 15% in some developing countries. Although approximately 10% to 30% of blood donors have specific antibodies against GBV-C, affected individuals are not excluded from the donation of blood, assuming that the virus is apathogenic. Consequently, serological diagnostics on GBV-C are not routinely performed. Two serological markers for GBV-C infection exist: GBV-C viremia can be determined using a PCR method; and antibodies to the envelope region E2 (anti-E2) are detected by ELISA (Table 1). As they are mutually exclusive, either GBV-C viremia...
or the presence of anti-E2 is detectable in GBV-C infected individuals. GBV-C viremia may persist for decades but in most cases, GBV-C viremia is transient and ends with seroconversion to anti-E2, resulting in immunity to new infections. However, this does not seem to be a lifelong immunity (Table 1). Transmission of GBV-C occurs parenterally and mucosally, similar to HIV, HBV and HCV infections. Hence coinfection of GBV-C and HIV is common and persistence of GBV-C viremia (GBV-C RNA positivity) is prolonged in HIV infection.

Until now six genotypes of GBV-C have been described with significant variation in their regional distribution and in particular virologic characteristics.

HIV and GBV-C coinfection: Pas de deux

In 1998 the first cohort studies described a modulating impact of GBV-C coinfection on HIV infection (Toyoda 1998, Heringlake 1998): The GBV-C viremic subgroup presented with lower HIV viremia, higher CD4 cell counts, slower progression to AIDS and improved survival as compared to the GBV-C nonviremic patients. Such beneficial effects in GBV-C viremic HIV-infected individuals could be confirmed in several further studies by different research groups (Lefrère 1999, Yeo 2000, Tillmann 2001, Xiang 2001) and could be confirmed as well in HAART treated HIV-positive individuals (Tillmann 2004+2006, Nunnari 2003, Williams 2004). In these studies the modulatory effects were associated to persisting GBV-C viremia exclusively but were not present in those with cleared GBV-C infection (anti-E2-positive) or in HIV-infected individuals without GB virus C contact (GBV-C negative). A meta-analysis of studies from the HAART era described overall an improved response to ART and clinical benefit for HIV/GBV-C coinfected patients, which is more pronounced in studies with longer follow-up periods (Zhang 2006).

Conflicting results came from some studies (reviewed in Battharai 2012), which did not find an effect of GBV-C viremia on HIV infection (Sabin 1998, Birk 2002, Bjorkman 2004, van der Bij 2005), including two studies in women (Kaye 2005, Williams 2005). One of these studies summarized GBV-C viremic and anti-E2-positive patients as GBV-C positive group (Sabin 1998). Another study focused on GBV-C viremia at study entry (van der Bij 2005). In this study the subgroup with persistant GBV-C RNA over the whole observation period had a superior clinical outcome. A less pronounced potential gender-specific modulating effect of GBV-C on HIV in women may exist (Kaye 2005, Williams 2005). But in a study investigating the GBV-C status in HIV-infected pregnant women a lower HIV viral load in GBV-C viremic mothers and less vertical transmission of HIV from mother to child were described in the HAART era but not in the pre-HAART era (Handelsman 2008). The lower risk for vertical transmission of HIV seems to be associated with replicative GBV-C infection in the child rather than by GBV-C status of the mother. Surprisingly the risk for vertical transmission of GBV-C was found to be increased under HAART in HIV/GBV-C coinfected pregnant women (Bhanich-Supapol 2009). In addition there is evidence from a multicenter trial, that GBV-C genotype 2 coinfection was associated with higher CD4 T cell counts (Schwarze-Zander 2006). This observation may explain regional differences and at least in part conflicting results from cohort studies from different regions.

In summary, most studies found more pronounced antiretroviral and immunological effects in ART-treated GBV-C RNA positive patients. However, other studies did not find any difference. No study to date described a negative influence of GBV-C viremia on the effect of ART.
Table 2: Beneficial effects of replicative GBV-C coinfection on HIV-disease

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CD4 T cells</td>
<td>• HIV plasma viremia</td>
</tr>
<tr>
<td>• Response to ART</td>
<td>• Mother to child transmission of HIV</td>
</tr>
<tr>
<td>• Survival</td>
<td>• Progression to AIDS or death</td>
</tr>
<tr>
<td>• Quality of life</td>
<td>• T cell activation</td>
</tr>
</tbody>
</table>

**GBV-C, HIV, and HCV: Ménage à trois**

Triple-infected patients with HIV, HCV and GBV-C had less progressed liver disease as compared to those without GBV-C infection (Barbosa 2009, Berzsenyi 2009), and an improved response to interferon/ribavirin therapy of HCV (Hofer 2011) indicating as well a potential interdependency of GBV-C with HCV. But if harm reduction is exclusively seen in the chronically replicative GBV-C / HIV coinfection is it necessary to keep GBV-C viremia ongoing like a tamagotchi game? A couple of cases with GBV-C seroconversion during follow-up from GBV-C RNA positive status to anti-E2 positivity have been associated with a particularly worse prognosis (Williams 2004, Bjorkman 2004, van der Bij 2005). Therefore concerns raised about the impact of interferon treatment of HCV-infection, which had been shown to be effective in terminating viral replication of GBV-C and to induce Anti-E2 seroconversion (Yu 2001, Hofer 2011). But in a large multicenter trial in interferon-treated HIV/HCV coinfected individuals the immunological and clinical outcome was not disimproved in GBV-C coinfected individuals who cleared their GBV-C viremia during the treatment period (Schwarze-Zander 2006).

**Proposed pathomechanisms**

Up to now the fundamental chicken or egg dilemma remains unsolved whether GBV-C viremia is an epiphenomenon or the cause for an improved outcome of HIV infection. A major drawback of the first descriptions of potential clinical benefits by GBV-C on the course of HIV disease was the lack of any pathophysiologic concept. Meanwhile many different hypotheses have been postulated about direct inhibitory effects of GBV-C on HIV replication, about competition of both viruses at certain steps of action during the replication cycle, and about immunomodulatory mechanisms in the host hypothetically induced by GBV-C. Meanwhile – after more than a decade of research – it has been shown that more than one way leads to Rome. The knowledge about the pathophysiology of GBV-C coinfection in HIV looks rather like a varied bunch of pleiotropic effects of numerous different modes of (inter-)action. The modulating effects of GBV-C on HIV disease (table 3) have been explained by attachment inhibition, entry inhibition, downregulation of CD4- and chemokinereceptors including upregulation of their corresponding ligands, enhancement of innate immunity, downregulation of immune activation and apoptosis, and modulation of T cell responses. The elucidation of the underlying molecular pathomechanisms is still fragmentary. However, GBV-C treads several independent pathways, using E2-protein, NSSA-protein, and Anti-E2-antibodies. Hence it might be speculated, that the mankind share a long coevolution together with GBV-C and retroviruses, which could explain why HIV – in contrast to SIV in other primates – until recently was not able to establish a stable endemic. Hypothetically in the past spread of HIV could have been limited by two other viral diseases, both formerly highly
prevalent in Africa where HIV had its origin: The chemokine receptor inhibition by GBV-C might have prevented transmission, especially vertical transmission, which is a result of perinatal GBV-C transmission in HIV infected mothers (Handelsmann 2007, Bhanich-Suparol 2009). On the other side periodical epidemics of pox might have killed efficiently any human host of HIV, because a fatal course in pox is common especially in cases with preexisting cellular immunodeficiency. The possible result of this two competing coinfections: HIV was – until recently – not able to establish a stable endemic in humans over a long time.

Table 3: Proposed mechanisms of interactions between GBV-C, HIV and their host

<table>
<thead>
<tr>
<th>Mechanism (Agent)</th>
<th>Pathway / Effector</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of HIV entry</td>
<td>GBV C E2-protein directly blocks the fusion peptide of HIV and potentially modifies its conformation</td>
<td>Inhibition by a peptide sequence from E2 (269-286) Jung 2007, Mohr 2009, Herrera 2009</td>
</tr>
<tr>
<td>GBV-C-E2-Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCR4 and CD4 downregulation</td>
<td>Decreased CD4 and CXCR4 expression and increased release of the CXCR4 ligand SDF-1.</td>
<td>Inhibition by a peptide sequence from NS5A (152-167) Chang 2007, Ziang 2008, Schwarze-Zander 2010</td>
</tr>
<tr>
<td>GBV-C-NS5A protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR5 downregulation</td>
<td>Increase of CCR5 ligands (β-chemokines: RANTES, MIP-1α, MIP-1β)</td>
<td>Nattermann 2003, Xiang 2004, Tillmann 2002</td>
</tr>
<tr>
<td>Enhancement of innate immunity</td>
<td>GBV-C induces plasmacytoid dendritic cells and activation of interferon related genes.</td>
<td>Activated plasmacytoid dendritic cells (CD80+ pDCs), IFN-gamma- and RNA-dependent protein kinase R (PKR) mRNA levels higher in GBV-C viremic compared to nonviremic individuals. Exact mechanism is unknown</td>
</tr>
<tr>
<td>Normalisation of apoptosis</td>
<td>Normalized levels of CD95 (Fas-ligand) in GBV-C viremic HIV-infected individuals without HAART</td>
<td>Downregulation of T cell apoptosis in GBV-C coinfected individuals</td>
</tr>
<tr>
<td>Shift of T cell immunity to Th1 responses</td>
<td>GBV-C viremia resulted in a more stable Th1-cytokine profile (e.g. IL-2, IL-12) and less increase of Th2-cytokines (IL-4, IL-10).</td>
<td>Like the effects on innate immunity in part mediated by activation of activated plasmacytoid dendritic cells (CD80+ pDCs). Effects might explain the observation of reduced CD4 expansion in GBVC+/HIV+ individuals treated with interleukin-2. Effects are in part mediated by NS5A</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Mechanism (Agent)</th>
<th>Pathway / Effector</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceleration of T cellular immune</td>
<td>In GBV-C viremic HIV+ individuals less expression of CD38+, CCR5+, CD69, and CD25 on T cells</td>
<td>Maidana-Giret</td>
</tr>
<tr>
<td>activation</td>
<td>GBV-C viremia reduces IL-2 induced T cell proliferation</td>
<td>2009</td>
</tr>
<tr>
<td>Inhibition of HIV-attachment</td>
<td>Anti-E2-antibodies precipitate and neutralise HIV particles in vitro and inhibit CCR5- and CXCR4-tropic HIV replication</td>
<td>Mohr 2010</td>
</tr>
<tr>
<td>(Anti-GBV-C-E2-antibodies)</td>
<td>Inhibition of HIV by attachment-inhibition to target cells but not by entry-inhibition</td>
<td></td>
</tr>
</tbody>
</table>

The story of GBV-C coinfection in HIV started with observational epidemiology and revealed an unexpected clinical observation: GBV-C presents as a non-pathogenic virus in humans and as a beneficial coinfection in HIV-infected individuals. At this point science started at bedside and went to bench in the last years. A puzzling diversity of pathomechanisms had been described meanwhile and may have raised more questions than answers. For more detailed information to the complex role of GBV-C in the pathophysiology of HIV-infection it is referred to recent reviews of the scientific literature in this evolving field of infectiology (Bhattari 2012, Maidana Giret 2012, Schwarze-Zander 2012, Shankar 2011).

How to deal with GBV-C coinfection in clinical practice?

Beyond the tales of a potentially beneficial infection the impact of GB virus C may be in understanding the pathophysiology of virus to virus- and virus to host-interactions rather than a role in clinical practice:

1. Until now it is neither recommended to test HIV-infected individuals for their GBV-C serostatus nor for GBV-C replication by PCR beyond clinical studies. But some authors claim such tools for clinical practice (Batharai 2012).
2. HIV-positive individuals should be informed that there is no evidence that (an artificial) GBV-C infection, which happens after HIV seroconversion will be of benefit in the course of HIV infection. It cannot be predicted whether an infection with GBV-C will remain chronically replicative. Coinfections with GBV-C in an in vitro model show evidence for an inhibition of HIV replication when GBV-C infection occurs before HIV infection but not later (Xiang 2001).
3. There is no evidence from studies to support the deferral of HCV therapy in HIV/HCV/GBV-C coinfected patients, although interferon therapy can terminate chronic GBV-C replication. However, during interferon therapy in controlled studies there is still a need for screening for GBV-C serostatus, individual counselling and further prospective follow-up.

We are still in the early stages of GBV-C history. Over the last few years we have accrued some fascinating insights into possible mechanisms of HIV and GBV-C interaction and the roles that individual host factors may play. At present, GBV-C gives us the opportunity to obtain insight into clinically relevant regulation pathways of HIV. This may help us develop new therapeutic concepts. These concepts may be both clinically and therapeutically promising because an additional benefit of GBV-C remains evident in several studies after the initiation of ART.
References


Chang Q, McLinden JH, Stapleton JT, Sathar MA, Xiang J. Expression of GB virus C NSSA protein from genotypes 1, 2, 3 and 5 and a 30 aa NSSA fragment inhibit human immunodeficiency virus type 1 replication in a CD4+ T-lymphocyte cell line. J Gen Virol 2007;88:3341-6.


The increasing age of HIV patients and the comorbidity with arterial hypertension, diabetes mellitus, lipometabolic disorders and hepatitis will cause the number of kidney disease occurrences to increase. Diabetes and hypertension increase the risk of renal insufficiency tenfold and account for 71% of dialysis cases in the US (Winston 2008). The data of the Multicenter AIDS cohort show that, in male patients, the prevalence for diabetes is at 12%, which is 4 times as common as in the age-based normal population (Winston 2008). Renal insufficiency is a risk factor for cardiovascular disease of which half of all patients die (USRDS 2010), and in HIV patients it is an independent predictive factor for mortality. Increased creatinine is an indicator for kidney disease, the internationally valid classification of renal insufficiency follows the GFR (given in ml/min/1.73 m²):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Kidney damage, normal or increased GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>II</td>
<td>Kidney damage and slightly reduced GFR</td>
<td>60 – 89</td>
</tr>
<tr>
<td>III</td>
<td>Moderate reduction in GFR</td>
<td>30 – 59</td>
</tr>
<tr>
<td>IV</td>
<td>Severe restriction of GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>V</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**Nephroprotection**

Although AIDS-related mortality has fallen with the use of ART, the incidence of dialysis treatment in HIV remains unchanged and in the US it particularly affects HIV-infected Afro-Americans, in whom the risk of kidney failure is tenfold higher than that of non-infected persons (Lucas 2007). At the same time, there is a significant increase in organ failure of the heart, liver and kidneys (Selik 2002). Acute kidney failure occurs twice as often as in non-infected patients, and adjusted hospital mortality is also significantly higher (Wyatt 2006). The following principles should be followed for nephroprotection – give up nicotine, keep blood pressure below 140/80 mm Hg (or <130/80 mmHg in the case of renal damage) and provide for prevention or treatment of diabetes mellitus or other metabolic syndromes. The HIV-related changes in the glomerulum and the tubular system are a good reason to begin and continue ART. This has also been reflected in the international therapy guidelines in which kidney involvement in HIV is another reason for beginning ART (Choi 2009).

**Clinical manifestation/diagnosis of nephropathy**

The clinical picture of renal damage is often unspecific, with tiredness, poor concentration, loss of appetite, high blood pressure and possibly new edemas. Based on the cause of the kidney disease, one can differentiate between pre-renal, intra-renal (glomerular, tubular, interstitial) and postrenal. A sonography quickly supplies information about a post-renal drainage impediment (renal retention?) and about the size of the kidney (reduced with a narrow parenchyma in the case of chronic renal insufficiency). The anamnesis provides an indication for a pre-natal cause (NSAR, infections, sepsis, contrast agent?) The diagnosis is supplemented by a Urinstix or sediment and the determination of creatinine, electrolytes (K, Na, Ca), phosphate, anemia, metabolic acidosis (blood-gas analysis), dysfunction of the calcium-phosphate, metabolism, possible venal thrombosis and newly diagnosed arterial hypertension are all dependent in their extent on the duration of the kidney disease and can help to differentiate between acute and chronic renal failure.
Creatinine, Cystatin, GFR:

An increased serum creatinine can only be expected after occurrence of a more than 50% reduction of the glomerular filtration rate (GFR), and is also dependent on muscle mass and gender, which means it is not a good sole marker for renal function. Cystatin C is constantly generated by all germ-bearing cells, but is nonetheless questionable when taking into account a chronic inflammation with HIV (Dhamidharka 2002, Jaroszewicz 2006). Clearance measurements can detect the “creatinine-blind” area of an early renal insufficiency faster. There are four procedures to determine GFR, of which the CKD-Epi formula is the one which has become established after scientific consideration:

1. Cockroft and Gault formula:
   - \((140\text{-age}) \times \text{kg body weight} \div \text{serum creatinine mg/dl} \times 72\) For women, the result is multiplied by 0.85.

2. MDRD formula (more precise, but requires additional laboratory data):
   - Creatinine clearance (MDRD) = \(170 \times \text{Krea [mg/dl]}^{-0.999} \times \text{age}^{-0.176} \times \text{(urea [mg/dl]}^{-0.178} \times \text{albu-[mg/dl]}^{-0.318} \) (for women: x 0.762), correlates well with HIV (Ravasi 2009)
   - Creatinine clearance [MDRD2] = \(186 \times \text{Krea [mg/dl]}^{-1.154} \times \text{age}^{-0.203} \times 1 \) (for women: x 0.762), (for people of color: x 1.212).

3. Cystatin C clearance: cystatin C is a low molecular weight protein which is constantly generated by the organism, filtered freely and regardless of gender, muscle mass, or age, with a minor intraindividual variability (<5%). However, determination is by no means inexpensive. The formula is:
   - \(78 \times \frac{1}{\text{CysC (mg/l)}} + 4 \) or \(87 \times \frac{1}{\text{CysC (mg/ml)}} - 6.9\)

4. CKD-EPI formula (Levey 2009)
   - \(\text{GFR} = a \times (\text{Serum creatinine} \div b)^c \times (0.993)^{ap}\)
   - The variable a conforms to race and gender (women of color = 166, caucasian women = 144, men = 141), b to gender (women 0.7, men 0.9). The variable c adapts the formula to the serum creatinine value: women <0.7 mg/dl = -0.329; >0.7 mg/dl = -1.209 or -0.411 and -1.209 for men. The formula can be directly converted at www.nephromatic.com/egfr.php.

Proteinuria:

The extent of proteinuria with loss of protein, the imbalance of serum protein fractions and residual kidney function with possible fluid retention all dictate edemas, loss of efficiency, susceptibility to infections, and hyperlipidemia. As in the case of diabetes mellitus, microalbuminuria (Micral-Test in the urine) shows a risk for the kidney and mortality due to cardiovascular events with HIV (Wyatt 2012). HIV patients with confirmed microalbuminuria are 25 times likelier to develop proteinuria, which, if it continues despite ART, is accompanied by a doubled risk of mortality (Wyatt 2012). HIV patients should therefore be examined just as carefully for signs of kidney disease as diabetes patients.

Together with “nephritic sediment”, proteinuria, is a major symptom of glomerulonephritis (GN) and its extent should be quantified. Clinically, a difference is made between nephrotic syndrome (loss of protein), acute nephritic syndrome (acanthocytes as a sign of GN), rapid-progressive GN (loss of renal function within a few days), asymptomatic proteinuria or hematuria and chronic GN. These all need to be treated differently and require the collaboration of a nephrologist. HIV-associated nephropathy (HIV-AN) is a form of glomerulonephritis and is diagnosed in cases of nephrotic syndrome with edema, hypoalbuminemia, hyperlipidemia and proteinuria of more than 3.5 g/day. However, even a mild proteinuria is possible.
Urine sediment and sticks:
Alongside salts and crystals (e.g., from HIV drugs such as indinavir), as well as epithelia, the existence of erythrocyturia together with the number and form of the erythrocytes is of significance for a differential diagnosis. The occurrence of proteinuria and erythrocyturia is pathognomonic for glomerulonephritis and, together with nephritic sediment, usually confirms the diagnosis. Under a polarizing microscope, a trained eye can easily identify the renal (glomerular) origin of the erythrocytes, on the basis of glomerularly deformed acanthocytes. More than five acanthocytes per field of vision is a significant sign for GN. Extensive erythrocyturia (bleeding) below the renal pelvis (tumor of the urinary tract collection system) can be excluded by sonography and, if necessary, by cystoscopy. A leukocyturia must first be clarified microbiologically (Uricult®: midstream urine) in order to administer antibiotics according to the resistance situation, whereby a bacterial interstitial nephritis may also exist. In the case of a sterile leukocyturia, the possibility of urogenital tuberculosis should also be considered. However, it can also be the expression of an interstitial kidney disease, e.g., when taking indinavir, and can lead to the loss of renal function.

Glucosuria (with a normal blood sugar level/drop in the normal glucose level of the kidney) or phosphaturia are signs of a tubular disorder, such as can occur with medication (e.g., with TDF).

Routine tests for renal impairment
The routine checkup of an HIV-infected person should include tests for sodium, potassium, calcium, phosphate (every three months) and creatinine (creatinine clearance). The urine should be tested for glucosuria, proteinuria, erythrocyturia and leukocyturia every 3 months.

If there is a significant elevation in proteinuria or serum creatinine, a nephrologist should be consulted (renal biopsy if necessary). There is no time to waste in the case of a rapid increase of creatinine (to look for rapid-progressive glomerulonephritis), an increase of LDH connected with hyperbilirubinemia and thrombocytopenia (hemolytic uremia syndrome, HUS), or severe electrolyte imbalance (especially hyperkalemia), or acidosis that cannot be controlled, which can also occur on therapy as lactic acidosis.

An asymptomatic, slight proteinuria with no rise in creatinine can be observed in up to one third of untreated patients and should be monitored quarterly. The extent of the proteinuria can be assessed based on the urine protein / creatinine ratio of spontaneous urine, which when normal is <1 (e.g., urine protein 120 mg/dl and urine creatinine 30: proteinuria of 4 g/day).

A decrease in renal function in patients with HIV infection could be interpreted as a symptomatic HIV infection, and antiretroviral therapy may be considered. When employing imaging techniques, the use of a contrast medium (CM) for the urinary tract should be avoided, especially in cases of renal insufficiency, proteinuria and all forms of low intravasal volume (including cirrhosis of the liver), in order to avoid causing CM-induced renal failure.
HIV-associated nephropathy (HIV-AN)

HIV-AN is characterized by rapid loss of renal function, especially in African-Americans, and was first described in 1984. In the US, HIV-AN is the third most common reason for dialysis in African-Americans aged 20–64 years (Winston 2008). The genetic predisposition probably results from the reciprocity of the human gene MYH9 (nonmuscle myosin heavy chain 9) with HIV and a neighbouring apolipoprotein L1 gene as promoter of HIV-AN. As mutations of the ApoL-1 gene led to an evolutionary advantage in coping with sleeping sickness, HIV-AN is found almost exclusively in people of black African origin (Soleiman 2011, Kopp 2008, Kao 2008). Despite hemodialysis, the one-year survival rate amounts to approximately 50%; ART has reduced the dialysis risk through HIV-AN by 40%. In addition, the one-year survival rate on dialysis has increased from 25 to 75% thanks to ART (Winston 2008).

Most patients have a poor immune status with <100 CD4 T cells/µl (only 20% are in the normal range). Individual cases of sudden renal insufficiency within acute HIV syndrome have been reported. But there seems to be no correlation with HIV viral load or duration of HIV infection.

Nephrotic proteinuria usually presents clinically as more than 3.5 g/day, but a minor proteinuria is also possible. Progression is fast and can lead to end-stage renal disease (dialysis) in less than 10 months (Szczech 2001). Blood pressure is normal or slightly increased; the kidneys are within the normal size range when examined by ultrasound scan. Despite hemodialysis, the one-year-mortality rate is 50%; ART has reduced the risk of requiring dialysis by 40% and the one-year survival rate with dialysis has increased when using ART from 25 to 75% (Bruggemann 1997, Winston 2008).
The histological findings in biopsies correspond mostly (70%) to a focal segmental sclerosing glomerulonephritis (FSGN), which is also frequently observed in “malignant hypertension” in African-Americans. However, other causes of a glomerulonephritis, such as an amyloid kidney are also possible with HIV (Daugas 2005). Single case descriptions with the histological course of disease have confirmed the direct infection of the glomerular basal membrane with HIV, and have documented an impressive positive effect of ART on histological changes (Winston 2001). Experience with other FSGN forms has shown that only early intervention with ART – i.e., before scarring of the glomeruli due to the underlying disease – has a chance of success. This calls for a rapid reaction: HIV-AN is independent from the CD4 T cell count and viral load and the HIV must be treated. There is no specific recommendation for the selection of specific therapy. However, the different means of renal elimination (adjustment of dose) should be taken into consideration. ACE inhibitors or angiotensin receptor blockers should be added (see Table 2). The use of steroids is controversial (1 mg/kg/day for 2 to 11 weeks), but is favored in the US alongside starting ART, particularly in cases with a course similar to lupus (Haas 2005, Gupta 2005, Choi 2009).

The question of whether a case of HIV-AN needs to be confirmed by means of a kidney biopsy is the subject of discussion. Should the overall situation (i.e., genetic predisposition) suggest such a diagnosis, it is absolutely justified to begin ART in case of an HIV infection, and to await the success of the therapy over an observation period of 3 months. During this period, the viral load should be completely suppressed, the blood pressure well adjusted, if necessary diabetes treated and the therapy supplemented with a lipid therapy (Szczech 2009). It is often the case that renal function improves and proteinuria is retrogressive with this therapy. The decision to perform a biopsy and its performance should be placed in the hands of a nephrologist, who should possibly be consulted, depending on the extent of proteinuria and restriction of GFR (<60 ml/min/1.73 m²). Thanks to triple diagnostics made up of light and electron microscopy together with immunohistochemistry, kidney puncture can clarify the many causes of kidney damage and their prognosis.

Other cases of post-infectious glomerulonephritis with HIV

In caucasian HIV patients, IGA nephropathy, membranous and membranoproliferative GN must all be regarded as typical results of infection. At 5.6–32%, non-black African HIV patients show a considerably higher prevalence of proteinuria than non-infected persons (Soleiman 2011). Furthermore, many pathogens are able to trigger or support a post-infectious or other chronic GN. Viral infections such as CMV, EBV, HZV, influenza, adenovirus, hantavirus or parvovirus B19 do this as well as HIV. After malaria, syphilis and infections with staphylococci, pneumococci, legionella, salmonelli and other infectious agents, an acute post-infectious glomerulonephritis can also occur. In addition, there is a risk of circulatory renal failure in the case of profuse diarrhea in the context of an infectious bowel disorder.

In the case of membranous glomerulonephritis, malignant tumors and hepatitis (B and C) must be ruled out as a classical “secondary GN”. Chronic hepatitis C can lead to a membranoproliferative GN, or through cryoglobulinemia cause vasculitis with renal involvement.

The most common form of renal disease in Germany is IgA nephropathy, which can also be triggered by HIV, respiratory infections or infection with hepatitis A. With post-infectious GN, the underlying infection is treated first, and is then monitored so that the necessity of a possible additional immunosuppression can be deliberated
between nephrologist and HIV specialist. It is treated specifically (see below); the underlying infection is treated simultaneously. Irrespective of the liver histology, HCV-associated GN can also be a reason for therapy (observe dosing interval adjustments). However, only a greatly reduced dose or no ribavirin at all should be used if the creatinine clearance is less than 50 ml/min/1.73 m² because of the danger of prolonged anemia. In contrast, the new oral HCV agents boceprevir and telaprevir do not need to be dose-adjusted. In untreated HIV patients, hemolytic-uremic syndrome (HUS) or thrombotic-thrombocytopenic microangiopathy syndrome (TTP) can occur, characterized by the combination of creatinine increase, signs of hemolysis (LDH increases thrombopenia) and neurological symptoms with kidney failure. Pathophysiologically, the induction of pro-coagulatory effects of GP 120 (HIV) on endothelial cells can probably be assumed (Mikulak 2010). In principle, plasma separation or a therapy with immunoabsorption is necessary, in order to halt the otherwise bad prognosis, which can go all the way to the need for dialysis.

Principles of therapy of glomerulonephritis

The underlying cause of a post-infectious glomerulonephritis should be treated first, including hepatitis B, C and HIV infection. Kidney failure caused by hantavirus (transmitted through mouse or rat droppings) has a positive prognosis and its spontaneous course can be predicted. Particular attention should be paid to the adjustment of blood pressure. Target values are <140/80 mmHg or, in the presence of proteinuria, <130/80 mmHg. ACE inhibitors as well as AT-II-receptor antagonists are used to control blood pressure, usually in combination with diuretics. Proteinuria should be treated with an ACE inhibitor, at high doses if necessary, irrespective of the blood pressure measurement, and should be combined additionally with AT-II receptor antagonists if the proteinuria is more than 0.5 to 1 g/day. The protein intake is reduced to 0.6–0.8 g/kg/day (low protein diets like the Mediterranean diet may be helpful). High proteinuria (>3.5 g/24 h) calls for anticoagulation if the serum albumin concentration drops to levels below 25 g/l, as the renal loss of coagulation factors (AT III and many others) results in hypercoaguability and otherwise deep vein thrombosis can be expected (Phenprocoumon at INR 2–3 or NMH, if necessary dosed according to factor Xa determination in case of renal insufficiency). Fluids should be restricted to 1.5 to 2 l/day and adapted according to body weight and amount of edema. Not smoking is of vital importance because nicotine causes an increase in the risk of progression of glomerulonephritis. Hyperlipidemia should be treated after dietary arrangements have been exhausted. HMG-CoA reductase inhibitors are ideal, provided that they are combined with antiretroviral therapy (see chapter on Drug Interactions). Fibrates or fibrates plus statins may only be used carefully when renal function is reduced. Analgesics should be avoided as much as possible, especially the “small” analgesics such as ASA and paracetamol. If creatinine clearance reaches a value of less than 50 ml/min/1.73 m², treatment should be managed by a nephrologist.

Treatment of hypertension

Antihypertensive drugs offer an array of side effects, including hyperkalemia with ACE inhibitors. At a creatinine count of 1.4 mg/dl do not use potassium-saving diuretics; at a creatinine count >1.8 mg/dl only loop diuretics such as furosemide or torasemide should be used.
Table 1: Blood pressure adjustments

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Dosage (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Lisinopril, benazepril-HCL,</td>
<td>Dynasi® 5 mg QD, increase slowly to 20 mg/day</td>
</tr>
<tr>
<td></td>
<td>fosinopril sodium, enalapril,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etc</td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Metoprolol, bisoprolol</td>
<td>Beloc-Zok® (mite) 1x1</td>
</tr>
<tr>
<td>AT-II receptor</td>
<td>Valsartan, candesartan,</td>
<td>Blopress® first 2-4 mg/day, increase carefully to 16 mg/day</td>
</tr>
<tr>
<td>antagonists</td>
<td>telmisartan, etc</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Hydrochlorothiazide +</td>
<td>Dytide H® 1x1</td>
</tr>
<tr>
<td></td>
<td>triamterene</td>
<td></td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>Amlodipine</td>
<td>Norvasc® 5 mg qd, after &gt;1 week increase to BID if necessary</td>
</tr>
</tbody>
</table>

Renal safety of antiretroviral therapy

The spectrum of an allergic or autoimmune reaction in the kidney is no different from the skin or other internal organs. Reactions can be humoral or T cell-mediated and can lead to renal insufficiency. The spectrum ranges from the type I immune reaction (acute interstitial nephritis after exposure to medication) to the type IV T cell-mediated reaction (special forms of a chronic interstitial nephritis). Even the one-off use of an analgesic (e.g., ibuprofen) can lead to renal failure. This is possible with antiretroviral drugs. Any change of treatment should always be followed by a check of renal function after 14 days in case of any noticeable renal changes, then every 4 weeks in the first year.

Acute renal failure or acute tubular necrosis can also occur during treatment with acyclovir, gancyclovir, adefovir, aminoglycosides or pentamidine. Tubular dysfunction may also occur with ddI, d4T or 3TC. An acute allergic interstitial nephritis can arise in connection with a hypersensitivity reaction when taking abacavir. In patients taking atazanavir and T-20, membranoproliferative GN has been observed. Ritonavir and efavirenz can also cause kidney damage (Winston 2008). A number of specific drug-toxic renal damage effects should be familiar:

Typical side effects of antiretroviral therapy

Crystal-associated nephropathy

Renal problems due to crystalluria and nephrolithiasis have become rarer with the boosted doses used today versus the days of broad use of indinavir TID. Not until a mixed mass occurs in combination with calcium, however, does it become radio-opaque, which means it can be confused with a calcium–oxalate stone. Urate stones are transparent on x-rays.

Many medications can cause crystalluria and it is often a combination of agents that leads to nephrolithiasis. These agents include ampicillin, acyclovir, aspirin, ciprofloxacin, methotrexate, vitamin C, sulfonamide and other drugs that lead to an increase in uric acid. Forced fluid intake, Buscopan® and analgesics often lead to resolving acute renal colic without the need for hospitalization. Should it become necessary to consult a urologist, the risks involved in using contrast medium must be clarified.

Elevation of creatinine under long-term indinavir therapy was often observed at the end of the 1990s (Fellay 2001, Boubaker 2001). Typical signs of indinavir nephropathy include sterile leukocyturia and an echogenic transformation of the renal parenchyma in otherwise normal kidneys. Discontinuing indinavir leads to normal function in most cases. One should pay heed to the possibility of tuberculosis in the renal tract with sterile leukocyturia.
Hypophosphatemia and tubulotoxic damage, Fanconi’s syndrome

When the agents filtered from the glomerulum in primary urine exceed the transport capacity of the reabsorbing tubular cells they are excreted with the urine. The most prominent example is the glucose threshold of the kidneys (180 mg/dl). However, a transport dysfunction in the tubular system can also be caused by drugs such as cidofovir, tenofovir and adefovir. This is known as secondary (drug-induced) Fanconi's syndrome and is distinguished by a malfunction of the tubular system without there necessarily being any impairment of the GFR. There is an increased amount of phosphate, amino acids and glucose in the urine, whereas phosphate in the blood is reduced. The loss of amino acids, phosphate, glucose, bicarbonate and other organic and inorganic substances, as well as water, can become clinically manifest in the form of increased urination, thirst, tiredness, bone pain or weakness, and lead to secondary changes in the bone metabolism.

Not every hypophosphatemia (<0.8 mmol/l) is Fanconi’s syndrome. Hypophosphatemia also occurs under the influence of alcohol, with diabetes, cachexia, diarrhea or a disorder of vitamin D metabolism or hyperparathyroidism. About 10% of cases are found in untreated HIV-positive patients, 23% in people on ART and up to 31% in those taking tenofovir. The reasons are many and varied, including a low phosphate absorption (normal: 1200 mg/day). Unusual levels (<0.8 or 0.6 mmol/L) should be monitored and the patient examined for other symptoms of Fanconi’s syndrome. The determination of intact parathormone, vitamin D or an anamnesis with diuretics, vomiting or a tumor may indicate other causes of hypophosphatemia. The secretion ratio of phosphate to creatinine can be a sign of tubular damage if, despite hypophosphatemia, more than 10% of the filtrated phosphate is secreted (Jamison 1982).

In case reports, renal failure has above all been described in patients with other reasons for renal insufficiency, mostly in ART combinations that include boosted PI regimens and tenofovir as well as secondary disorders and cirrhosis of the liver or hepatitis. Nephrologists advise caution in selecting antiretroviral therapy for patients with proteinuria, nephritic syndrome, cirrhosis of the liver, and/or dyslipoproteinemia. Nephrotoxic agents such as cidofovir, adefovir and tenofovir should be avoided in these patients. In principle, it is possible to administer NRTIs, but in individual cases, the patient’s resistance profile permitting, a combination of two boosted PIs, a combination of an NNRTI plus a PI or a combination of raltegravir and maraviroc can be considered kidney-neutral solutions in individual cases. Careful monitoring of serum creatinine, proteinuria, erythrocyturia and serum phosphate is recommended.

Tenofovir and the kidney

In view of the broad use of tenofovir, more attention must be devoted to long-term renal toxicity in the future. In a meta-analysis of 17 studies, a slight reduction of GFR on TDF (-3.92 ml/min) and a slightly increased risk of renal failure (+0.7%) were observed. However, this was not considered reason for restrictive use, if attention is paid to the renal function (Cooper 2010). Based on 455,392 patient years, the incidence of unwanted renal occurrences in the manufacturer’s database since drug approval amounts to 29.2 renal events per 100,000 patient years (Nelson 2006). In the prospective studies GS903E and GS934, a creatinine increase to >1.5 mg/ml was observed during an observation period of 144 weeks in less than 1% of patients, and proteinuria of more than 100 mg/dl in less than 5%. However, patients suffering from renal insufficiency were excluded from these studies (Gallant 2008).
The leading renal event when taking tenofovir is Fanconi’s syndrome (22.4/100,000 patient years). This is diagnosed in conjunction with hypophosphatemia, glucosuria (renal diabetes mellitus with normal blood sugar) and a mild proteinuria. It occurs on average seven months after starting therapy and disappears some four to six weeks after discontinuation (Izzedine 2004). An isolated case of hypophosphatemia without glucosuria in HIV cannot be defined as Fanconi’s syndrome and can just as well be due to malnutrition, vitamin D deficiency, diuretics or alcohol, and doesn’t necessarily mean tenofovir must be discontinued.

In the registration studies the incidence of renal events (changes in creatinine clearance, glucosuria, proteinuria, hypokalemia and acidosis) when taking tenofovir was no higher than in the control groups. With patients treated previously, however, hypophosphatemia was observed in 13% after 24 weeks (113 weeks: 22%). This was more often than in the placebo arm, but not associated with other tubulotoxic symptoms (Gallant 2004, Gallant 2006). The median time to occurrence of renal side effects amounted to nine months in one study (Izzedine 2004). The risk is increased through the combination with nephrotoxic agents, kidney disease or renal insufficiency in the patient history, sepsis, dehydration, extremely advanced HIV disease or severe hypertension (Nelson 2006). Cohort analyses show CD4 T cells <50/µl, age >45 years, diabetes mellitus and long-term previous treatment with ART as risk factors (Moore 2007).

Like the other NRTIs, tenofovir is eliminated renally and must be dose-adjusted in cases of renal insufficiency. Contrary to earlier case studies and the fact that ritonavir increases the Cmax and the AUC of tenofovir by about 30%, combination with boosted PIs is possible. This is also confirmed by in vitro studies (Izzedine 2005, Ray 2005). In cohort studies, a reduction of GFR of 7–10 ml/min was observed, whereby the total GFR remained in the normal range, but there was an apparently faster drop in GFR when tenofovir is combined with PIs instead of NNRTIs (Goicoechea 2008, Winston 2008). The use of tenofovir during pregnancy does not seem to be associated with damage to renal function in neonates (Linde 2010, personal correspondence).

In the first year of treatment with tenofovir patients with healthy kidneys should be monitored monthly, followed by quarterly monitoring. The determination of creatinine, (calculated) GFR, phosphate and glucose in serum and urinstix with a check for proteinuria, glucosuria and erythrocyturia are sufficient. Patients with kidney dysfunction are monitored more often. In the case of additional nephrotoxic agents or drugs which are also excreted via the renal transporter (aminoglycosides, amphotericin B, famcyclovir, gancyclovir, pentamidine, vancomycin, cidofovir, IL-2), renal function is monitored weekly.

**Dosage of antiretrovirals in renal insufficiency**

In each case, the technical information of the individual agents apply. Because NNRTIs and PIs are almost exclusively hepatically eliminated, a dose rate adjustment is normally only necessary for NRTIs, unless an insufficiency of the liver is also present. In the case of limited renal function and combination with a CYP 3A4 inhibitor, maraviroc must be dosed according to substance and GFR (product information). In fixed-dose combinations (FDCs), the most strongly accumulating substance is always decisive. Thus, FDCs should be avoided in patients with a GFR <50 ml. In the case of hepatitis C therapy, ribavirin should be omitted in patients with renal insufficiency (prolonged anemia) if the creatinine clearance is less than 50 ml/min/1.73 m². T-20 can be used up to an endogenous creatinine clearance of 30 ml/min/1.73 m² without dose reduction; no data is available for more severe renal insufficiency.
Table 2: Dosage of antiretroviral medications in presence of renal insufficiency (in each case diurnal dosages, if not otherwise stated). HD=Hemodialysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Standard dose</th>
<th>CrCl (ml/ min)</th>
<th>Dose in renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT (Retrovir®)</td>
<td>2 x 250 mg</td>
<td>&gt;10</td>
<td>2 x 250 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10</td>
<td>300–400 mg</td>
</tr>
<tr>
<td>3TC (Epivir®)</td>
<td>1 x 300 mg or</td>
<td>&gt;10</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td>2 x 150 mg</td>
<td>30–49</td>
<td>1 x 150 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30</td>
<td>150 mg (15 ml) on day 1; 100 mg (10 ml)/day thereafter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5</td>
<td>50 mg (5 ml) on day 1; 25 mg (2.5 ml)/day thereafter</td>
</tr>
<tr>
<td>AZT+3TC (Combivir®)</td>
<td>2 x 1 tab.</td>
<td>&gt;50</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
<td>Not recommended</td>
</tr>
<tr>
<td>ABC (Ziagen®)</td>
<td>2 x 300 mg</td>
<td>&gt;50</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>AZT+3TC+ABC (Trizivir®)</td>
<td>2 x 1 tab.</td>
<td>&gt;50</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
<td>Not recommended</td>
</tr>
<tr>
<td>d4T (Zerit®)</td>
<td>2 x 40 mg (&gt;60</td>
<td>&gt;50</td>
<td>Standard dose half standard dose</td>
</tr>
<tr>
<td></td>
<td>kg) 2 x 30 mg (&lt;60</td>
<td>30–49</td>
<td>quarter standard dose</td>
</tr>
<tr>
<td></td>
<td>kg)</td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>ddl (Videx®)</td>
<td>1 x 400 mg (&gt;60</td>
<td>&gt;60</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td>kg) 1 x 250 mg (&lt;60</td>
<td>30–59</td>
<td>Half standard dose</td>
</tr>
<tr>
<td></td>
<td>kg)</td>
<td>10–29</td>
<td>1 x 150 or 100 mg</td>
</tr>
<tr>
<td></td>
<td>(combined with</td>
<td>&lt;10</td>
<td>1 x 100 or 75 mg</td>
</tr>
<tr>
<td></td>
<td>TDF never exceed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 x 250 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF (Viread®)</td>
<td>1 x 300 mg</td>
<td>&gt;50</td>
<td>Standard dose every 24 h</td>
</tr>
<tr>
<td></td>
<td>(TDF disoxoproxil</td>
<td>30–49</td>
<td>1 tab. every 48 h</td>
</tr>
<tr>
<td></td>
<td>fumarate)</td>
<td>10–29</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15 (incl. HD)</td>
<td></td>
</tr>
<tr>
<td>FTC (Emtriva®)</td>
<td>1 x 200 mg</td>
<td>&gt;50</td>
<td>Standard dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–49</td>
<td>200 mg every 2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–29</td>
<td>200 mg every 72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15 (incl. HD)</td>
<td>200 mg every 96 h</td>
</tr>
<tr>
<td>TDF (Truvada®)</td>
<td>1 x 1 tab.</td>
<td>&gt;50</td>
<td>Standard dose every 24 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–49</td>
<td>1 tablet every 48 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30 and HD</td>
<td>Not recommended</td>
</tr>
<tr>
<td>TDF+ FTC (Truvada®)</td>
<td>1 x 1 tab.</td>
<td>&gt;50</td>
<td>Standard dose every 24 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–49</td>
<td>1 tablet every 48 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30 und HD</td>
<td>Not recommended</td>
</tr>
<tr>
<td>TDF+ FTC+ EFV (Atripla®)</td>
<td>1 x 1 tab.</td>
<td>&gt;50</td>
<td>Standard dose every 24 hrs</td>
</tr>
<tr>
<td>TDF+ FTC+ ETR (Eviplera)</td>
<td></td>
<td>&lt;50</td>
<td>Not recommended</td>
</tr>
<tr>
<td>MVC (Celsentri®)</td>
<td>2 x 300 mg</td>
<td>50–80</td>
<td>Reduction of the standard dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50–30</td>
<td>Only in combination with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30</td>
<td>CYP 3A4-Hemern: see literature</td>
</tr>
</tbody>
</table>
Oils and renal insufficiency

Pneumocystis pneumonia

As high dose co-trimoxazole is nephrotoxic, its use must be carefully weighed. Systemic administration of pentamidine should also be avoided in patients with renal insufficiency.

Table 3: PCP treatment in renal insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR normal</th>
<th>GFR &gt;50 ml/min</th>
<th>GFR 10–50 ml/min</th>
<th>GFR &lt;10 ml/min</th>
<th>Dose adaptation for HD/CAPD/cont. NET</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Co-trimoxazole</em></td>
<td>160/800mg 3 x TID (total of 120 mg/kg daily)</td>
<td>(100% every 12 h)</td>
<td>(100% every 12–24 h)</td>
<td>(50% every 24 h)</td>
<td>HD: + half dose after dialysis CAPH: no adaptation CVVH: GFR &lt;10</td>
</tr>
<tr>
<td>Dapsone</td>
<td>100 mg every 24 h</td>
<td>50–100%</td>
<td>50%</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>750 mg every 12 h</td>
<td>100%**</td>
<td>100%**</td>
<td>100%**</td>
<td>HD: no adaptation CAPD: no adaptation* CAPH: (GFR &lt;10)**</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>4 mg/kg every 24 h</td>
<td>100%</td>
<td>100% every 24–36 h</td>
<td>100% every 48 h See text</td>
<td>HD: (GFR &lt;10)** CAPD: (GFR &lt;10)** CAPH: (GFR &lt;10)**</td>
</tr>
</tbody>
</table>

* no studies available, normal dosage recommended, ** no studies available, dosage as for GFR <10 ml/min recommended.
(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

Toxoplasmosis encephalitis

Table 4: Treatment of cerebral toxoplasmosis with renal insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR normal</th>
<th>GFR &gt;50 ml/min</th>
<th>GFR 10–50 ml/min</th>
<th>GFR &lt;10 ml/min</th>
<th>Dose adaptation for HD/CAPD/cont. NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine</td>
<td>50–75 mg every 24 h</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>HD: no adaptation CAPD: no adaptation CAPH: no adaptation</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>150–300 mg every 6 h</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>HD: no adaptation CAPD: (GFR &lt;10)* CAPH: (GFR &lt;10)* CVVH: GFR normal</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>2 g every 6 h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

* no studies available, dosage as for GFR <10 ml/min recommended.
(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).
CMV, HSV, HZV infection

Table 5: Treatment of CMV, HSV, HZV in renal insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR normal</th>
<th>GFR &gt;50 ml/min</th>
<th>GFR 10–50 ml/min</th>
<th>GFR &lt;10 ml/min</th>
<th>Dose adaptation for HD/CAPD/cont. NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>5–10 mg/kg every 8 h</td>
<td>5 mg/kg every 8–12 h</td>
<td>5 mg/kg every 12–24 h</td>
<td>2.5 mg/kg every 24 h</td>
<td>HD: Dose after dialysis CAPD: GFR &lt;10 CAVH: 3.5 mg/kg every 24 h CVVHD: 6.5–15 mg/kg every 24 h</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>5 mg/kg every 12 h</td>
<td>3 mg/kg every 12 h if GFR 25–50 ml</td>
<td>3 mg/kg every 24 h if GFR 10–25 ml</td>
<td>15 mg/kg every 24 h</td>
<td>HD: Dose after dialysis CAPD: GFR &lt;10 CAVH: 3.5 mg/kg every 24 h CVVHD: 2.5 mg/kg every 24 h</td>
</tr>
<tr>
<td>Valgan-cyclovir</td>
<td>900 mg every 12 h</td>
<td>GFR 40–59 ml/min</td>
<td>450 mg every 12 h GFR 25–39 ml/min</td>
<td>450 mg every 24 h GFR 10–24 ml/min</td>
<td>450 mg every 48 h for induction</td>
</tr>
<tr>
<td>Foscavir</td>
<td>90 mg/kg every 12 h</td>
<td>50–100%</td>
<td>10–50%</td>
<td>Avoid</td>
<td>HD: Dose after dialysis CAPD: 60 mg/kg every 48–72 h CAVH: GFR 10–50</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>5 mg/kg every 7 days</td>
<td>100%</td>
<td>0.5–2 mg/kg every 7 days</td>
<td>Avoid</td>
<td>HD: GFR 10–50 CAPD: GFR 10–50 CAVH: avoid</td>
</tr>
<tr>
<td>Famcyclovir</td>
<td>250 mg every 8 h p.o.</td>
<td>Every 12 h</td>
<td>Every 48 h</td>
<td>50% every 48 h</td>
<td>HD: Dose after dialysis CAPD: ? CAVH: GFR 10–50</td>
</tr>
</tbody>
</table>

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

References


Metabolic abnormalities are common side effects of ART. With a growing cardiovascular risk from the increasing age of the HIV population, diagnosis and therapy of HIV-associated cardiovascular diseases are becoming more and more important (Neumann 2002a, Dakin 2006).

**Coronary artery disease (CAD)**

In the D:A:D study, the most extensive study of its kind including more than 23,000 patients, a 26% increase in the incidence of myocardial infarction (MI) was found with each year of ART exposure (Friis-Møller 2003, Law 2006). However, the event rate was small, with 3.5 MIs per 1000 patient-years. Antiretroviral therapy was an independent risk factor for CAD along with the classic cardiovascular risk factors like age, gender and particularly smoking (Law 2006). Recent publications from Lundgren’s group report that known CAD and diabetes exhibit an especially high risk for subsequent cardiovascular events (CAD: 7.5-fold; diabetes: 2.4-fold) (Worm 2009). Therefore, in patients with known CAD or diabetes plus ART risk factors should be consequently treated and the patients should be monitored closely for new symptoms of CAD especially because a recent publication suggests insufficient treatment of this group of patients (Reinsch 2012).

Prevention and early diagnosis of CAD in HIV-infected patients older than 45 years and with an elevated cardiovascular risk profile should be routine in current therapeutic management of HIV infection. Primary and secondary prevention aims at modifying known risk factors (Lundgren 2008a). Hypercholesterolemia and hypertriglyceridemia are common side effects of PIs. However, there are also some antiretroviral therapies that reduce lipid values (Colafigli 2008).

Of interest is the effect of NRTIs on the occurrence of myocardial infarction. The D:A:D study reported an increased rate of MI for abacavir and ddI (Sabin 2008). An elevated incidence of cardiovascular events was also found in a retrospective analysis of the SMART study as well as in another retrospective analysis of a Danish workgroup (Obel 2010). Inflammation may be the cause of this increased cardiovascular event rate (Lundgren 2008b). On the contrary, a recent FDA meta-analysis plotting data of almost 10,000 patients could not find a statistical significant difference of MI events between subjects receiving abacavir-containing ART and other ART regimens (Ding 2011).

When using PIs the increased event rate was associated with an increase in classic risk factors such as diabetes and hyperlipidemia which may explain some of the events. Patients undergoing therapy with abacavir also were likely to be male and had an increased rate of risk factors like increased age, diabetes and pre-existing cardiovascular disease. Further investigation is needed to clarify how much classical risk factors contribute to the MI event rate. When looking at NNRTIs and some PIs (nelfinavir, saquinavir) and NRTIs (AZT, d4T, 3TC, tenofovir) there was no hint of an increased cardiovascular event rate (Worm 2010). To what extent these results have an effect on medical care of HIV-infected patients remains unclear.

Data collected in the SMART-study showed an increase in cardiovascular event rate during cessation of ART (El-Sadr 2006). It was suggested that an increase of inflammation is responsible for this finding. (Kuller 2008). Thus, the primary goal of ART still is the virologic control of HIV-infection. This should not be jeopardized by changing the medication to a metabolic more favourable treatment.
Besides ART and the classical risk factors there is some evidence that HIV itself may promote atherosclerosis by chronic inflammation. Studies focusing on subclinical atherosclerosis predict an increasing prevalence of CAD in the near future (Lo 2010, Triant 2009).

Even without ART it has been shown that HIV-infected subjects exhibit a marked cardiovascular risk profile (Neumann 2003, Neumann 2004a+b). Most notably, cigarette consumption is two- to three-fold higher than in the non-HIV-infected population. Prevention of coronary heart disease is based on the guidelines for non-HIV-infected patients (Smith 2006, Perk 2012) (Table 1) and the EACS guidelines (Lundgren 2008a).

Cessation of smoking and healthy food choices are the first steps in modifying cardiovascular risk profile. The consumption of fruits, vegetables, whole grain bread and low fat dairy products as part of a balanced diet should be encouraged. Hyperlipidemia can further be approached by a careful change in ART and by lipid lowering drugs (Dube 2003). Statin therapy might interact with the metabolism of common antiretroviral drugs. In particular, several PIs act as substrates for isoenzyme 3A4, a subgroup of the cytochrome p450 system. Inhibition of isoenzyme 3A4 by antiretroviral drugs can increase the blood concentration of statins and induce side effects. In contrast to most other statins, pravastatin and fluvastatin are not modulated by isoenzyme 3A4. Therefore, these two drugs are particularly preferred for HIV-infected patients (see the chapter on Lipodystrophy). Certain prevention programs have shown to be able to reduce the cardiovascular risk profile of HIV-infected patients (Lima 2008).

### Table 1: Prevention of coronary heart disease

- **Stop Smoking**
- **Make healthy food choices**
- **Modulation of LDL cholesterol**
  - Low risk (0-1 risk factors): <160 mg/dl (4.14 mmol/l)
  - Intermediate risk (2 or more risk factors): <130 mg/dl (3.36 mmol/l)
  - High risk (i.e., CAD or diabetes mellitus): <100 mg/dl (2.59 mmol/l)
- **Optimize blood glucose value (HbA1c <6.5%)**
- **Reduce alcohol consumption (<15 g/d)**
- **Regular exercise training (1-2 h per week)**
- **Optimize blood pressure (systolic: <130 mmHg, diastolic <85 mmHg)**

HIV-infected patients with cardiovascular risk factors should undergo an annual cardiac check-up, including a resting ECG and estimation of the cardiovascular disease risk. Symptomatic patients need further cardiovascular examinations (exercise ECG, stress echocardiography, laboratory work-up and, in some cases, scintigraphy of myocardium or coronary angiography). Clinical symptoms of coronary heart disease mostly occur due to a critical stenosis of more than 75%. In randomized clinical trials low-dose aspirin (100 mg/d), β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins decrease the risk of mortality and re-infarction. If aspirin is not tolerated it may be substituted by drugs that block the ADP-receptor on platelets such as clopidogrel 75 mg/d. A calcium antagonist, nitrates, ranolazin and/or procoralan can be supplemented for symptomatic treatment.

The indication for invasive vascular diagnostic and intervention depends on current guidelines (http://www.escardio.org/knowledge/guidelines). Clear indications for coronary angiography are a documented exercise-induced ischemia, typical clinical symptoms together with ST-alterations in the ECG, increases in cardiac enzymes.
and/or a marked cardiovascular risk profile. It is worth emphasizing that HIV infection is not an exclusion criteria for invasive procedures. Successful coronary interventions have been performed on HIV-infected patients, including catheter procedures with implantation of drug-eluting stents (DES) (Saporito 2005, Glazier 2006, Neumann 2010) and coronary artery bypass operations (Filsoufi 2006). However, there are some reports that show an increased rate of re-stenosis after DES and increased rate of “major adverse cardiac events” following surgical revascularization in HIV-infected patients compared to non-HIV-patients (Boccara 2008, Ren 2009).

Congestive Heart Failure

Congestive heart failure includes a variety of myocardial alterations. In HIV-infected patients, HIV-associated dilated cardiomyopathy is of major interest. It corresponds to a dilated and less contractile left ventricle (Dakin 2006, Butt 2012). Myocarditis is still the most thoroughly studied cause of dilated cardiomyopathy in HIV disease. Until now, a variety of pathogens has been found in the myocardial tissue of HIV-infected patients (Patel 1996, Wu 1992). Furthermore, HIV itself appears to infect myocardial cells in a patchy distribution. Myocardial damage by gp120 and cytokine-mediated apoptosis is presumed (Fiala 2004).

In addition to a direct impact of HIV or other pathogens, dilated cardiomyopathy was reported in association with an autoimmune reaction. Cardiac-specific autoantibodies (anti-α-myosin antibodies) have been reported in up to 30% of HIV-infected patients with cardiomyopathy. However, several studies indicate that in HIV-infected patients dilated cardiomyopathy is associated with cardiotoxic agents (e.g., pentamidine, interleukin-2, doxorubicin) or as an effect of malnutrition (Nosanchuk 2002). Furthermore, it is under discussion whether antiretroviral drugs may induce cardiac dysfunction due to mitochondrial toxicity (Lewis 2006, Purevjav 2007). In this context a recent retrospective study of a large cohort of HIV-infected patients showed an association of tenofovir intake and incident heart failure (Choi 2011).

Depending on the study the prevalence of heart failure in the pre-HAART era was between 9% and 52% in HIV-infected patients (Ntshoke 2005) and 29% in patients with AIDS (Levy 1989). Since the introduction of HAART the prevalence of dilated cardiomyopathy seems to have decreased. In an Italian cohort a prevalence of 1.8% at the end of the 1990s was reported (Pugliese 2000).

Unfortunately, heart failure is often not recognized. In a prospective study of 416 HIV patients with unknown heart disease the frequency of cardiac dysfunction was 17.7% (Twagitirimukza 2007). Diastolic dysfunction was found in up to 48% of subjects in the HIV-HEART study (Reinsch 2010). Besides left ventricular dysfunction, cardiomyopathy often includes dilatation and reduced contraction of the right ventricle. However, a Danish study that enrolled 90 HIV-infected patients did not find an increased rate of right ventricular dysfunction (Kjaer 2006).

The diagnosis of chronic heart failure is based on clinical findings and symptoms. In addition to exercise intolerance, patients often exhibit dyspnea and edema. Nocturia, night cough (cardiac asthma), peripheral cyanosis and an increase of weight may also occur. In these cases, ECG, x-ray and echocardiography may lead to the diagnosis of heart failure.

Of proven value for diagnosis and follow-up is the serum parameter b-type natriuretic peptide (BNP or NTproBNP). The diagnostic value of BNP has been confirmed in the setting of HIV infection and heart failure (Neumann 2009). Exercise intolerance can be determined by a 6 minute walk test, exercise ECG or spiroergometry. In some cases, further diagnosis can be performed with an MRI or CT revealing scar tissue or coronary artery calcification (Breuckmann 2007). Invasive diagnosis includ-
ing myocardial biopsies is often recommended in unexplained cases of chronic heart failure. Stable chronic heart failure patients in an early stage should be monitored annually. In advanced stages the monitoring should include ECG, echocardiography and occasional BNP measurements every 3 to 6 months. Therapy of congestive heart failure depends on current guidelines (www.escardio.org/) and begins with moderate and regular exercise in combination with a healthy diet, including a reduced fluid and salt intake. Therapeutic options that could eliminate the causes of heart failure (such as revascularization, operative valve replacement in the case of a primary vitium or intensive antibiotic therapy for bacterial myocarditis) have priority. In these cases, cooperation with a specialized center is recommended. Contemporary treatment of congestive heart failure includes medication with a beta-blocker, an ACE-inhibitor and an aldosteron-antagonist for neurohumoral blockage as a fundamental treatment that should at lest be considered for every patient suffering from heart failure. Diuretics are often added for symptomatic relief.

In the setting of sinus rhythm, ejection fraction <35% and symptomatic heart failure additional ivabradine can reduce hospitalization rate and increase LV function and quality of life. If ejection fraction remains below 35% besides optimal medical treatment for 3 months primary prevention with an implantable cardioverter defibrillator (ICD) to reduce the risk of sudden death is indicated. Cardiac resynchronization therapy has to be considered in symptomatic patients in cooperation with a cardiologist.

Co-morbidities such as anemia, diabetes, COPD, gout, depression and sleep disordered breathing are associated with worse prognosis. Case reports also describe heart transplantation and treatment with an assist device in HIV patients (Sims 2011). For these cases cooperation with a specialized center is mandatory. Non-steroidal anti-rheumatics (NSAR), class I antiarrhythmic drugs, dronedarone, calcium channel blockers (verapamil, diltiazem and short-acting dihydropyridine derivatives), glitazones for the treatment of diabetes and addition of angiotensin receptor antagonist or renin inhibitor to established therapy with ACE-inhibitor and aldosteron antagonist should be avoided. Chronic heart failure is associated with a reduced life expectancy. In cases of NYHA III-IV, the annual mortality rate rises to 25%. While in some cases a total recovery has been described (Fingerhood 2001, Tayal 2001), the majority of patients with HIV-associated dilated cardiomyopathy still have a progression of left ventricular dysfunction and a poor prognosis (Felker 2000). It is unclear whether ART has an influence on the recovery of ventricular function. Potentially helpful for the assessment of prognosis in HIV cardiomyopathy is the evaluation of contractile reserve by stress echocardiography (Wever-Pinzon 2011). Early diagnosis and conventional therapy seem to be the most promising ways to reduce disease progression.

**Pericardial effusion**

While pericardial effusion in the context of HIV infection is still common in African cohorts (Siwa 2011, Chillo 2012) the prevalence in a German cohort studied in the HIV-HEART study was below 1% (Lind 2011). However, the majority of HIV-associated pericardial manifestations are described as asymptomatic. Nevertheless, the spectrum ranges from acute or chronic pericarditis to an acute pericardial tamponade (Silva-Cardoso 1999, Park 2010). Causes may include HIV itself, opportunistic pathogens, immune reconstitution syndrome or
neoplasms (Stotka 1989). By far, the most frequent cause of pericardial effusion in African cohorts is tuberculous pericarditis (Reuter 2005). However, non-HIV-associated causes of pericardial effusion, such as uremia, trauma, irradiation, and drugs have to be considered. In some cases of lipodystrophy an increase in the cardiac lipid tissue could simulate an extensive pericardial effusion (Neumann 2002b). Echocardiography is referred to as the standard method for diagnosis and follow-up of pericardial diseases. Nevertheless, further diagnosis should be performed by computer tomography and/or magnetic resonance tomography when a neoplasm or an increase in the cardiac lipid tissue is suspected. Pericardial puncture has to be considered for symptomatic patients and pericardial tamponade. If possible, a causative therapy should be applied. Pericardiotomy might be an option as well.

Cardiac arrhythmias

Cardiac arrhythmias can depend on medication. Antiretroviral drugs, e.g., efavirenz, foscarnet, pentamidine, or therapy with methadone, are expected to prolong the QT interval, an alteration in ECG that may cause Torsade de pointes tachycardia (Castillo 2002). Further drug combinations such as a macrolides and a chinolones may have the same effect on the QT interval. Results of the HIV-Heart study showed that prolongation of the QT interval is frequently found (20%). However, a correlation with antiretroviral drugs was not established (Reinsch 2009). Another prospective study also showed no correlation between QT prolongation and therapy with PIs (Charbit 2009).

Initiation or change of medication that might influence the QT interval should be controlled regularly by ECG. In case of arrhythmias, electrolyte and glucose concentrations have to be determined and corrected if necessary. Magnesium may be used for termination of Torsades de pointes tachycardia. Furthermore, heart rhythm disorders may occur together with myocardial infection. Dilatation of the ventricles carries an increased risk of life-threatening arrhythmias and sudden cardiac death (Lanjewar 2006). Ventricular arrhythmias were observed in the context of immune reconstitution syndrome (Rogers 2008). Conduction abnormality, bundle branch block and sinus arrest have been reported to occur with lopinavir/r and in combination with atazanavir (Chaubey 2009, Rathbun 2009).

The new anti-arrhythmic substance dronedarone is contraindicated together with ritonavir because of metabolism by CYP 3A4.

Valvular heart disease / endocarditis

Valvular heart disease of HIV-infected patients occurs as a bacterial or mycotic endocarditis. The hypothesis that HIV infection alone makes a subject more susceptible to infective endocarditis has not been validated. However, intravenous drug users have a ten- to twelve-fold increased risk for infective endocarditis than non-intravenous drug users. The most frequent germ is *Staphylococcus aureus*, detected in more than 40% of HIV-infected patients with bacterial endocarditis. Further pathogens include *Streptococcus pneumoniae* and *Hemophilus influenzae* (Currie 1995). Mycotic forms of endocarditis, which may also occur in patients who are not intravenous drug users, mostly belong to *Aspergillus fumigatus*, Candida species or *Cryptococcus neoformans* and are associated with a worse outcome.

A retrospective study showed no difference in the clinical outcome of *Staphylococcus aureus* endocarditis comparing HIV-patients and non-HIV-patients (Fernandez 2009). Signs of infective endocarditis include fever (90%), fatigue and lack of appetite. An additional heart murmur may also be present (30%). In these cases, repeated blood
cultures should be taken and transesophageal echocardiography is mandatory (Bayer 1998). Due to the fact that the detection of the infectious agent is often difficult, antibiotic therapy should be started early when endocarditis is presumed (Duke criteria), even without the microbiology results. Antibiotic prophylaxis of endocarditis is not generally recommended for HIV-positive patients. According to current guidelines for infectious endocarditis, antibiotic prophylaxis is only recommended for a very small patient population. For detailed information go to http://www.escardio.org/.

**HIV-associated pulmonary arterial hypertension**

One complication of HIV-infection is the development of pulmonary arterial hypertension. As pulmonary hypertension in HIV-patients clinically and histologically resembles idiopathic pulmonary arterial hypertension (PAH), HIV infection was included as one cause of PAH in the classification of pulmonary hypertension (Evian Classification, last modified 2008 Dana Point (Simonneau 2009)). Pulmonary hypertension is defined as mean pulmonary artery pressure >25 mmHg at rest (Badesch 2009).

The most recent study showed a prevalence of HIV-associated PAH of 0.45% (Sitbon 2008). The incidence is around 1/1000 HIV patients/year. Compared to other forms of pulmonary hypertension HIV-associated PAH has a worse prognosis.

The etiology of HIV-associated PAH is a combination of vasoconstriction and vascular remodeling with endothelial dysfunction proliferation of endothelial and smooth muscle cells and finally vessel obliteration. As the majority of HIV-positive subjects does not develop pulmonary hypertension, a complex genesis including genetic predisposition is likely. At the beginning there is inflammation which is fueled by HIV-proteins tat, pg120 and in particular nef (Hassoun 2009). Pulmonary hypertension leads to an increased afterload of the right ventricle with hypertrophy, right heart dilatation and finally heart failure.

In a prospective study women were more likely to be affected (1:1.4) by HIV-associated PAH and intravenous drug abuse was the most common way of infection (53%) (Krings 2007, Reinsch 2008).

Dyspnea on exertion is the most common symptom of pulmonary hypertension. At the time of diagnosis 2/3 of patients can be classified in advanced stages of heart failure (NYHA III/IV). Further symptoms are lower limb edema, (dry) cough, syncope, angina, fatigue and weakness.

On physical examination one should pay attention to signs of right heart failure as there are edema, tachycardia, jugular vein distention and hepatomegaly. On auscultation one may find right parasternal systolic murmur indicating tricuspid insufficiency and splitted second heart sound.

Based on clinical suspicion (dyspnea, syncope, edema, cough) further diagnostic work-up should consider pulmonary hypertension as one possible diagnosis. ECG and chest x-ray show indirect signs. With the help of transthoracic echocardiography one can determine systolic pulmonary artery pressure (sPAP) and assess right ventricular form and function.

In the case of elevated sPAP and signs of right ventricular strain pulmonary hypertension is probable. For definite diagnosis and acute vasodilator testing right heart catheterization is mandatory. To rule out other possible reasons for pulmonary hypertension such as chronic obstructive pulmonary disease or pulmonary thromboembolism, a CT scan and lung function test are often needed.

There are several therapeutic options to reduce pulmonary artery pressure. The world consensus conference in Dana Point acknowledged the endothelin receptor antag-
onists bosentan and ambrisentan as well as sildenafil as class A for WHO functional class II. Metabolism of sildenafil interferes with PIs such as ritonavir so that increased plasma level concentrations can be expected. Carefully dosing is required (Chinello 2012). Further therapeutic substances in more advanced stages of PAH include derivates of prostacyclin intravenously, subcutaneously and inhalation (Barst 2009). HIV-associated PAH has only been studied in uncontrolled clinical trials. Bosentan and long-term infusion of epoprostenol seem to improve hemodynamics and exercise tolerance (Sitbon 2004). General measures include diuretics, oral anticoagulation, oxygen and if appropriate digoxin and rehabilitation. Physical stress and pregnancy should be avoided. Every effort should be made to prevent pneumonia. Before initiating are therapy acute vasodilator testing is mandatory. A long-term response to calcium channel blockers after positive testing was observed in 1.6% of subjects suffering from HIV-associated PAH (Montani 2010). ART has been shown to improve prognosis and is thus recommended independent of CD4 cell count or clinical stage of HIV infection (Zuber 2004, Degano 2010). The patient with HIV-associated pulmonary hypertension should be diagnosed and followed in a specialized center.

**Further cardiac manifestations**

Heart neoplasms are rarely found in HIV-infected patients. These manifestations occur predominantly diagnosed in advanced stages of the disease. On autopsy, the rates of cardiac-localized Kaposi’s sarcoma and lymphoma are less than one percent. Some infections of the heart in HIV-positive subjects may not only result in myocarditis but in abscesses. Several opportunistic pathogens including *Toxoplasma gondii* and trypanosomes have been reported to cause abscesses in the heart. These manifestations are believed to decrease with ART. As well as neoplasms and abscesses, vascular alterations including vasculitis and perivasculitis have been described as further cardiovascular manifestations in HIV-infected patients.

<table>
<thead>
<tr>
<th>Table 2: Cardiac diseases in HIV-infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pericardial diseases</strong></td>
</tr>
<tr>
<td>• Pericardial effusion</td>
</tr>
<tr>
<td>• Pericarditis (viral, bacterial, mycotic)</td>
</tr>
<tr>
<td>• Neoplasm (Kaposi’s sarcoma, lymphoma)</td>
</tr>
<tr>
<td><strong>Myocardial diseases</strong></td>
</tr>
<tr>
<td>• HIV-associated dilated cardiomyopathy</td>
</tr>
<tr>
<td>• Myocarditis (acute or chronic)</td>
</tr>
<tr>
<td>• Neoplasm (Kaposi’s sarcoma, lymphoma)</td>
</tr>
<tr>
<td>• Drug side-effects (especially antiretroviral therapy)</td>
</tr>
<tr>
<td><strong>Endocardial diseases</strong></td>
</tr>
<tr>
<td>• Infective endocarditis (bacterial, mycotic)</td>
</tr>
<tr>
<td>• Nonbacterial thrombotic endocarditis</td>
</tr>
<tr>
<td><strong>Vascular diseases</strong></td>
</tr>
<tr>
<td>• Atherosclerosis</td>
</tr>
<tr>
<td>• Vasculitis, perivasculitis</td>
</tr>
<tr>
<td>• Pulmonary arterial hypertension</td>
</tr>
</tbody>
</table>

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References


23. HIV and Pulmonary Diseases

BERNHARD SCHAAF, MARTIN HOWER

Due to the better management of people with HIV infection, comorbidities of the older patient have become more important. The spectrum of lung diseases in HIV-infected patients encompasses complications typical for HIV such as tuberculosis, bacterial pneumonia, lymphomas and HIV-associated pulmonary hypertension, but also includes typical everyday pulmonary problems like acute bronchitis, asthma, COPD, bronchial carcinomas and lung fibrosis (Table 1). With ART classical diseases such as PCP and TBC have become more rare, so that pulmonary mortality went down (Grubb 2006, Morris 2011). HIV influences toll-like receptors and other factors of immunologic function which lead to a greater risk of pneumonia (Morris 2011). However, particularly in patients with advanced immune deficiency, it is vital to take all differential diagnoses into consideration. Anamnestic and clinical appearance are essential clues when it comes to telling the difference between the banal and the dangerous. This chapter presents an outline of differential diagnoses in patients with respiratory complaints. PCP, mycobacterioses and pulmonary hypertension are covered in detail in other chapters.

Table 1: Pulmonary complications in patients with an HIV infection

<table>
<thead>
<tr>
<th>Infections</th>
<th>Neoplasia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumocystis jiroveci</strong></td>
<td>Kaposis sarcoma</td>
<td>Lymphocytic interstitial pneumonia (UP)</td>
</tr>
<tr>
<td><strong>Bacterial pneumonia</strong></td>
<td>Non-Hodgkin lymphoma</td>
<td>Non-specific interstitial pneumonia (NSIP)</td>
</tr>
<tr>
<td><strong>S. pneumoniae</strong></td>
<td>Hodgkin lymphoma</td>
<td>Cryptogenic organizing pneumonia (COP)</td>
</tr>
<tr>
<td><strong>H. influenzae</strong></td>
<td>Bronchial carcinoma</td>
<td>Pulmonary hypertension COPD Bronchial</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td>hyperreactivity</td>
</tr>
<tr>
<td><strong>B. catarrhalis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P. aeruginae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rhodococcus equi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nocardia asteroides</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mycobacteria**

- **M. tuberculosis**
- Atypical mycobacteria

**Other**

- Cytomegalovirus
- Aspergillus spp.
- Cryptococcus neoformans
- Histoplasma capsulatum
- Toxoplasma gondii

Side effects of ART:

- Dyspnea + cough in hypersensitivity reaction to abacavir
- Dyspnea + tachypnea in lactic acidosis
- Pneumonia with T-20 therapy;
- Pulmonary infiltration, lymph nodes and fever in IRIS

Anamnese

The most important question of all: What is the immune status? The number of CD4 T cells provides an excellent indication of the individual risk of a patient to suffer from specific opportunistic infections. More important than the nadir is the current CD4 T cell count. In patients with a CD4 T cell count of more than 200/µl, infection with typical opportunistic HIV-associated diseases is very unlikely. Here
one generally tends to expect more “normal” problems like acute bronchitis and bacterial pneumonia. However, tuberculosis should always be considered a possibility. Although the risk of becoming infected with tuberculosis grows with increasing immunodeficiency, more than half of all tuberculosis infections in HIV-positive patients occur at a CD4 T cell count of above 200/µl (Wood 2000, Lange 2004). At less than 200 CD4 T cells/µl the typical complication is PCP, while bacterial pneumonia is the most common pulmonary disease. Pulmonary Kaposi’s sarcoma and pulmonary Toxoplasma gondii infection tend to appear at less than 100 CD4 T cells/µl but are rarely seen. At cell counts below 50/µl, pulmonary infections with CMV (mostly in combination with PCP), invasive pulmonary aspergillosis (IPA), endemic fungi (Histoplasma capsulatum, Coccidioides immitis) and infections with atypical mycobacteria occur. Especially in patients with advanced immunodeficiency, the pulmonary illness may only represent an organ manifestation of a systemic infection (e.g., aspergillosis). Rapid invasive diagnostic procedure is advisable in patients with less than 200 CD4 T cells/µl.

**What is the medical history of the patient?** Someone who has had PCP once is at higher risk of having it again. A patient with COPD might have just an exacerbation of his pulmonary disease.

**What medication is the patient taking?** Someone taking cotrimoxazole regularly makes PCP unlikely. The risk of bacterial pneumonia may also be reduced (Beck 2001). In the case of PCP prophylaxis with pentamidine inhalation however, atypical, often apically pronounced manifestations of PCP are to be expected.

**Has the patient recently started ART?** Pulmonary symptoms after starting ART might result from an Immune Reconstitution and Inflammatory Syndrome (IRIS). The list of etiologies includes a number of infective and non-infective causes (Grubb 2006). Low CD4 T cell count and high viral load are risk factors. In a retrospective analysis, IRIS was seen in 30% of patients with TB, atypical mycobacteriosis and cryptococcosis (Shelburn 2005). Because of HLA testing, hypersensitivity to abacavir is rarely seen. Dyspnea (13%), cough (27%) and pharyngitis (13%) are common symptoms (Keiser 2003) of hypersensitivity. Some patients even develop pulmonary infiltrates. T-20 seems to increase the risk of bacterial pneumonia, at least among smokers. Dyspnea and tachypnea are also seen in lactic acidosis secondary to nucleoside therapy.

**Does the patient smoke?** Although smoking is more harmful to HIV-positive than to HIV-negative persons, it is more common among HIV-positives (Crothers 2011). Smoking promotes the formation of a local immune deficit in the pulmonary compartment: it reduces the number of alveolar CD4 T cells and the production of important pro-inflammatory cytokines (Wewers 1998) and suppresses the phagocytosis capacity of alveolar macrophages (Elsner 2004). All HIV-associated and HIV-independent pulmonary diseases are more common in smokers than in non-smokers. This starts with bacterial pneumonia and PCP, but also applies to asthma, COPD and pulmonary carcinomas (Hirschtick 1996, Crothers 2011). Motivating the patient to restrict nicotine intake is an important task, more so in HIV. Strategies that promise success and are supported by the evidence of studies include participation in motivational groups, nicotine substitutes and taking buproprion (interactions, particularly with ritonavir, should be taken into consideration).

**Where does the patient come from?** Another important question is that of the traveling history and/or origin of the patient. There are places where diseases such as histoplasmosis and coccidiomycosis occur endemically. Histoplasmosis, for example, is more widespread in certain parts of the US and in Puerto Rico than PCP, while it is rare in Europe. Tuberculosis plays a greater role among immigrants.
How did the patient become infected with HIV? Intravenous drug users suffer more often from bacterial pneumonia or tuberculosis (Hirschtick 1995). Pulmonary KS is almost exclusively found in MSM.

What are the symptoms? PCP patients typically have dyspnea and a non-productive cough. A large quantity of discoloured sputum is more likely to indicate a bacterial cause or a combination of infections. It is typical for the onset of bacterial pneumonia to be more acute. Patients usually go to the doctor after only 3–5 days of discomfort, whereas patients with PCP suffer from symptoms for an average of 28 days (Kovasc 1984).

What does the chest X-ray look like? See Table 2.

<table>
<thead>
<tr>
<th>Chest X-ray</th>
<th>Typical differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without pathological findings</td>
<td>PCP, asthma, KS of the trachea</td>
</tr>
<tr>
<td>Focal infiltrates</td>
<td>Bacterial pneumonia, mycobacteriosis, lymphoma, fungi, lung cancer</td>
</tr>
<tr>
<td>Multifocal infiltrates</td>
<td>Bacterial pneumonia, mycobacteriosis, PCP, KS</td>
</tr>
<tr>
<td>Diffuse infiltrates</td>
<td>PCP (centrally pronounced), CMV, KS, UP, cardiac insufficiency, fungi</td>
</tr>
<tr>
<td>Miliary image</td>
<td>Mycobacteriosis, fungi</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>PCP</td>
</tr>
<tr>
<td>Cavernous lesions</td>
<td>Mycobacteriosis (CD4 &gt; 200), bacterial abcess (Staph., Pseudomonas), lung cancer</td>
</tr>
<tr>
<td>Cystic lesions</td>
<td>PCP, fungi</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Bacterial pneumonia, mycobacteriosis, KS, lymphoma, cardiac insufficiency</td>
</tr>
<tr>
<td>Bihilar lymphadenopathy</td>
<td>Mycobacteriosis, KS, sarcoidosis</td>
</tr>
</tbody>
</table>

KS = Kaposi sarcoma, PCP = Pneumocystis pneumonia, LIP = Lymphoid interstitial pneumonia, BC = Bronchial cancer

Pulmonary Complications and Comorbidities

COPD, bronchial cancer, pulmonary hypertension, lung fibrosis und pulmonary infections are more common in HIV patients (Crothers 2011). Pulmonary infections are less frequent with ART while non infectious pulmonary disease become more frequent (Crothers 2011, Morris 2011).

Bacterial pneumonia

Bacterial pneumonia occurs more often in HIV-infected patients (Crothers 2011), and, like PCP, leaves scars in the lung. This often results in a persistent restriction of pulmonary function (Alison 2000) and significantly worsens the long-term prognosis of the patient (Osmond 1999). The risk increases with higher immunosupression an age. Thus, contracting bacterial pneumonia more than once a year is regarded as AIDS-defining. The introduction of ART went hand in hand with a significant reduction in the occurrence of bacterial pneumonia (Jeffrey 2000, Grau 2005, Madeddu 2009, Crothers 2011).

However, HIV-infected patients more often present with less symptoms and a normal leucocyte count (Feldman 1999). Below 200 CD4 T cells/µl, multifocal and interstitial manifestations are more common in pneumococcus infections (Rizzi 2008). What
is also important for the risk stratification of the patient, in addition to the usual criteria of the CRB-65 Score (Confusion, Respiratory rate, Blood pressure, >65 years, Lim 2003) is the CD4 T cell count. The mortality of patients with a count of less than 100 cells/µl is increased more than six-fold. It probably makes sense when dealing with patients with a pronounced immune deficiency not to rely on the risk scores validated for immunocompetent patients and to admit apparently less severely ill patients to the hospital for treatment (Cordero 2000). For details of microbiologic pathogens and treatment go to chapter “AIDS”.

Pneumococcus vaccination is recommended. At a CD4 T cell count lower than 200/µl, however, there is no proof of benefit of vaccination. Due to the frequency of secondary bacterial infections, an annual influenza vaccination is also advisable.

**Which diagnostic strategy makes sense with pulmonary infiltrates?**

The intensity of the diagnostic workup in a patient with pulmonary infiltrates is based on the HIV stage and the expected spectrum of pathogens. With a CD4 T cell count of more than 200/µl, non-invasive basic diagnostics and a calculated antibiotic therapy are justified. With 25–60%, the bacteremia rate is higher than in immunocompetent patients (Miller 1994), so two blood cultures and a microscopic and cultural sputum examination (include mycobacteria) should be done in inpatient settings.

In advanced stages (below 200 CD4 T cells/µl), and if a short time management is possible, bronchoscopy is primarily recommended (Dalhoff 2002). The diagnostic success rate in HIV-infected patients with pulmonary infiltrates is 55–70% and reaches 89–90% when all techniques including the transbronchial biopsy are combined (Cadranel 1995). The sensitivity of a bronchoalveolar lavage (BAL) amounts to 60–70% in bacterial pneumonia (patients without previous antibiotic treatment), and 85–100% in PCP (Baughman RP 1994). Due to the high sensitivity of the BAL, transbronchial biopsy with possible complications is only recommended in the diagnosis of PCP if there is a negative initial diagnostic workup and in patients taking chemoprophylaxis (Dalhoff 2002).

In individual cases the possibility of antigen detection in the urine should be considered (e.g., pneumococcus, legionella, cryptococcus, histoplasma). The determination of the cryptococcos antigen in serum has a high predictive value for the detection of invasive cyptococcosis (Saag 2000). A chest CT is sometimes helpful in the diagnostic workup (high resolution CT, HRCT). PCP, for example, might be depicted in an HRCT, but might be missed in a conventional chest X-ray. Surgical open biopsies and CT-controlled trans-thoracic pulmonary biopsies are rarely necessary.

**Asthma bronchiale**

Beside COPD, asthma bronchiale is the most common pulmonary comorbidity in HIV-infected patients. Symptoms like cough, dyspnea or recurrent bronchitis a hyper-reactive bronchial system or asthma bronchiale should be considered. If an immuno-suppressing disease like HIV infection would at least protect patients from manifestations of exaggerated immune reaction such as allergies and asthma or makes is unclear. In the pre-ART era the incidence of asthma seemed to be not influenced by the presence of HIV (Wallace 1997). A recent US study shows a lower incidence of asthma with ART and low viral load (Crothers 2011). Interestingly, HIV positive children have more Asthma (Siberry 2012). Immunoreconstitution with ART is associated with an increase in the incidence of asthma in children (Foster 2008).
COPD and emphysema

COPD is together with pneumonia the most common pulmonary complication in HIV-infected patients (Crothers 2011). They have a higher rate to get lung emphysema (Crothers 2006). Patients with HIV and COPD have less quality of life (Drummond 2010). Each patient should be asked about COPD symptoms and a spirometry test should be offered. It is possible that a pathogenetic synergy arises from smoking and the pulmonary infiltration with cytotoxic T cells due to HIV infection (Diaz 2000, Yearsley 2005, Caner 2009). In another study ART was shown as an independent factor of obstruction, perhaps COPD can occur in IRIS (George 2009). Smoking crack increases the risk of pulmonary emphysema even more. Here, it seems that superficial epithelial and mucosal structures are destroyed (Fliegil 1997). Furthermore, crack can lead to unusual manifestations such as pneumothorax or alveolar infiltrates.

Lung fibrosis and Lymphoid interstitial pneumonia (LIP)

Lung fibrosis is a rare disease, but more frequent in HIV-infected patients (Crothers 2011). Manifestations like COP, NSIP, UIP and alveolar proteinosis are described (Crisan 2009). LIP is a form of pneumonia that takes a chronic or subacute course and is extremely rare in adults. Radiologically, its reticulonodular pattern makes it similar to PCP. This illness occurs paraneoplastic, rarely idiopathic, and as in HIV and EBV disease, parainfectious. In contrast to PCP, patients with LIP usually have a CD4 T cell count of more than 200/µl and normal LDH values. A CD8-dominated lymphocytic alveolitis with no pathogen detection is characteristic. Definite diagnosis often calls for an open pulmonary biopsy. LIP is considered sensitive to steroids. The role of ART is unclear, especially as LIP has occasionally been observed in the context of immune reconstitution during ART. Other interstitial pneumonias, like cryptogen organizing pneumonia (COP with BOOP as histology) or nonspecific interstitial pneumonitis (NSIP) are also seen in association with HIV (Khater 2004).

Bronchial carcinoma (BC)

Multiple studies, including one metaanalysis, show a two- to eight-fold increased incidence of bronchial carcinoma (Hessol 2006, Shiels 2009, Polesel 2010, Crothers 2011). In ART era more patients die for BC than for the most AIDS-defining malignancies (Engels 2008). See also chapter “Non-AIDS-defining Malignancies”.

Less common opportunistic infections

In children CMV pneumonia is more often as PCP (Zampoli 2011), in adults it is less frequent. The significance of the pathogen in the later stages may well be underestimated, since histological examination of autopsy material showed pulmonary CMV infections in up to 17% (Waxman 1997, Afessa 1998, Tang 2005). However, in respiratory insufficiency due to PCP a CMV pneumonia should be considered and perhaps treated, because a coinfection has a higher mortality (Boonsarngsuk 2009). The detection of CMV in BAL repeatedly gives rise to discussion regarding clinical relevance. At over 90%, seroprevalence is high, and colonisation of the respiratory tract is common. Transbronchial biopsy may prove CMV infection, blood markers (CMV-PCR or pp65 antigen) may be helpful. Regarding invasive pulmonary aspergillosis (IPA), which only occurs in the late stages and usually in conjunction with additional risk factors such as neutropenia or steroid therapy (Mylonakis 1998) please refer to the chapter on Opportunistic Infections.
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24. HIV and rheumatic diseases
NILS VENHOFF, ULRICH A. WALKER

Introduction
HIV-infected individuals are at an increased risk of developing musculoskeletal diseases. The rates of musculoskeletal complications underlie a large range of variation (Buskila 1990, Munoz 1991). In the era of highly active antiretroviral therapy (ART) rheumatic disorders have declined significantly but continue to be prevalent, with new manifestations emerging (Calabrese 2005). The clinical spectrum includes articular, muscle and osseous symptoms, metabolic complications and inflammatory multisystem manifestations.

Arthralgia
Arthralgia is a common but unspecific complaint of HIV-infected persons. Intermittent articular symptoms appear frequently during acute HIV infection (Hecht 2002). The prevalence of arthralgia in HIV-infected persons was 5% in retrospective and 45% in prospective studies (Buskila 1990, Munoz 1991). Arthralgia was most frequently observed in the knees, shoulders and elbows. An HIV-specific, intermittently painful articular syndrome has been described. The arthralgia in this syndrome has a short duration lasting only a few hours but may require opioid analgesics (Pouchot 1992).

Arthritis
Reactive arthritis and Reiter’s syndrome
Reactive arthritis has a higher prevalence (10%) in both HIV-infected paediatric and adult cohorts compared with an HIV-negative population. Patients have asymmetric oligoarthritis which mainly affects the lower extremities. Enthesopathy is frequent in reactive arthritis and sacroiliitis may occur. Among the extra-articular manifestations, conjunctivitis, urethritis, circinate balanitis and keratoderma blennorrhagicum are typical. The involvement of the axial skeleton is less frequent in HIV-associated spondyloarthritis. HLA-B27 is found in HIV-associated Reiter’s syndrome as often as in HIV non-infected patients. The association of spondyloarthopathy and HLA-B27 is found in caucasians but not in patients of African descent. Rapid improvement with effective ART sulfasalazine and anti-TNF-alpha biologics has been described (McGonagle 2001, Gaylis 2003).

HIV-associated arthritis
An arthritis without the typical symptoms pointing towards Reiter’s syndrome (e.g., enthesopathy, mucocutaneous involvement or HLA-B27 gene expression) may present at any time during the course of chronic HIV infection. HIV-associated arthritis mainly manifests as a non-erosive oligoarthritis of the lower extremities (Mody 2003). The typically sterile synovial fluid shows slightly increased leukocyte counts, whereas radiological signs of arthritis are usually not found. HIV was isolated from the synovial fluid in only one report (Withrington 1987). HIV-associated arthritis is most frequently self-limited and lasts less than 6 weeks.
Table 1: Differentiating reactive arthritis and HIV-associated arthritis.

<table>
<thead>
<tr>
<th></th>
<th>Reactive arthritis</th>
<th>HIV-associated arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint involvement</td>
<td>Asymmetric oligoarthritis</td>
<td>Variable</td>
</tr>
<tr>
<td>Enthesopathy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mucocutaneous involvement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Synovial fluid leucocytes (cells/μl)</td>
<td>2000–10,000</td>
<td>500–2000</td>
</tr>
<tr>
<td>HLA B27</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Chronic or relapsing</td>
<td>Self-limiting</td>
</tr>
</tbody>
</table>

Psoriasis and psoriatic arthritis

The incidence of psoriatic arthritis in HIV-infected patients is about 2% (Mody 2003). In general, the severity of psoriasis parallels the impairment of the immune system. Treatment with antiretrovirals generally improves HIV-associated psoriasis. On the other hand, psoriatic manifestations may be exacerbated in advanced HIV infection and may be extremely resistant to therapy. Anti-TNF-alpha agents have been successfully and mostly safely administered to a few patients (Linardaki 2007).

Septic arthritis

Immunodeficiency is a risk factor for septic complications in the musculoskeletal system. Musculoskeletal infections are nevertheless quite rarely observed in HIV-infected patients. Two large cohorts studied 3,000 and 4,000 patients and retrospectively identified 14 and 30 cases of musculoskeletal infections (Ventura 1997, Vassilopoulos 1997). Septic arthritis appears to be associated with simultaneous intravenous drug abuse while a clear association with diminished CD4 T cell counts has not been determined. Septic arthritis usually affects young men and commonly involves the large joints of the lower extremities (Ventura 1997). Pyogenic organisms predominate at CD4 T cell counts above 250/μl. Opportunistic pathogens are observed when the CD4 counts decline below 100/μl (Ventura 1997). Septic tenosynovitis and bursitis have also been described. Among the atypical mycobacteria *M. haemophilum* (50%) and *M. kansasii* (25%) are the most frequent pathogens isolated in musculoskeletal infections. In HIV-infected patients *M. tuberculosis* is not more frequently isolated in infectious arthritis than in HIV-negative individuals. *M. tuberculosis* infection may however be unmasked after the initiation of ART due to immune reconstitution (Jellis 2002).

Articular complications of antiretroviral therapy

Arthralgia, monarthritis, oligoarthritis and adhesive capsulitis have been associated with the use of indinavir in particular (Brooks 2000). Unlike the situation in the urogenital tract, indinavir crystals were not detected in the synovial fluid (Brooks 2000). A prospective survey suggested that joint pain may also be associated with other PIs (ritonavir and saquinavir) (Florence 2002).

Gout

Hyperuricemia has been observed in up to 42% of HIV-infected individuals. The annual incidence of gout is 0.5% in HIV-infected patients, an order of magnitude higher than the incidence in the normal population (Creighton 2005). Urate may result from increased cell turnover in uncontrolled HIV replication. Urate serum levels may also be increased by antiretrovirals (Walker 2006). Didanosine, for example, causes hyperuricemia. In a multivariate cohort analysis, hyperuricemia was associated with factors previously identified in HIV-uninfected individuals, but also...
with the use of some antiretrovirals, particularly d4T and ddI (Walker 2006). Urate elevation may result from the mitochondrial toxicity of these drugs, because mitochondrial damage increases the formation of lactate, which stimulates urate reabsorption at the proximal tubulus of the kidney. Mitochondrial failure also causes ATP depletion which promotes urate production in the purine nucleotide cycle. Finally, antiretroviral therapy also induces imbalances in the cytokine milieu which may participate in precipitating gouty attacks (Sebeny 2010).

**Myopathy**

Muscular complaints may have many etiologies in HIV-infected patients. Acute rhabdomyolysis is the most serious complication but the clinical spectrum also features HIV-associated polymyositis, dermatomyositis, inclusion body myositis, nemaline rod myopathy, HIV wasting syndrome and pyomyositis.

*Rhabdomyolysis* may either complicate primary HIV infection (Chariot 1994), result from secondary infections, or from ART. Rhabdomyolysis has also been triggered by abacavir hypersensitivity (Fontaine 2005) and observed with raltegravir (Zembower 2008, Dori 2010). The interaction of some PIs with statins may also promote rhabdomyolysis. The formation of a *macroenzyme creatine kinase* (*macro CK*) has been observed in up to half of the patients treated with tenofovir. A macro CK should be suspected when a disproportionally elevated CK-MB isoenzyme activity is observed. This laboratory phenomenon does not reflect a myocardial complication or a skeletal myopathy and is therefore without clinical significance.

**AZT myopathy** is probably the most frequent muscle complication in HIV-infected patients. AZT interferes with the replication of mitochondrial DNA (mtDNA) resulting in mtDNA depletion and impaired respiratory chain function (Dalakas 1990). This myopathy appears to be specific for AZT because it does not appear to be induced by other NRTIs. Affected patients experience skeletal muscle weakness with either dynamic or static exercise. The serum CK is often normal or only minimally elevated but muscle histology reveals a high frequency of ragged-red fibres in the Gomori Trichrome Stain. Histochemistry reveals a high frequency of cytochrome c oxidase-negative fibers which by electron microscopy also harbor abnormal mitochondria. AZT myopathy resolves within months after AZT cessation. Uridine supplementation prevented AZT myopathy in a mouse model (Lebrecht 2008).

**HIV-associated polymyositis** can be observed at any stage during the course of HIV infection (Johnson 2003). Serum CK levels are often elevated but do not correlate with the severity of the disease. In a prospective trial of consecutive HIV-infected ART-naive patients with clinically suspected skeletal myopathy or raised serum CK levels one third of the cases had an inflammatory condition on skeletal muscle biopsy. HIV-associated myopathy was detected in 0.2% of 4998 HIV-infected patients (Johnson 2003). The muscle is typically infiltrated by CD8 T lymphocytes. Viral antigen and nucleic acids have been detected in endomysial lymphocytes. HIV-associated polymyositis is clinically and histologically indistinguishable from idiopathic polymyositis but mostly has a good outcome, as it responds well to immunosuppressive therapy or may even resolve spontaneously. About half of the patients simultaneously have a diffuse infiltrative lymphocytosis syndrome (DILS) (Johnson 2003). **Dermatomyositis** and **inclusion body myositis** were only rarely observed with HIV infection. In inclusion myositis, HIV-specific CD8 T cells appear to recognize antigens on the surface of muscle fibers (Dalakas 2007).

**Nemaline rod myopathy** of adult onset is also a rare complication of HIV infection (Dalakas 1987). Patients progressively develop a painless muscle weakness and wasting with elevated serum CK. Muscle biopsy discloses atrophic type 1 fibers car-
rying numerous intracytoplasmic nemaline rod bodies, whereas necrotic fibers and inflammatory infiltrates are not features of the disease. Despite absence of muscle inflammation, some patients may respond to treatment with prednisone, which suggests an autoimmune mechanism.

Severe muscle atrophy may be caused by the AIDS-defining wasting syndrome which has become rare since the widespread introduction of ART. Muscle biopsy reveals either diffuse or isolated type II fiber atrophy, mild neurogenic atrophy, or thick filament loss without inflammation.

Pyomyositis is a rare microbial infection, which mainly affects male patients with low CD4 cell counts (Patel 1997). *Staphylococcus aureus* is most frequently isolated but other organisms have also been identified.

### Bone complications

#### Osteonecrosis

HIV-infected patients have a 100-fold elevated risk of osteonecrosis compared with the general population. At the hip, the most frequent localization of osteonecrosis, the prevalence was estimated as 4.4% by MRI (Miller 2002). The annual incidences of symptomatic and asymptomatic osteonecrosis of the femoral head were 0.3% and 0.7% (Morse 2007). Hip osteonecrosis is frequently bilateral and may also be associated with avascular necrosis of other bones. Eleven percent of initially asymptomatic patients may require hip replacement (Morse 2007). Chronic inflammation, corticosteroids in the setting of immune reconstitution and anti-cardiolipin antibodies have been identified as risk factors but were not confirmed in all studies (Miller 2002, Morse 2007). Hypertriglyceridemia secondary to PI treatment was suggested as a risk factor for osteonecrosis in some but not all studies (Miller 2002).

#### Bone mineral loss

Osteopenia and osteoporosis are highly prevalent among patients with HIV infection. The loss of bone minerals and rarefaction of the trabecular architecture with consecutive loss of bone stability is of multifactorial origin. In addition to the classical risk factors (low BMI, nicotine consumption, alcohol, steroids, hypogonadism, vitamin D deficiency, immobilisation) which are more frequent in HIV-infected patients compared with the general population both ART and HIV-infection affect bone metabolism (Bolland 2007, Dolan 2006, Jacobson 2008, Arnsten 2007, Grund 2009). Other risk factors such as opiate abuse and hepatitis C virus infection are prevalent in HIV infected patients. The suggested association between PI treatment and osteoporosis in some cross-sectional studies was not or only partially confirmed in longitudinal studies (Dolan 2006). Some PIs appear to lower bone mineral density (BMD) mainly in the vertebral column (Duvivier 2009).

The use of the nucleotide analogue tenofovir is associated with bone demineralization. Tenofovir inhibits the replication of mitochondrial DNA in the proximal tubules of the kidney and through this mechanism induces a Fanconi syndrome with tubular phosphate loss (Lebrecht 2009). Due to this mechanism some patients develop osteomalacia, despite the absence of vitamin D deficiency (Wanner 2009). One published study described an estimated annual loss of BMD of 2% in men treated with tenofovir (Jacobson 2008). The GILEAD 903 study detected a significantly higher loss in BMD between weeks 24 and 48 in the tenofovir arm compared with the d4T arm (Gallant 2004, Cassetti 2007). The iPrEx trial investigated pre-exposure prophylaxis and randomly assigned HIV-seronegative men to either a combination of TDF and FTC, or to placebo. After 24 weeks, there was a significantly higher loss of bone mass density in the arm assigned to oral FTC-TDF, underscoring the notion that bone loss involves a mechanism independent of HIV infection (Mulligan 2011).
Table 2: Bone complications in HIV infection

<table>
<thead>
<tr>
<th>Osteopenia/Osteoporosis</th>
<th>Osteomalacia</th>
<th>Osteonecrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced bone mass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased risk of fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic without fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common in HIV</td>
<td>Defective bone mineralization</td>
<td>Avascular infarct of bone</td>
</tr>
<tr>
<td>Prevalence: osteopenia 60%, osteoporosis 10–15%</td>
<td>Increased risk of fractures</td>
<td>Acute bone pain</td>
</tr>
<tr>
<td>Etiology multifactorial</td>
<td>Bone pain</td>
<td>Increased prevalence in HIV</td>
</tr>
<tr>
<td></td>
<td>Pseudo fractures (Looser-zones)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High prevalence (80%) of vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic risk factors1</td>
<td>Dietary deficiency</td>
<td>Advanced HIV disease</td>
</tr>
<tr>
<td>10-year fracture probability</td>
<td></td>
<td>(low CD4 T cell counts)</td>
</tr>
<tr>
<td>(FRAX)</td>
<td>Lack of sunlight exposure</td>
<td>Glucocorticosteroids</td>
</tr>
<tr>
<td>Kapitel 2: age &gt;40 years</td>
<td>Dark skin</td>
<td>Intravenous drug use</td>
</tr>
<tr>
<td>Kapitel 3: HIV</td>
<td>Malabsorption</td>
<td>Alcohol</td>
</tr>
<tr>
<td>DXA in any patient with</td>
<td>Renal phosphate loss</td>
<td>Bisphosphonates (osteonecrosis</td>
</tr>
<tr>
<td>≥1 of the following:</td>
<td>(Fanconi syndrome)</td>
<td>of the jaw)</td>
</tr>
<tr>
<td>1. postmenopausal women</td>
<td>Tenofvir</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>2. men ≥50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. low impact fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. hypogonadism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. glucocorticoids (&gt;5 mg/day &gt;3 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations for re-screening2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum: vitamin D, calcium, phosphate, alkaline phosphatase (bone specific), PTH-levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If hypophosphatemic consider Fanconi’s syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td>DXA scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral spine X rays lumbar/ thoracic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rule out secondary causes if BMD abnormal3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conservative: weight unloading, rest</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery: Pridie-drillings, bone transplantation, hip replacement</td>
<td></td>
</tr>
</tbody>
</table>

1 Age, female, hypogonadism, family history of hip fracture, BMI ≤19kg/m², vitamin D deficiency, smoking, immobilisation, alcohol, glucocorticosteroids (>5 mg daily for >3 months)
2 If T-score normal, repeat after 3–5 years in groups 1 & 2, no re-screening in groups 3 & 4 unless risk factors change. Re-screening of group 5 if steroid use ongoing
3 Hyperparathyroidism, hyperthyroidism, malabsorption, hypogonadism/amenorrhoea, autoimmune diseases, chronic inflammatory diseases, diabetes mellitus, chronic liver disease

BMD=bone mineral density, FRAX=fracture risk assessment tool (www.shef.ac.uk/FRAX/)

Another randomized, 96-week study confirmed the increased loss of BMD with tenofovir in comparison with abacavir (Stellbrink 2010). Bone demineralization was also observed with the NRTIs AZT+3TC and ddI (Pan 2006, Jacobson 2008, van Vonderen 2009) but the changes in BMD were rare and less prominent.
Loss of BMD is associated with increased rates of bone fractures in HIV-infected patients (Triant 2008). Compared to uninfected individuals HIV-infected persons have a significantly increased risk of developing fractures of spine, hip and wrists. Due to the absence of HIV-specific data the prophylaxis and treatment of bone loss should follow the recommendations for the general population. In 2009, the EACS provided the first European guidelines for screening, prophylaxis and treatment of bone diseases in HIV-infected patients (Table 2). The decision to initiate treatment of bone loss is based on several factors such as the presence of bone fractures, the age of the patient, the BMD measured by DXA and the 10-year probability of fracture which can be calculated by the WHO fracture risk assessment tool (FRAX) (http://www.shef.ac.uk/FRAX/). Vitamin D replacement (800–2000 IU daily combined with calcium) is recommended in persons with insufficient dietary intake. In HIV-infected adolescents receiving TDF, vitamin D replacement antagonized the TDF-induced a loss of BMD and decreased serum parathyroid hormone levels (Havens 2012). Due to the relative paucity of data with regard to the long term bone safety data, TDF should be used with caution in children. It has been demonstrated that bisphosphonates increase the BMD also in HIV-infected individuals but it remains unclear whether prophylactic treatment with bisphosphonates prevents fractures in HIV-infected patients and whether or not it increases the risk of osteonecrosis in these patients.

Osteomyelitis

Bone infections tend to occur at lower CD4 counts than joint infections. *Staphylococcus aureus* is the most frequent pathogen but polymicrobial infections are observed in a considerable proportion of HIV-associated osteomyelitis (Vassilopoulos 1997, Ventura 1997).

Multisystem manifestations

Vasculitis

A wide range of vasculitic manifestations were reported in HIV-infected individuals and include polyarteritis nodosa, Behcet’s Disease, coronaritis, Henoch-Schonlein purpura, drug-induced hypersensitivity vasculitis and cryoglobulinemic vasculitis. A large vessel vasculitis with multiple aneurysms predominantly observed in African patients and Kawasaki Disease described in infants and adults with HIV-infection appear to be associated with immune reconstitution syndrome.

Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS may be confused with Sjogren’s syndrome (SS) because DILS also presents with bilateral painless parotid gland enlargement, lacrimal gland enlargement and sicca symptoms. DILS is characterised by peripheral CD8 lymphocytosis and antigen-driven CD8 T cell infiltration in multiple organs. The prevalence of DILS in HIV-infected ART naive patients is 3–4%. The symptoms usually manifest several years after HIV seroconversion and reflect an excessive host response to HIV. A disproportionately greater degree of salivary gland enlargement distinguishes DILS from SS and may be complicated by compression and irreversible paralysis of the facial nerve. Whereas extraglandular complications are more frequent in DILS, autoantibodies and rheumatoid factor are observed less often (Basu 2006). Extraglandular complications of DILS consist of lymphoid interstitial pneumonitis (LIP) (31%), muscular (26%) and hepatic (23%) involvement (Johnson 2003). An isolated involvement of the peripheral nerve system has also been described (Chahin 2010). Muscle manifestations are indistinguishable from polymyositis. Antiretroviral therapy is
effective and probably also accounts for the declining incidence of DILS in the ART era (Basu 2006). Low dose steroids are effective in the treatment of the glandular swelling and symptoms. Treatment of LIP may require higher doses of prednisone (1 mg/kg body weight/day). DILS needs to be distinguished from parotid lipomatosis, a parotid gland swelling due to abnormal fat deposition. Parotid lipomatosis is associated with high doses of ritonavir. These doses are generally no longer applied today. Gallium scans may distinguish parotid lipomatosis by virtue of its low tracer accumulation in glandular tissue from DILS which features an intense tracer accumulation.

**Sarcoidosis**

Sarcoidosis is observed rarely during the natural course of HIV infection, probably because of the important role of CD4 lymphocytes in granuloma formation (Lenner 2001, Foulon 2004). Most HIV-infected patients with symptomatic sarcoidosis had CD4 counts below 200/µl. Sarcoidosis is now mostly observed in patients with marked increases in CD4 cells while on ART (Lenner 2001, Foulon 2004). In the setting of immune reconstitution, the interval between the introduction of ART and the onset of pulmonary sarcoidosis was longer (several months) than that reported for granuloma formation secondary to infections (a few weeks).

**Systemic lupus erythematous (SLE)**

Preexisting SLE generally improves during the course of untreated HIV infection, which is consistent with the importance of CD4 T cells in the pathogenesis of SLE (Chowdhry 2005). Conversely, ART and immune reconstitution can induce the first manifestation or reactivation of SLE. It has also been described that the HIV infection took a rapidly progressive course when immunosuppressive therapy was initiated in order to treat SLE. Difficulties in the differential diagnosis between SLE and HIV infection may arise because there are many clinical and laboratory similarities. For example, oral ulcerations, sicca syndrome, alopecia, arthritis, fever and neuropathies can be features of both conditions (Drake 2003). Furthermore, anti-HIV antibody tests can be falsely positive in SLE. Thus, positive HIV-antibody tests should be confirmed by antigen or nucleic acid detection. Low serum complement components C3 and C4 and increases in the C3 split product C3d in the serum are indicative of SLE activity.

**Laboratory changes**

Polyclonal B cell stimulation is a characteristic of untreated HIV infection. After the commencement of ART, naive and antigen-experienced T cell pools expand. This expansion may explain the high prevalence of autoimmune phenomena observed in HIV-infected individuals (King 2004). Rheumatoid factor, cold agglutinins, anti-nuclear antibodies (ANA) and anti-neutrophilic cytoplasmatic antibodies (ANCA) are frequently detected. HIV is a known trigger of antiphospholipid antibody production. Anti-ß2-glycoprotein I (GPI) antibodies were found in nearly 50% of patients, but the lupus anticoagulant was mostly negative (Loizou 2003). Clinical complications in terms of the antiphospholipid syndrome are rare in HIV-infected patients, probably because the anticardiolipin antibodies appear only transiently and vanish when ART is begun. Cryoglobulins (type II and III) were detected in one third of HIV-infected individuals, but are much more frequent in hepatitis C virus coinfected (Scotto 2006). The prevalence of cryoglobulinemia is declining in the ART era.
Anti-rheumatics in HIV-infected patients

For symptomatic relief of musculoskeletal symptoms, NSAIDs can be used similarly to the guidelines in HIV-negative patients. Indomethacin (50 mg tid) might have an advantage because of its ability to inhibit HIV replication in vitro (Bourinbaiar 1995). When antirheumatic treatment is needed hydroxychloroquine (3–4 mg/kg body weight/day) and sulfasalazine (500 mg–2000 mg/day) are the first choice because both drugs have no immunosuppressive effects and do not enhance viral replication (Disla 1994). Hydroxychloroquine even has some antiretroviral activity (Sperber 1997). Methotrexate (10–20 mg once weekly) was successfully used in HIV-infected patients despite its immunosuppressive effect (Maurer 1994). Case reports described successful treatment of HIV-associated spondyloarthritis with anti-TNF-alpha biologic agents (Calabrese 2004). Anti-TNF-alpha treatment also improved rheumatoid arthritis and psoriatic arthritis in HIV-infected patients but did not affect CD4 counts or viral load (Cepeda 2008). Anti-TNF-alpha biological agents have been associated with the activation of latent tuberculosis. Prophylactic isoniazid is recommended.

References


25. HIV-related Thrombocytopenia

HEINZ-AUGUST HORST

Thrombocytopenia is one of the most frequently observed hematological complications of HIV infection. The incidence increases among patients not receiving adequate antiretroviral treatment and does not appear to vary according to the mode of acquisition of HIV (Heyward 1988, Finazzi 1990, Sloand 1992). A 10-year cumulative incidence of up to 45% has been reported (Eyster 1993). Even in patients with previously well controlled HIV infection a discontinuation of antiretroviral therapy can lead to the rapid occurrence of thrombocytopenia (Bouldouyre 2009). Thrombocytopenia is mostly mild and asymptomatic. Platelet counts of <30,000/µl have only been seen in 6–24% of the cases with HIV-related thrombocytopenia (Finazzi 1990, Mientjes 1992). HIV-related thrombocytopenia has been generally attributed to two different mechanisms: First, an immunologically driven destruction of the platelets and second, an insufficient platelet production by the megakaryocytes. While in early HIV infection increased platelet destruction appears to be predominant, production failure is often the main cause of thrombocytopenia in late-stage patients (Najean 1994).

Table 1: Differential diagnoses of thrombocytopenia, except HIV.

- Pseudo-thrombocytopenia
- Toxic bone marrow suppression: drugs, e.g., TMP-SMX, rifampicin, ethambutol, radiation
- Infection: HCV, H. pylori, CMV, MAC
- Malignant lymphoproliferative B cell disorders: e.g., chronic lymphocytic leukaemia, diffuse large B cell lymphoma
- Immunologic: Systemic lupus erythematoses, immune thyroiditis, Evans syndrome, heparin
- Other causes: HUS, TTP, PNH, hypersplenism, liver cirrhosis

Clinical manifestations

The clinical course of patients with HIV-related thrombocytopenia is often asymptomatic. However, a spectrum of bleeding problems including petechiae, epistaxis, ecchymosis, menorrhagia, hemorrhage of the gingivae may occur. Severe bleeding of the gastrointestinal tract or the CNS are rarely observed and are most likely at platelet counts <30,000/µl. In contrast to patients with immune thrombocytopenic purpura (ITP) patients with HIV-related thrombocytopenia often present with splenomegaly and lymph node enlargement. Spontaneous remissions of HIV-related thrombocytopenia have been observed in 10–20% of the cases, mostly with mild thrombocytopenias (Walsh 1985, Abrams 1986).

Diagnosis

HIV-related thrombocytopenia is a repeatedly confirmed isolated decrease of the platelet count <100,000/µl. In the peripheral blood the platelets often show an increased variability in size. In the bone marrow the number of megakaryocytes is normal or increased.

HIV-related thrombocytopenia has to be distinguished from cases of EDTA-induced pseudo-thrombocytopenia and from other causes of “true” secondary thrombocytopenias, which include myelotoxic drugs, hepatitis C virus (HCV), cytomegalovirus (CMV) and Mycobacterium avium complex (MAC) infections. The risk of heparin-
induced thrombocytopenia is probably increased in HIV-infected patients (Thompson 2007). In rare cases thrombocytopenias induced by antiretroviral therapy (ART) have been observed (Lebensztejn 2002, Camino 2003). Furthermore, the distinction from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome is of great importance. These diseases show a peripheral platelet destruction not related to an immune mechanism, occur in higher frequency with HIV infection, and are life threatening. Important causes of thrombocytopenia are summarised in Table 1.

**Therapy**

The therapy of HIV-related thrombocytopenia is based on two principles: antiretroviral therapy (ART), and in severe cases an additional treatment with agents used in non-HIV immune thrombocytopenia, i.e., glucocorticoids, intravenous immunoglobulins, or anti-(Rh)D. In refractory cases splenectomy is also a treatment option (George 1996, Godeau 2007). The treatment besides ART is based on the recent international consensus report and the guidelines of the American Society of Hematology (Provan 2010, Neunert 2011). Treatment options are summarized in Table 2.

**Table 2: Therapy of HIV-related thrombocytopenia**

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic and thrombocytes &gt;30,000/µl</td>
<td>ART</td>
</tr>
<tr>
<td>Thrombocytes &lt;30,000/µl or thrombocytes &lt;50,000/µl and significant mucous membrane bleeding</td>
<td>ART plus First-line therapy: glucocorticoids Subsequent therapies*: intravenous immunoglobulins, anti-(Rh)D, rituximab, splenectomy</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>Platelet transfusions, high-dose glucocorticoids, intra-venous immunoglobulins, either alone or in combination</td>
</tr>
</tbody>
</table>

* Subsequent therapies after failure of glucocorticoids should be given according to the experience of the treating physician since only a few prospective randomised studies are available (Vesely 2004).

**ART:** leads to a significant recovery of the platelet count within three months of treatment in most patients (Arranz Caso 1999, Servais 2001). This effect is independent of the antiretrovirals utilised and the platelet count at the start of therapy (Arranz Caso 1999). Importantly, during treatment interruptions often thrombocytopenias develop, particularly in patients with a history of HIV-related thrombocytopenia (Ananworanich 2003, Bouldouyre 2009). A therapy in addition to ART is indicated for patients with a platelet count <30,000/µl or a platelet count of <50,000/µl with a significant concomitant mucous membrane bleeding or risk factors for bleeding, such as peptic ulcers or hypertension (George 1996).

**Glucocorticoids:** are currently the standard first-line therapy of HIV-related thrombocytopenia. A dose of 0.5–1.0 mg/kg body weight prednisolone or prednisone results in a significant increase in platelet counts in 60–90% of the patients (Gottlieb 1983, Abrams 1986). After a response, which can be expected within a few days, the initial dose should be continued for 3–6 weeks. Then, depending on the platelet count, which should be kept >60,000/µl, the glucocorticoid dose should be tapered within weeks and discontinued if possible. In the case of a life-threatening bleed we recommend higher dosages (i.e., 1 g methylprednisolone/day for three days with sub-
sequent dose reduction). In order to avoid a long-lasting therapy with prednisolone or prednisone and possible side effects, a short-term protocol with high-dose dexamethasone may be used. After treatment with 40 mg of dexamethasone for four consecutive days in patients with non-HIV immune thrombocytopenia a response can be seen in 85% of patients. A relapse does occur in 50% of the responding patients within six months. These patients require a prolonged therapy with glucocorticoids or a different treatment (Cheng 2003). After four cycles of dexamethasone given for four days every 14 days in 74% of the patients a long-term response (median time of 8 months) can be seen (Mazzucchoni 2007). Using steroids it has to be kept in mind that particularly prolonged treatment is associated with a high risk of even fatal infectious complications (Portielje 2001, Zimmer 2004).

Intravenous immunoglobulins: are costly and often given after failure of glucocorticoids, in the case of contraindications against glucocorticoids or in a situation with life-threatening bleeding. The standard dose is 1 g/kg body weight for 1–2 days. The response rate is approximately 60%. Without maintenance therapy the platelet count will decrease in most patients and it drops to the pre-treatment levels after about a month (Godeau 2007).

Anti-(Rh)D: The intravenous anti-(Rh)D application is an interesting treatment option of HIV-related thrombocytopenia. The mechanism of action is assumed to be mediated through the destruction of antibody-coated (Rh)D positive red blood cells (RBC). The preferential clearance of antibody-coated RBC by macrophages particularly in the spleen leads to an Fc receptor blockade sparing the destruction of autoantibody-coated platelets (Scaradavou 1997). The response rate in HIV-related thrombocytopenia was 64% (Scaradavou 1997). The peak platelet count was significantly higher and the duration of response significantly longer in HIV-positive patients treated with anti-(Rh)D compared to intravenous immunoglobulins (Scaradavou 2007). WhinRho® SDF (Cangene Corporation) is the first anti-D immunoglobulin approved for use in HIV-related thrombocytopenia. The recommended initial dose for adults is 50 µg/kg body weight administered i. by a 3–5 minute infusion. In patients with a hemoglobin level less than 10 g/dl a reduced dose is recommended. It has to be kept in mind that anti-(Rh)D is only suitable for (Rh)D positive patients who are not splenectomized. An important adverse event is a decrease of the hemoglobin level by hemolysis. In a large study of 272 patients the mean hemoglobin decrease was 0.8 g/dl (Scaradavou 1997). Patients with pre-existing hemolysis (Evans syndrome) should not be treated with anti-(Rh)D.

Splenectomy: is effective even after failure of treatment with glucocorticoids and intravenous immunoglobulins. Most studies in HIV-positive patients showed a high response rate of more than two-thirds of patients with a normalization of the platelet count in most responders. Although relapses occur most of the patients show a sustained increase of their platelet count (Oksenhendler 1993). Worsening of the immunodeficiency by splenectomy leading to an acceleration of the HIV infection was a major concern about this procedure which, however, was not seen at long term follow up (Oksenhendler 1993). Independent of HIV status patients undergoing splenectomy are at increased risk of life-threatening bacterial infections. For prophylaxis polyvalent pneumococcal vaccine, Hemophilus influenzae type b, and meningococcal vaccine should be given at least two weeks prior to splenectomy. A response in HIV-positive patients with CD4 T cells of less than 400/µl is uncertain (Greub 1996). Considering the other treatment options splenectomy should only be performed in individuals presenting with therapy-resistant severe HIV-related thrombocytopenia. Particularly because of morbidity splenectomy should be postponed for at least 6 months after diagnosis since late partial or complete responses can occur
subsequent to efficient HIV suppression and additional therapy of the thrombocyto-
topenia.

**Rituximab:** received increasing attention as a promising drug for the treatment of refractory non-HIV immune thrombocytopenia (Godeau 2007). Successful treatment was also reported in HIV-related thrombocytopenia (Ahmad 2004). However, particularly in HIV-positive patients with low CD4 T cells (<100/µl), rituximab should only be used after thoroughly considering the possibly increased risk of infections caused by B cell depletion through the anti-CD20 antibody. Several HIV-negative cases of progressive multifocal leukoencephalopathy with fatal outcome have been observed after rituximab therapy (Carson 2009). A systematic review of the literature on the efficacy of rituximab in adults (age >15 years) with non-HIV immune thrombocytopenia revealed a response rate (thrombocytes >50,000/µl) of 62%. A response was usually seen 3–8 weeks after the first infusion of rituximab and lasted from 2–48 months (Arnold 2007).

**Interferon-α:** significantly increased platelet counts in a small randomized, placebo-controlled study on patients with HIV-related thrombocytopenia. At a dose of 3 million units three times weekly for four weeks an increase of >60,000 platelets/µl was observed within three weeks of treatment. Subsequent to therapy interruption the platelet counts slowly returned to pre-treatment values (Marroni 1994). They can be increased again on re-institution of interferon-α therapy. Treatment of refractory HIV-related thrombocytopenia may be particularly promising in patients coinfected with HCV. Adverse events of interferon-α are flu-like symptoms, depression and, less frequently, cytopenias.

**Thrombopoietin receptor agonists:** are a new treatment option in non-HIV immune thrombocytopenia. In a phase III study a platelet response occurred in 79% of the splenectomized and in 88% of the non-splenectomized patients with non-HIV immune thrombocytopenia after s.c. treatment with the peptide romiplostim. These responses were durable (platelet count >50,000/µL for >6 weeks) in 38% of the splenectomized and in 61% of the non-splenectomized patients (Kuter 2008). The recommended starting dose for romiplostim is 1 µg/kg given s.c. once weekly. It is than adjusted to 1–10 µg/kg weekly according to the platelet count. An increment can be expected after 7–10 days.

A response rate of more than 80% in non-HIV thrombocytopenia was also reported for the small molecule eltrombopag, which can be administered orally (Bussel 2006+2007). The recommended starting dose is 50 mg once daily. It has to be adjusted to 25–75 mg daily according to the platelet count. A platelet response can be expected after 7–10 days. For patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, eltrombopag was approved at a starting dose of 25 mg once daily. Furthermore, a positive effect of eltrombopag on the platelet count was shown in HCV-associated thrombocytopenia (McHutchison 2007). It might be necessary to adjust the dose of eltrombopag when given with ART. The co-administration of the protease inhibitors lopinavir/ritonavir with eltrombopag decreased the plasma concentration of eltrombopag by 17% (Wire 2012). Romiplostim and eltrombopag received FDA and EMA approval. A systematic evaluation regarding the role of thrombopoietin receptor agonists in HIV related thrombocytopenia and data on the long-term safety, however, are still missing.

**Platelet transfusion:** Since the increased platelet destruction is an important mechanism in HIV-related thrombocytopenia, platelet transfusions are only useful in the rare situation with life-threatening bleeding. In this situation platelet transfusions are combined with high dose glucocorticoids (e.g., methylprednisolone 15 mg/kg for 3 days) and intravenous immunoglobulins (1 g/kg for 2 days) (Godeau 2007).
Additional treatment options: Promising results for many other drugs have been reported including cytotoxic and immunosuppressive agents, i.e., azathioprine and cyclosporin A. However, in most studies the numbers of patients are few and long-term safety data are missing (Vesely 2004). This is particularly true for the treatment of HIV-related thrombocytopenia.

References


26. HIV and Sexually Transmitted Diseases

STEFAN ESSER

Epidemiology

A sexually transmitted disease (STD) seldom occurs without other diseases. Every STD can contribute to the transmission of HIV or other venereal diseases. In the case of an STD, the sexual partners of the patient should be informed, examined, and treated, if necessary.

Since the end of the 90s, the incidence of syphilis has been increasing in Western Europe and the US. In patients with newly diagnosed syphilis infections in Germany, prevalence of HIV infection is approximately 45% (RKI 2010). In recent years, there are also reports of regional epidemics of lymphogranuloma venereum (LGV) in Europe, which was regarded as an STD mainly in the tropics and subtropics. Men having sex with men (MSM) are particularly affected (in more than 90% of cases of LGV, and more than 60% of cases of syphilis). HIV-infected persons seem to be more vulnerable to STDs than HIV-negative people (RKI 2004, 2005).

Human papilloma virus (HPV) is among the most frequently sexually transmitted pathogens in woman as well as men. Usually self-limiting in otherwise healthy people, HPV infections may persist in HIV-infected patients more often and can cause condylomata acuminata and precancerous, intraepithelial neoplasia. Over time chronic HPV infection may result in malignancies such as cervical or anal carcinoma. In spite of use of antiretroviral treatment the incidence of HPV-associated cancers is much more frequent in HIV-infected patients than in the general population.

Also infections like hepatitis C (Larson 2011, Obermeier 2011) and shigella (RKI 2005, Aragón 2007, Daskalakis 2007), usually not sexually transmitted, have accumulated regionally in HIV-infected MSM in some large German cities linked with certain sexual practices.

The incidence of STDs increases more rapidly in HIV-infected persons. Screenings in different countries find a high prevalence of asymptomatic sexually transmitted coinfections in HIV-infected cohorts (Heiligenberg 2012). MSM in cities still practice high-risk sexual behaviours frequently (Dirks 2011, Mayer 2012). STI screening in HIV-infected persons should be performed routinely (RKI 2010, Esser 2011, Heiligenberg 2012, Mayer 2012). STDs are HIV indicator diseases (Sullivan 2011). All STD patients not known to be HIV-positive should be offered an HIV test.

Following is a detailed description of the most important STDs. Sexually transmitted diseases like hepatitis B as well as herpes simplex or bacterial vaginoses will be described in other sections of this book.

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Esser S. HPV-Infektion: Von der Feigwarze bis zum Analkarzinom. 5. DOAK (Deutsch-Österreichischer AIDS-Kongress) 15. bis 18. Juni 2011 Hannover, Deutschland (K 27/28)

Syphilis (Lues)

Syphilis is caused by *Treponema pallidum*, a bacterium belonging to the Spirochaetaceae family. The bacteria are mainly transmitted by direct sexual contact with infected persons, and penetrate into the organism through microlesions in the mucosa or the skin. Even kissing can cause an infection. In case of unprotected sexual contact, the risk of transmission ranges from 30 to 60%. Hematogenous or congenital transmissions very seldom occur in western countries.

Clinical course

The incubation period is usually 14 to 24 days. Approximately 40 to 50% of infections show no symptoms or are self-limiting. Persistent infections may affect various organ systems, going through stages of the course of the disease. However, these stages can be skipped or repeated. The highest risk of transmission is during the clinical symptomatic stages of early syphilis (primary and secondary syphilis), especially in case of a primary lesion in stage I. During the late latency period (>1–2 years after infection) and the clinically symptomatic late stages (tertiary syphilis: 2–50 years post infection) syphilis is considered to be non-infectious.

**Primary syphilis**: 2–3 weeks after infection the primary lesion with ulcus durum (hard chancre, erosive chancre) appears at the site of inoculation. This indolent, sturdy ulcer with infiltrated borders usually yields a clear treponema-rich exudate when compressed or squeezed. The chancre is accompanied by a usually strong one-sided lymphadenitis, swelling of the lymph nodes. This primary complex will spontaneously resolve after 4 to 6 weeks without treatment.

**Secondary syphilis**: Variable general symptoms occur after 4 weeks up to 6 months at varying intervals, among these generalized swelling of the lymph nodes and symptoms in various organs. Even an ocular involvement manifesting as episcleritis or iritis can be seen in secondary syphilis. The clinical variety of the frequent syphilids on the skin or the mucous membranes varies from exanthema (usually with palmoplantar participation) to roseola, alopecia syphilitica, moist papule, angina specifica, to condylomata lata (genital and perianal) as well as pigment changes (leukoderma specificum) and lues maligna. Headaches at night are a sign of an early syphilitic meningitis cerebrospinalis. As the risk for neurosyphilis is markedly increased in HIV-infected patients a lumbar puncture is recommended especially when the patient shows symptoms or the time of infection is not certain.
Latent syphilis: When the infection is brought under control by the immune system the clinical features usually disappear entirely. However, during this latency period, syphilis remains serologically detectable and a relapse or progression is possible. During the early latency period (<1–2 years after infection) the syphilis can still be transmitted by blood.

Tertiary syphilis: Years after primary infection, the so-called gummata may appear. These can affect any organ, showing tubercous or granulomatous changes with a tendency to ulceration and cicatricial healing. Major cardiovascular features of tertiary syphilis are asymptomatic aortitis, aortic insufficiency, coronary ostial stenosis and aortic aneurysm. Tertiary syphilis of the central nervous system (CNS) has many manifestations, which involve the meninges and the arteries and parenchyma of the cerebral cortex. Meningovascular syphilis is characterized by an obliterative endarteritis of the meningeal vessels with subsequent arterial thrombosis and ischemic necrosis in the brain and spinal cord.

Quarternary syphilis: In untreated patients, a late neurosyphilis occurs in various forms after some years. In case of tabes dorsalis, a shooting and burning pain, sensory ataxia, reflective pupilloplegia (signs of Argyll Robertson syndrome) and optic atrophy are observed. Regarding syphilitic meningitis, cranial nerve paresis, an increase of intracranial pressure and other neurological symptoms are seen. In case of progressive paralysis symptoms like headache and a change in personality prevail followed by dysplasia (a speech disorder), cramps, dementia and apoplectic attacks. An untreated progressive paralysis will lead to death in 4 to 5 years.

Connatal/Congenital Syphilis: Diaplacental transmission usually happens in the 4th to 5th month of pregnancy. Depending on the stage of syphilis in a pregnant woman, it will lead to an abortion or a lues connata of the infant, progressing in the following ways: Lues connata praecox, rhinitis syphilitica, interstitial hepatitis, encephalomeningitis with hydrocephalus communicans hypersecretorius as well as Parrot’s pseudoparalysis. The typical stigmata of lues connata tarda (from the age of 3) are saddle nose, Parrot’s ulcer and Hutchinson’s triad: Hutchinson’s teeth, keratitis parenchymatosa and labyrinthine deafness.

In HIV-infected patients, unusual manifestations and fulminant progress of syphilis are often observed (Gregory 1990). Reactivation of earlier infections as well as shorter latency periods and faster progression to the later stages including neurosyphilis occur in addition to symptoms of the coexistent stages. Neurosyphilis can be diagnosed in about 20% of syphilis/HIV-coinfected patients during the early syphilis stages (Esser 2011). Syphilis can lead to a temporary increase in HIV viral load and to an additional deterioration of the immune status even in patients on effective antiretroviral treatment.

Diagnosis

The diagnosis of syphilis in HIV-positive patients is not only complicated because of a nonspecific clinical course of the disease, but also due to unreliable screening tests and atypical syphilis serologies like a late IgM descent after treatment and fluctuating VDRL titers (Veneral Disease Research Laboratory test, detection of phosphatide antibodies).

Silvery-shiny, spiral treponema are noticable due to their typical rotating and bending movements when applying large-scale dark-field microscopy obtained from the stimulus secretion from the ulcus durum. A direct microscopic viral detection should be done when a primary syphilis lesion is suspected, particularly in the case of an initially prevailing seronegativity. As a first reaction, IgM antibodies will appear (diagnostic test and lipid antibody detection will still be negative).
Due to a possible overlap of disease stages, each serologically syphilis-positive patient should be neurologically examined. If possible, cerebral spinal fluid (CSF) should be collected as the diagnostic findings may have therapeutic consequences (see below). Interpretation of CSF results in HIV-infected patients should be done by experts on the basis of the ITPA index (intrathecal-produced *Treponema pallidum* antibodies), parameters of a cerebrovascular barrier disorder and the detection of lymphomono-cytic pleocytosis.

**Interpretation of syphilis serology in HIV-infected patients**

Syphilis serology is based in principle on treponema-specific diagnostic tests. These are TPHA (*Treponema pallidum* hemagglutination assay), TPPA (*Treponema pallidum* particle agglutination test), or ELISA (enzyme-linked immunosorbent assay). If positive, treponema-specific tests to confirm will follow, like IgM ELISA, IgM and IgG Western Blot or 19-s-IgM-FTA-ABS (treponemal antibody-absorption test). In the case of a reactive 19-s-IgM-FTA-ABS test in untreated patients or a reactivation of the test in treated patients (Lues non satis curate), there is always need for treatment. False-negative test results can be explained by inadequate production of antibodies or by suppression of IgM production due to high IgG levels. When in doubt, specific tests such as FTA-ABS or cardiolipin tests should be carried out, even though false-negative results may occur again. Should a syphilis infection be serologically confirmed, a quantitative evaluation of the non-treponema specific activity parameters (lipoid antibodies, e.g., VDRL test or KBR) is required. The prozone phenomenon refers to a false-negative response resulting from disproportionately high antibody titers that interfere with the formation of antigen-antibody lattice necessary to visualize a positive flocculation test. This effect can be expected during second-

![Figure 1: Diagnostic algorithm for assuming a syphilis infection](image-url)
ary syphilis and in syphilis/HIV-coinfected patients (Smith 2004). HIV-associated unspecific activation of B lymphocytes can also cause false positive VDRL tests.

The longer a patient has untreated syphilis the longer the normalisation of the syphilis activity parameters will take even after a successful syphilis therapy in HIV-infected patients. The IgM test may remain reactive for years. A successful therapy during this IgM-reactive period is indicated by a clear titer decrease of the non-treponema-specific activity parameters (reduction of VDRL by at least 2 titer levels within 3 months). Due to an increase of the previously decreased activity parameters, a re-infection or a re-activation may happen during this time. A re-infection or re-activation is assumed when the serological titers increase by more than two titer levels by the end of therapy compared to the initial value. A serological differentiation between re-infection and re-activation is not possible. As the activity parameters are not treponema-specific they often vary in HIV-infected patients, mainly when contracting additional infections. Repeated syphilis re-activations are an indication for liquor cerebrospinalis punctuation to exclude an untreated neurosyphilis.

**Therapy**

The generation period of *Treponema pallidum* is between 30 to 33 hours. Therefore, the therapy period should not be less than 10 to 11 days. A parenteral dose of penicillin is the therapy of choice at all stages. Resistance to penicillin has not been seen for *Treponema pallidum*. Recommendations for the early stages of syphilis include intramuscular injections of benzathine penicillin 2.4 MU (e.g., 1 ampule Pendysin® or Tardocillin® of 1.2 MU IM in each buttock) weekly for 1 week during early syphilis and in later stages of syphilis for at least 3 weeks. When the infection date is uncertain, lues should be treated like late-stage syphilis.

In cases of penicillin intolerance, doxycycline 100 mg BID orally, erythromycin 2 g/day orally for at least 2 weeks, azithromycin or ceftriaxone (intramuscular, intravenous) is recommended. Apart from ceftriaxone these alternatives are considered less effective than the intramuscular injection with penicillin.

Neurosyphilis is usually treated with 3 x 10 MU or 5x5 MU or 6 x 4 MU penicillin G, administered intravenously for 10–21 days. Current guidelines recommend an initial dose of 4 g ceftriaxone followed by 2 g daily intravenously for 10–14 days (Deutsche STD-Gesellschaft 2008).

Cross-reacting allergies (<10%) between penicillin and cephalosporin are possible. Alternative treatment options are doxycycline 100 mg BID or erythromycin 500 mg QD for at least 3 weeks. When treating with macrolides the possible development of resistance to *Treponema pallidum* should be considered (Lukehart 2004). Therefore, despite suspecting a penicillin allergy a controlled penicillin hardening under stationary conditions in reanimation readiness until the required full therapeutic dosage is administered is performed in specialized centers.

When starting syphilis therapy – irrespective of the stage – a Jarisch-Herxheimer reaction should be differentiated from a penicillin allergy. Depending on the stage of syphilis, the Jarisch-Herxheimer reaction is observed in just 20% of patients within 48 hours after the first administered dose of antibiotics. It is caused by a release of pyrogenic, a vasoactive endotoxin, the result of a fast decomposition of bacteria, showing exanthema and influenza-like symptoms such as shivering, fever, arthralgia or myalgia. The Jarisch-Herxheimer reaction can be avoided or at least reduced by administering a single dose of 1 mg/kg prednisolone orally or intravenously prior to the first dose of antibiotics.

A successful therapy should have a clinical and serological follow-up 3, 6, 12, 18 and 24 months after treatment. A successful therapy is reflected by the disappearance of
clinical symptoms and a clear titer decrease of the non-treponema-specific activity parameters (reduction of VDRL by at least 2 titer levels within 3 months). A repeated increase of the previously decreased activity parameters may mean a re-infection or a re-activation requiring treatment. This is assumed if the serological titer increases by more than two titer levels after the end of therapy in comparison to the initial result. Even in HIV-infected patients, the IgM test should not be reactive 2 years after a sufficiently administered syphilis therapy. In case the IgM test is no longer reactive, a repeated reactivity means a re-infection or re-activation, requiring further treatment (see above, interpretation of lues serology).

References

Gonorrhea (the clap)

Gonorrhea, also called the clap, is caused by the Neisseria gonorrhoeae bacteria. The bacterium can be found worldwide and depending on the region shows a varying and changing resistance profile. Gonorrhea is typically localized in the genitourinary mucosa and transmission is almost exclusively through sexual activity (exception: neonatal conjunctivitis); the incubation period lasts from 2 to 10 days.
**Clinical course**

The primary symptoms in men are urethritis, frequent strangury, a burning pain when urinating, and urethral pain. A typical symptom is the *bonjour drop*, a purulent discharge from the urethra after several hours of restricted micturition. It is often accompanied by a balanitis. Without treatment, gonorrhea can cause prostatitis. Symptoms are a burning after miction, pain in the intestinal area and an enlargement of the prostate. Furthermore, it can cause an epididymitis with pain and swelling. In women, the course of gonorrhea is often asymptomatic, although urethritis may occur. Only in pre-pubescent girls is a vaginal colonization possible. Involvement of the cervix and adnexa of the uterus may cause complications like peritonitis and pelvic inflammatory disease.

Extragenital manifestations of gonorrhea occasionally cause pharyngitis or proctitis. Perinatal transmission of gonococcal conjunctiva is rare. Which is why Credé's prophylaxis for newborns (temporary treatment with eye drops: originally 1% silver nitrate solution; later, erythromycin-containing eye drops or ointments) was stopped in Germany. Systemic infections with general symptoms like fever, arthritis and endocarditis including gonococcal sepsis are rare (Rompalo 1987).

**Diagnosis**

Microscopic preparations are taken urethrally, anally, pharyngeally and in women also endocervically. For four hours before the urethral smear, the patient should not urinate. The diagnosis will be confirmed by microscopy of preparations from intra-cellular, gram-negative diplococci using methylene-blue or gram stain. It is almost never necessary to do serological tests or immunofluorescence microscopy. Laboratory culture is mainly performed to confirm resistance. *Neisseria gonorrhoeae* was found in sex workers in Indonesia (Joesef 1994), 89% of whom were penicillinase-producing and in 98% resistant to tetracycline, but responded well to cephalosporins and fluoroquinolones. At the same time, a reduced response to quinolones by up to 24% was detected in the US (CDC 1998). Penicillinase-producing (resistant) gonococcal stains are seen in the US in 25%, in Asia 30%, and in Africa up to 90%. Also an increase of resistance to 3rd generation cephalosporins has been observed in many regions (Bala 2010, Ison 2010, Chisholm 2011). Resistance to ceftriaxone has been already reported (Carnicer-Pont 2012) as well as to macrolides like azithromycin (Chisholm 2009, Ison 2010). Systematic evaluation of antibiotic resistance in Germany has not been done. Gonorrhea is often treated without laboratory culture and resistance testing. A small German study in the Heidelberg and Stuttgart regions with 65 smears from patients with uncomplicated gonorrhea during the years 2004/2005 (Enders 2006) found resistance to penicillin in 21.5%, to tetracyclins in 29.2%, to ciprofloxacin in 47.7% and to azithromycin in 7.7%. All isolates were fully susceptible to ceftriaxone, cefixime and spectinomycin, which are not available any longer. Comparable results were published in Berlin from 1995 until 1997 (Wagner 2001) looking at 85 isolates. About 30% of patients with symptomatic gonorrhea are coinfected with chlamydia serotypes D-K.

**Therapy**

Therapy depends on geographical resistance profiles. With respect to fluoroquinolone-resistant bacteria strains, a one-time IM dose of 250 mg ceftriaxone (Rocephin®) (CDC 2004) is the treatment of choice in Germany. Coadministration of a one-time dose of 1000 mg azithromycin (Zithromax®) or doxycycline 200 mg daily for seven days should be considered due to resistance of *Neisseria gonorrhoeae* and frequent chlamydia coinfections.
Chlamydia infection, lymphogranuloma venereum

Genital infections with *Chlamydia trachomatis* are nearly twice as prevalent as gonococcal infections. There are several serotypes that can cause different diseases. Serotypes D-K are broadly distributed in Europe and cause urogenital infections, which can be sexually transmitted as well as conjunctivitis or pneumonia after perinatal transmission. Serotypes L1, L2 and L3 cause lymphogranuloma venereum (LGV). LGV used to be known strictly as a tropical disease but has undergone a renaissance in Europe and the US (Gotz 2004, Krosigk 2004).

Clinical course

In men, symptomatic genital chlamydia, serotypes D-K, may be present as urethritis. As in gonorrhea, epididymitis, prostatitis or proctitis may occur. Reiter’s syndrome with conjunctivitis and reactive arthritis is also possible. A chlamydial infection in about 20% of the female patients may manifest as urethritis, cervicitis, salpingitis, endometritis, proctitis and arthritis. The cervicitis mainly contains purulent fluorine. Possible consequences of a salpingitis are sterility by tubal occlusion or ectopic pregnancy.

In lymphogranuloma venereum caused by serotypes L1–3, a primary lesion occurs at the entry location. Some weeks later a painful swelling of the regional lymph nodes develops that tends to exudate. After healing this may lead to scars, which may cause discharge disorders and fistula due to a blocking in the lymphatic vessels. Especially in HIV-infected MSM, extremely painful and therapy refractory proctitis as well as preanal and intra-anal ulcerations by chlamydial infections with serotypes L1–3 may occur (RKI 2004 und 2005, Peerenboom 2006).

Diagnosis

The best methods to confirm the diagnosis of infection with *Chlamydia trachomatis* are amplification tests (PCR). This is more sensitive, and at least as specific as the results obtained by cell cultures (Morre 2005) used in the past. Using dry cotton wool, apply with pressure for a few seconds to collect epithelioid cells, which should
be sent in dry storage to the lab (routine in most labs). The samples should be tested for serotypes D-K. PCR tests of serotypes L1, L2 and L3 are only done on request in specialized labs. A positive test result for all chlamydial serotypes described above leads to a therapy indication.

Antigenic tests by ELISA or direct immunofluorescence tests are possible as well, but there is a lack of sensitivity in 75% and a lack of specificity in 97–99% in patients with low chlamydial prevalence resulting in a high number of false-positive test results.

**Therapy**

The therapy of choice is doxycycline (Supracyclin®) 100 mg BID for 7 to 10 days. Alternatively, ofloxacin (Tarivid®) 200 mg BID or erythromycin (e.g., Erythrocin®) 500 mg QID for 7 days can be given. Even a one-time dose of 1000 mg azithromycin (Zithromax®) has proven an effective treatment in uncomplicated cases. The treatment of lymphogranuloma venereum requires a longer-term therapy. Doxycycline should be administered for at least 3 weeks.

**References**


**Genital ulcers (Ulcus molle, soft chancre, chancroid)**

Genital ulcers are caused by an infection by *Haemophilus ducreyi*. It is an endemic infection found primarily in tropical or subtropical regions. Officially, less than 100 cases per year were diagnosed in Germany in the years 1999 to 2004 (Health Report of the Federal Government, 2006). However, the estimate for unknown cases is higher.

**Clinical course**

Usually, the incubation period is 2 to 7 days causing one or more frayed-looking ulcers at the entry location, mostly in genitourinary or perianal locations. These ulcers are not indurated (soft chancre) but characteristically cause severe pain. In about half of the patients the regional lymph nodes are swollen resembling the lymph-
phogranuloma venereum, mainly unilateral and very painful. Balanitis, phimosis or paraphimosis occur less frequently.

**Diagnosis**

Due to the manifold symptoms partly resembling other ulcer-causing genital infections such as syphilis or even herpes simplex, a clinical diagnosis is difficult. Microscopy of ulcer smears may demonstrate gram-negative bacteria. But a purulent punctate from affected inguinal lymph nodes offers more reliable results. Sometimes a biopsy from the ulcer is necessary to distinguish it from a malignancy.

**Therapy**

It is recommended to give a single dose of 1000 mg azithromycin (Zithromax®) (Martin 1995). Alternative therapies are erythromycin (e.g., Erythrocin®) 500 mg QD for 4 to 7 days, or ciprofloxacin (e.g., Ciprobay®) 500 mg BID for 3 days. Lymph nodes that are severely swollen or in danger of bursting open should not be split but punctured for relief.

**References**


**Condylomata acuminata (fig warts)**

Human papillomavirus (HPV) exclusively infects epithelial cells and are one of the most frequently transmitted viral infections in men as well as in women. It takes at least 3 weeks from the incubation period to clinical manifestation, but may also take months or years. Even a transmission via smear infection or contaminated objects is possible. Besides frequent casual sex and smoking, immune deficiency and other diseases in the genito-anal region are the main risk factors for an HPV infection. In general, HPV infections are seen more often in HIV-infected patients. HPV infections tend to persist longer in HIV-infected persons resulting more often in the development of clinical symptoms. Patients who have anogenital warts should be offered HIV testing especially if they have other HIV risk factors. The numerous different HPV subtypes may cause infections in the anogenital region in patients older than 20. HIV patients suffer very often from genito-anal co-infections with various onco-gene high-risk HPV subtypes. In recent years an increase of HPV-caused benign fig warts has been observed despite ART as well as intraepithelial neoplasms and carcinoma, both cervical and anal. In immunodeficient patients HPV-associated lesions have low rates of spontaneous remission and are very resistant to therapy (frequent relapses). The risk of developing anal cancer is 80 times higher in HIV-infected MSM than in the general population. The incidence is 35/100,000 person-years (Chiao 2006, Silverberg 2012). Most of HIV-infected anal cancer patients have condylomata acuminata in their medical history (Hoffmann 2011). Screening and early treatment of genito-anal condylomata acuminata and intraepithelial neoplasia may reduce the incidence of anal cancer in HIV-infected persons.
**Clinical course**

Most HPV infections are asymptomatic or subclinical. Even symptomatic HPV infections may end with a spontaneous remission. The most frequently diagnosed clinical manifestations of sexually transmitted HPV infections are genito-anal warts or Bowenoid papulosis as well as giant condyloma (Buschke-Lowenstein tumor), cervical or anal intraepithelial neoplasias (classified CIN or AIN I-III lesions including the erythroplasia of Queyrat) or at least carcinoma. In HIV-infected patients, the risk of persistent HPV infections is seven times higher and correlates inversely with the CD4 T cell count (Piketty 2003). In HIV-infected patients, HPV infections are more often symptomatic and chronic. In addition, the risk of relapse is considerably higher than in non-infected patients, even after treatment. Malignant transformation is the most important complication involving the high-risk HPV subtypes.

Condylomata acuminata are hyperkeratotic and verrucous papules of the anogenital region. Condylomata acuminata are usually caused by HPV 6 or HPV 11, so-called low-risk HPV types, which itself do not tend to induce malignant transformation. Therefore, fig warts are not inevitably the beginning of genito-anal intraepithelial neoplasms and carcinoma but it is difficult to differentiate between them. Besides the preferred localization in genital as well as peri- and intra-anal regions, fig warts may also occur enorally and in the urethra. Condylomata are usually asymptomatic but can affect the sexual life of patients and may cause hygiene and psychogenic problems. Pruritus, burning or bleeding are rare and are generally caused by mechanical stress.

**Diagnosis**

Analogous to cervical intraepithelial neoplasia (CIN) and cervical cancer in women, regular screening (every 1 to 3 years) for condylomata acuminata, anal intraepithelial neoplasia (AIN) and anal carcinoma is advised for all HIV-infected patients. Screening should include clinical inspection, palpation, colposcopy, proctoscopy, cytology (Pap smear) and, if necessary, a histopathological examination of biopsies. **Condylomata acuminata** is a clinical diagnosis. An exploratory biopsy is recommended before therapy starts to confirm it is not a malignancy. In case of therapy resistance, early relapse or a fast or infiltrating growth, an exploratory biopsy is imperative. Meanwhile, cytologic examination of microscopic preparations (smear tests) are done in order to differentiate it from preliminary cervical or anal carcinoma. Cytological results of smears from the cervix are divided with the classification of Papanicolaou. For anal smears the Bethesda System is used: Normal results are differentiated from inflammation and atypical cells: Atypical squamous cells (ASC: -US (undetermined significance), -H (cannot exclude HSIL), atypical glandular cells (ACG), low-grade or high-grade squamous intraepithelial lesion (LSIL or HSIL). However, the sensitivity and specificity of these tests are still not sufficient (Panther 2004, Jablonka 2011). A review of anal cytologic examinations has shown a prediction of biopsy results for anal dysplasia with a sensitivity of 69–93% and a specificity of 32–59% (Chiao 2006). Every suspicious cytologic finding should be monitored with a contemporary colposcopy or proctoscopy (Duerr 2006). Specialized centers offer the “High Resolution Anoscopy” as a gold standard, which improves the test results of peri- and intra-anal inspections with regard to necessary exploratory biopsies, especially after the application of acetic acid (3 per cent mucosa, 5 per cent skin) and an additional staining with Lugol’s solution. Suspicious lesions have to be biopsied. Histologically, examinations of intralesional biopsies differ in Condylomata acuminata, intraepithelial neoplasia divided in severity grades I-III (IN) and invasive cancer. The abbreviation of the anatomic location of the lesion is specified in front of the IN grade. The descrip-
tion AIN III is in accordance with an anal carcinoma in situ. The determination of the HPV subtype allows for differentiation between high- and low-risk types and is still not a routine diagnostic method, because of its subordinate role in therapy decisions (Ledger 2000). When high-risk HPV-types are detected, some experts recommend to shorten the period between control examinations of the affected region. Just like women, HIV-infected men, mainly those suffering from condyloma anamnesis, should have a proctological follow-up at least once a year (Chiao 2006, Scott 2008, Wexler 2008, Jamieson 2006, Esser 2011). To avoid fatal tumor growth and mutilating operations (rectum amputation etc) it is recommended to do thorough genito-anal inspections and regular proctological exams by means of high resolution anoscopy with cytological smears and exploratory excision, which are timely and specific (Kreuter 2009, Pindea 2008). Rectal palpation and external inspection of the anogenital regions are not sufficient as a preventive medical checkup for HIV-infected patients. Should an anal carcinoma be palpable, it has, in general, already progressed extensively. Until today, there are no good reports on how often intra-anal, HPV-associated lesions are isolated without involving the external genito-anal regions. Nowadays there are surveys trying to find out how often colposcopic and proctoscopic exams should be offered in addition to the routine genito-anal palpations and inspections, and exactly who should be examined.

**Therapy**

Until now there is no satisfying therapy for Condylomata acuminata. Relapses still occur frequently even after adequate treatment in immune competent HIV-negative patients (40–60%). However, therapy delays (watch & wait) should be avoided and all clinically striking findings should be removed at an early stage even at the risk of operating multiple times. Therapy includes the most complete operative removal possible with histological follow-up of the nature of the tumor and its invasive depth. Besides surgical excision, electrosurgery, the condyloma may be removed by means of laser surgery, infrared coagulation, caustica (trichloroacetic or podophyllotoxin) or cryotherapy with liquid nitrogen (high healing effect initially – high relapse risk). All the destructive treatments have disadvantages. Since virus-harboring keratinocytes can remain in the clinically normal surrounding tissue, relapses are as frequent as 50% in immunocompetent patients and in up to 70% in immunodeficient patients within 4 months. In clinical practice, attending physicians often try to reduce the high relapse risk by an adjuvant local immune therapy with imiquimod (Aldara®) cream or interferon-beta. Both agents are expensive and a local therapy takes time (at least 3 months). Imiquimod is licensed for the topical treatment of HPV-associated lesions. As demonstrated in several controlled studies imiquimod treatment is safe and effective and has the lowest relapse rate of all treatments (6–13% in immunocompetent patients). Imiquimod is not approved for the treatment of anogenital warts in immunodeficient patients and intraepithelial neoplasias but results of successful treatments of genital warts (Cusini 2004), Bowenoid papulosis and Bowen’s disease in HIV-infected patients have been published (Kreuter 2008). In our own experience imiquimod can be successfully used as the sole therapy for flat, less hyperkeratotic condyloma. There are formulas for imiquimod-containing suppositories (off-label). However, the treatment period takes several weeks without surgical intervention, often complicated by compliance-reducing side effects such as inflammation, pruritus and burning. Condyloma may also be systemically treated with interferon (there are often problems with health insurance due to a low success rate of 31% in the initial stages, although there are reports of a significantly lower relapse rate in comparison to further invasive therapies). Herbal 10% Camellia sinen-
sis ointment (Veregen®) is also approved for local therapy of genitoanal warts (Abramovits 2010). The only antiviral agent active against HPV is cidofovir but there is little experience in HIV-infected patients (Snoeck 2001). While various vaccines have been successfully used as prophylaxis for certain HPV-subtypes (HPV 6, 11, 16, 18), there is still no progress in the development of an effective therapeutic vaccination against symptomatic HPV infections. Primary results of the quadrivalent HPV vaccine in HIV-infected men show that the vaccine was generally safe, well-tolerated and highly immunogenic. Efficacy studies are now warranted (Wilkin 2010). Case reports about less relapses after operative removal and vaccination have been published (Swedish 2012).

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Shigelllosis

Shigella is a worldwide gram-negative bacteria related to the family of enteric bacteria which can be divided into different pathogenic serogroups (A-D) and serovars (group A: S. dysenteriae, B: S. flexneri, C: S. boydii, D: S. sonnei), depending on certain biochemical features and specific antigens. All shigella groups release an endotoxin which causes infection of the intestinal mucosa. S. dysenteriae type 1 also produces an exotoxin which often leads to severe symptoms involving insufficiency of the cardiovascular system and CNS disorders.

Humans are the only relevant hosts. Shigellosis is spread by fecal-oral transmission, most frequently through direct contact, i.e., by lack of proper hygiene and poor hand washing habits. Although shigella bacteria usually do not survive outside the human body, infection can be transmitted via contaminated water or food in warmer countries. As few as 100 perorally transmitted germs are enough to cause an infection. Shigella bacteria grow in the intestinal mucosa of humans and are shed in the feces. The incubation period is usually between 12–96 hours. Infections can be transmitted after a phase of acute illness and as long as the bacteria is excreted in stool, but usually no more than four weeks. Prevention of the spread of this highly contagious bacteria is complicated, as stool specimens can appear clinically normal.

With regard to sexual practices, sexually transmitted shigellosis appear rather frequently within certain risk groups such as MSM and cause regional outbreaks (RKI 2002+2005, Aragón 2007, Daskalakis 2007). In a survey by the Robert Koch Institute, most infected patients stated that they had sexual contacts in bars, parties or in saunas, where a direct or indirect contact of the mouth or anal regions by the fingers had taken place. In two outbreaks in Berlin in the years 2001 and 2004, the S. sonnei isolates in stool specimens showed similar isotopes and identical resistance patterns. Resistance was observed to TMP/SMX, tetracyclines, amoxicillin, ampicillin/sulbactam and mezlocillin (RKI 2002, Marcus 2004, RKI 2005). A more recent analysis investigated 52 cases of S. sonnei in MSM suffering with diarrhea in three major HIV clinics in Berlin and Hamburg. Results showed high rates of quinolone resistance especially high in HIV-infected MSM (for ciprofloxacin, 53% versus 21% in negative MSM). No resistance was found against carbapenem and newer cephalosporins, such as ceftriaxone, ceftazidime or cefepime (Krznaric 2012). However, resistance to the commonly administered antibiotics is increasing worldwide (Niyogi 2007, Gaudreau 2010).

Clinical course

Many infections with shigella may present as a mild, self-limited illness. However, the clinical course of shigellosis varies widely, from asymptomatic disease, watery diarrhea, dysentery (bloody and mucoid stools) up to life-threatening septic courses. Mostly, shigellosis begins with watery diarrhea and can develop into an inflammatory colitis. Abdominal pain (colitis and tenesmus) is a typical sign. Frequent defecation (up to 50 times a day) can cause dehydration and loss of proteins. Usually,
shigellosis resolves within 7 days. Fever, bloody, mucoid and ulcerous diarrhea are symptoms of severe cases. Focal ulcerations and necrosis appear most frequently in the distal colon that can develop into dilatation of the colon and colon perforation with following peritonitis and sepsis in extreme cases.

In rare cases (1–3%) shigellosis manifests outside the intestines: Cytotoxin (Shiga toxin) produced by S. dysenteriae serovar 1 is almost identical to Shiga toxin 1 (vero-toxin 1) enterohemorrhagic E. coli (EHEC) that also causes a hemolytic uremic syndrome (HUS). Other possible sequels are infectious arthritis and Reiter syndrome.

**Diagnosis**

Diagnosis is made by bacteriological investigation of freshly obtained stool or rectal smears. The stool sample is suspended in MacConkey agar to identify non-lactose fermenters such as shigella species. More selective media cultures and slide agglutination are then used to identify group and serotypes. The samples should be obtained before taking antibiotics and an antibiogram should be made. Results of resistance tests may be adjusted if therapy with antibiotics has already commenced. Identification of the infection sources and transmission paths help to define the serogroups and serovars involved.

**Therapy**

Since shigellosis is highly infectious, treatment with antibiotics is recommended. With antibiotics, the period of fecal shedding, diarrhea and illness is shortened (Christopher 2012). Quinolones, TMP/SMX, azithromycin, tetracyclines, doxycycline and ampicillin are suitable. Ampicillin is recommended for treatment of long-term carriers. In resource-limited areas, the drug of choice is ciprofloxacin (500mg BID) or TMP/SMX (160 mg/800 mg BID) for five to seven days, respectively. However, in Western metropolitan areas and in cases of MSM infected with shigella, the increasing resistance has to be considered (Niyogi 2007, Gaudreau 2010). In a recent analysis of 52 cases occurring in Hamburg and Berlin in 2010/2011, high resistance rates were found for doxycycline, tetracycline, aminoglycosides, all cephalosporins of the first two generations tested, and TMP/SMX. In total, 30% of the cases were resistant to amoxicillin and ampicillin, while 48% were resistant to ciprofloxacin. Compared to HIV-negative cases, HIV-infected patients had a significantly higher rate of quinolone resistance. For ciprofloxacin, resistance rates were 58% versus 20%, respectively. Most isolates were susceptible to newer cephalosporins such as cefixime and no resistance was found for carbapenems or newer cephalosporins such as ceftriaxone, ceftazidime or cefepime (Krznaric 2012).

A symptomatic therapy with oral fluid replacement can suffice for patients in overall good and stable condition. In the case of comorbid, very young or older patients, loss of fluid and electrolytes should be replaced via parenteral nutrition. Motility inhibitors such as loperamide should be avoided.

**Prevention**

Basic measures to prevent shigellosis infection are clean and hygienic conditions (personal hygiene, clean water and food, hygiene in community facilities, prevention of fly contamination). As shigellosis is usually passed through direct contact from human to human, the most effective prevention is frequent and careful hand washing to avoid fecal and oral smear infections. Hands should be washed with soap or with an alcohol containing disinfectant. In countries with poor hygienic condi-
tions one should follow the recommendation, “Peel it, boil it, cook it or forget it”. As shigellosis is highly contagious and HIV-infected patients possibly more vulnerable (Baer 1999), preventive measures against sexually transmitted shigellosis are more strict than with other STDs. Use of condoms for anal sex does not provide sufficient protection. Sexual contact should be avoided from the first days of diarrhea onwards until shigella bacteria are no longer detectable in the stool. Early diagnosis and treatment prevents further infection. During the course of illness, measures should be taken to disinfect all objects and surfaces which may have come into contact with the patient’s infectious excretions. Clothes, bed sheets and towels should be washed at least 60°C or be soaked in disinfectant for 12 hours before washing at normal washing temperature. Toilet seats and lids, as well as bed frames, sinks and bath tubs should be disinfected daily in health care facilities. Owners of bars and darkrooms as well as organizers of sex parties should install soap dispensers in the washrooms. Sharing of used and inadequately disinfected dildos or tubes with lubrication gels should be avoided. Operators of saunas should chlorinate their whirlpools. Other preventive measures for schools and other public facilities and food production companies, should follow preventive guidelines given by the authorities for disease control and prevention. People who are, or are suspected to be infected with shigellosis, are not allowed to work in facilities where food is produced or processed. This also applies to long-term carriers (asymptomatic shedders) of the infection. Admission to public facilities is possible after clinical recovery and three negative stool test results (stool samples after 1–2 days, respectively). The first sample should be taken after at least 24 hours after appearance of formed stool or 24 hours after ending a therapy with antibiotics. People in close contact with an infected patient should be tested after the incubation period and tested negative. An exception may be made if typical symptoms do not show and otherwise hygienic measures are followed. Close personal contacts and a lack of hygiene, especially in community facilities encourage a spread of shigellosis. If a shigellosis outbreak is suspected, a quick identification of the source of the infection and transmission factors (i.e, food) can avoid further spread of the infection. In any case, the public health department should be informed as soon as possible.

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27. HIV-associated Skin and Mucocutaneous Diseases

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Introduction

In comparison to the general population HIV-infected patients develop skin diseases more often (Rothengatter 2009). Skin and mucocutaneous diseases are important at the first diagnosis of HIV-infection and in determining the clinical stage of the patient. In 10% of cases, the first diagnosis of HIV infection is based on diseases of the skin and the mucous membranes (Itin 2008).

The spectrum of HIV-associated dermatoses has dramatically changed with ART in recent years. KS (Friedman-Kien 1981), OIs of the skin (e.g., the rodent ulcer herpes simplex infections) and the mucous membranes (e.g., Candida infections) have been observed as marker diseases of acquired immunodeficiency. Almost any HIV-associated or AIDS-defining disease can be manifested on the skin and mucous membranes before other symptoms appear. The broad spectrum comprises infections from viruses, fungi and bacteria as well as protozoa and parasites (Gottlieb 1981, Siegal 1981, Schöfer 1991, Schöfer 1999). KS and OIs have been reduced by the increasing use of ART in industrial countries, while side effects and incompatibilities with drugs, virus- and UV-associated epithelial tumors as well as other STDs in HIV-infected patients are on the rise (Costner 1998, Sepkowitz 1998, Kreuter 2002, Calista 2002). HIV-infected patients should, therefore, have regular dermatologic screening tests and treatment.

Skin and the mucous membranes are independent organs of the immune system. An immunodeficiency allows even harmless saprophytes on the body surface and follicle openings to penetrate into deeper tissue layers, and thus develop life-threatening infections. An increase in wound infections and pyoderma, as well as in clinically relevant methicillin-resistant infections have been seen in HIV-positive patients (Burkey 2008). In addition to common dermatoses (e.g., oral candidiasis, herpes zoster, seborrheic dermatitis) other diseases that have rarely or never been reported have been diagnosed in progressive immunodeficiency (cutaneous cryptococcosis, bacterial angiomatosis, oral hairy leukoplakia, Penicillium marneffei infections).

In tropical and subtropical regions, STDs like herpes genitalis, chancroid and other ulcerating diseases occurring on the genitals play a decisive role in spreading HIV. Syphilis and lymphogranuloma venereum (LGV) are experiencing a renaissance in Europe. Homosexual men are the main carriers in this new epidemic. Since 2000, the number of male syphilis patients in big cities has grown tremendously. In Germany, in 45% of newly registered syphilis infections, HIV infection is diagnosed at the same time (RKI 2008). Circumcisions decrease the risk of sexual transmission of HIV infection (Warner 2009, Giuliano 2009) for men but the best protection is the use of condoms.

The immune system protects the skin and the mucous membranes against the development of various malignant tumors (Schöfer 1998). Oncogenic viruses plus immunodeficiency increase the ratio of many neoplasias in HIV-infected patients. Some of these are KS (HHV-8), NHL (EBV, HHV-8) as well as cervical and anal carcinoma (HPV, especially HPV-16 and -18) (Esser 1998). In HIV-infected patients, younger people appear more at risk from cancer (Mitsuyasu 2008). The longer a cellular immunodeficiency exists, the more likely epithelial tumors will develop that affect the skin and the mucous membrane (basal cell carcinomas, cutaneous and mucocutaneous...
squamous cell carcinomas). This is also true for malignant melanomas. Despite ART, HPV-associated diseases is increasing. Due to a rising incidence of anal carcinomas, regular proctological examinations are recommended in addition to the current colposcopic monitoring, especially for HIV-infected MSM with known condylomata acuminata (Kreuter 2003). Avoiding risk factors and regular checkups may help to prevent cancer. The skin and the mucous membranes are easily accessible and suspicious lesions can be removed at an early stage.

Knowledge of diagnosis and therapy of HIV-associated dermatoses is interdisciplinary and indispensable for an efficient treatment of HIV-infected patients.

**Dermatological examination and therapy in HIV-infected patients**

Inspection of the whole skin surface, the mucous membranes of the mouth, the genitals, the anal region as well as palpation of the lymph nodes can be done without any special effort or expense. But even for an experienced physician, diagnostic and therapeutic problems may arise when examining HIV-infected patients – the clinical picture may differ from textbook knowledge. Skin and mucocutaneous diseases often show an unusual, more serious, faster and therapy-refractory clinical course (Ameen 2010). The spectrum of causes of an infection may differ considerably from HIV-negative patients (Imaz 2010). The coexistence of several infections means a serious immunodeficiency. Therefore, it is important to examine lesions correctly before starting therapy. In case of inconclusive test results punch biopsies should be done to obtain histological reports.

Standard treatment of the skin and the mucous membranes might come back negative in HIV-positive patients. The main reasons for this are an advanced immunodeficiency as well as resistance. In such cases, a higher dose over a longer period of time should be given, keeping in mind possible toxic side effects (Osborne 2003). Interactions, e.g., with azole antimycotics or aromatic retinoids, should be considered regarding patients on ART. Immunosuppressive therapies should be used cautiously, and only for a short period of time. UV treatment (e.g., PUVA therapy for psoriasis) should be considered carefully and closely supervised when used as viral infections may potentially be provoked, malignant tumors induced and the HIV viral load increased (Popivanova 2010). On the other hand, good therapy results of the UVB 311nm phototherapy in therapy-refractory itching papular dermatoses has been observed without showing deterioration of the immunological situation in individual cases. Diagnostics and therapy can require the whole repertoire of a clinical center primarily specialized in infectious diseases as well as the interdisciplinary cooperation of different expert groups.

**ART: Influence on skin and mucocutaneous diseases**

Some 27 antiretroviral agents have been licensed in the developed world. In the context of life-long treatment, ART-associated side effects are of decisive importance for prognosis, in particular regarding the skin and the mucosa. Regarding exanthemas, the differentiation of a drug reaction from other causes, e.g., an immune reconstitution syndrome, syphilis or viral exanthema presents a big challenge. The identification of the agent as the cause of exanthemas is often difficult in patients on multiple treatments.

The typical side effects of NNRTIs are drug exanthema. ART may cause lipodystrophy. Lipoatrophy, and not an AIDS-defining wasting syndrome, can probably develop with the NRTIs, whereas lipohypertrophies are seen with PIs (Carr 1998, Carr 2000).
These disorders of adipose tissue are often stigmatizing. But before considering a different medication or operative measures for treatment, a different ART regimen may be a possibility. The resistance profile, comorbidities and possible interactions should all be taken into consideration.

**Appendix: Frequent HIV-associated skin diseases**

**Acute HIV exanthema:** after HIV transmission, 40–90% of patients develop an acute, febrile, mononucleosis-like disease with constitutional symptoms and exanthema (see chapter on *Acute HIV-1 Infection*). This nonspecific eruption starts 1 to 3 weeks after transmission, and weeks before HIV seroconversion. The macular exanthema favors the upper trunk and is characterized as fairly non-pruritic with erythematous macules from 0.5 to 1 cm in diameter. Morbilliform or rubella-like eruptions and palmoplantar hyperkeratotic eczema occur less frequently. Histopathology reveals a non-specific perivascular and interstitial infiltrate in the upper- and mid-dermis (Barnadas 1997). Oral aphthous ulcers frequently in combination with shallow genital ulcers (bipolar aphthosis) are another important clinical symptom (Hulsebosch 1990, Porras-Luque 1998). Differential diagnosis includes viral infections (EBV, CMV), Mediterranean spotted fever (Segura 2002), secondary syphilis, drug eruptions (Hecht 2002, Daar 2001) and Behcet’s disease.

**Aphthous ulcers:** At least three different kinds of aphthous ulcers can occur in the oral cavity of HIV-infected patients. The most frequent diagnosis is recurrent aphthous stomatitis (canker sores) (1) with single or few painful lesions usually localized in the vestibule of the mouth. The ulcers occur at sites of mechanical injuries, are 3 to 10 mm in diameter and heal spontaneously after a few days. Single or multiple large aphthae (2) which are >1 cm in diameter and usually persist for several weeks are less common. Both variants are of unknown origin (Rogers 1997). In a few cases, especially when multiple small lesions occur, herpes simplex viruses can be involved. Large ulcers in combination with severe immunodeficiency can be caused by cytomegalovirus, usually part of a generalized CMV infection. Bipolar aphthosis (3) involving the oral and genital mucosal membranes is an important clinical symptom of acute HIV infection or Behcet’s disease. In addition to these clinical variants of aphthous ulcers several authors have discussed the direct role of HIV retroviruses in aphthous stomatitis (Kerr 2003). The treatment of recurrent aphthosis is based on topical anesthetics and corticosteroids. Large persistent aphthae can require intraleisional corticosteroids or systemic prednisone. Immunomodulators such as thalidomide are suggested for use as prophylaxis in patients with frequent and painful recurrences.

**Folliculitis:** pustular, papular or edematous-papular follicular lesions, involving the proximal limbs and the upper trunk. Possible causes include *Staphylococcus*, *Malassezia furfur*, *Demodex folliculorum* and drugs like indinavir. Treatment depends on the etiologic agent detected by bacterial swabs and histopathology if needed. Antimicrobials against staphylococcus and malassezia or changing the antiretroviral regimen may be required. DADPS, a 10% crotamiton or polidocanol ointment or low-dose UVB 311nm radiation are effective against severe pruritus in these patients (Holmes 2001, Simpson-Dent 1999). Today, it is well-established that ART-naive patients with pruritic eosinophilic folliculitis significantly improve after starting ARVs.

**Genital warts (**condylomata acuminata**):) See chapters on *STDs* (*Condylomata acuminata* ) and *Cervical and Anal Cancer*.

**Herpes simplex virus / Herpes zoster infections:** see chapter on *AIDS*. 
Immune reconstitution inflammatory syndrome (IRIS)-related skin reactions: ART supports the TH-1 immune response and the tuberculin test reactivity recovers (Girardi 2002). In association with this immune reconstitution clinical manifestations of herpes zoster, mucocutaneous herpes simplex infections, mycobacterial infections, eosinophilic folliculitis, foreign body granulomas and cutaneous sarcoidosis have been reported (Handa 2001, Hirsch 2004, Beatty 2010). These infectious, as well as some non-infectious inflammatory skin diseases occur within a few days to 3 months after the initiation of ART. The therapy depends on the severity of clinical manifestations and consists of specific antibiotics, steroidal and non-steroidal anti-inflammatory drugs (see chapter on IRIS).

Kaposi sarcoma: the most frequent malignant tumor of the skin and mucosal membranes associated with HIV infection (see chapter on Kaposi’s sarcoma).

Lipodystrophy: See chapter on Lipodystrophy syndrome.

Malignant cutaneous lymphomas: Malignant B and T cell lymphomas are rare in HIV-infected patients (Beylot-Barry 1999, Biggar 2001). Cutaneous B cell lymphomas usually grow as red to violaceous nodules and are easily mistaken for Kaposi’s sarcoma. They can also look like persistent hematoma or non-specific asymptomatic papules. A biopsy should be performed on any clinically unclear tumor of the skin. Cutaneous T cell lymphomas are rare malignancies in HIV-infected patients. The prevalence among 2,149 HIV-infected patients in Frankfurt was 0.06%. The clinical course starts with non-specific eczematous patches (Stage I), which are usually not diagnosed as cutaneous lymphoma even after several biopsies because of the paucity of findings such as cellular atypia. These lesions are usually diagnosed as eczematous dermatitis. A linear pattern of patchy or slightly infiltrated lesions in the relaxed skin tension lines can be an early clinical indication of cutaneous T cell lymphoma known as parapsoriasis (Munoz-Peres 1999). Histopathology becomes more evident during the plaque stage (Stage II), and is striking when in Stage III multiple tumors of the mycosis fungoides present. Biggar (2001) calculated a relative risk for cutaneous T cell lymphomas in HIV-infected patients of 15.0 in comparison to the general population. The leukemic phase (Sézary syndrome) is characterized by erythroderma involving the palms and soles. In patients with erythroderma who have darker skin types and lack the histopathological signs of cutaneous T cell lymphoma the so-called pseudo-Sézary syndrome has to be considered in the differential diagnosis (Picard-Dahan 1996). Therapy with potent topical steroids (e.g., clobetasol) is effective in the patch and plaque stages. Solitary tumors can be controlled by radiotherapy (20–24 Gy) or photodynamic therapy (Paech 2002). Widespread, multiple tumors and Sézary syndrome are treated with a combination of retinoids and interferons or chemotherapy. Recently, remission of a CD8-positive pseudolymphoma treated solely with ART was reported (Schartz 2003).

Molluscum contagiosum: A benign viral infection of the skin usually seen in children and often in association with atopic dermatitis. The pox virus causes multiple papular skin-colored lesions with a typical central umbilication. The diagnosis is usually made on clinical grounds. After several weeks or months, an inflammatory reaction indicates the onset of spontaneous healing. In adults, mollusca are detected in the anogenital area and regarded as a sexually transmitted disease (Agromajor 2002). In HIV-infected patients, the clinical manifestations can differ significantly from those seen in the normal host. Spontaneous healing is rare; most patients have high numbers of lesions, typically occurring in the face and neck region, which otherwise is a rare location. The presence of multiple mollusca on the face is a typical disease marker indicating advanced cell-mediated immunodeficiency (CD4 T cell count <100/µl) (Schöfer 1991, Schwartz 1992). The growth of mollusca in the
immunocompromised host is not always exophytic, sometimes endophytic lesions occur. Multiple mollusca have to be differentiated from hematogenous dissemination of cryptococcosis, histoplasmosis and coccidioidomycosis, which are usually associated with fever, headache and sometimes pulmonary infiltrates. In such cases, skin biopsies (and tissue culture) and chest x-rays are indicated. Single molluscum can exceed 1 cm in diameter and grow exophytically, which can cause confusion with keratoacanthoma, squamous cell carcinoma, basal cell carcinoma or common warts.

Mollusca are treated surgically with a special type of forceps, electrocautery, curettage or with liquid nitrogen. Recently, photodynamic therapy with 5-Aminolevulinic acid (Moiin 2003) and imiquimod 5% cream have also shown to be effective (Hengge 2000, Calista 1999, Calista 2000, Liota 2000, Smith 2002). Imiquimod is applied by the patient 3x/week (off-label). An inflammatory reaction (erythema) occurring after 3 to 4 weeks of topical treatment indicates the beginning of the immune reaction, which leads to complete resolution of the mollusca after 6–8 weeks.

**Oral hairy leukoplakia (OHL):** is a clinical manifestation of Epstein-Barr virus infection, almost exclusively found in patients with untreated advanced HIV disease. Non-cytolytic viral replication in the glossal epithelium, especially in the lateral parts of the tongue, leads to asymptomatic white verrucous plaques that do not rub off. OHL is clinically diagnosed; initially parallel white or grayish hyperkeratotic rows arranged vertically on the lateral aspects of the tongue are characteristic. Unilateral lesions are possible, but bilateral occurrence of several plaques is more typical. Important differential diagnoses include other leukoplakias, lichen planus mucosae and oral candidiasis (Patton 2002, Cherry-Peppers 2003). If the diagnosis is in doubt, a biopsy or cytology can confirm the diagnosis. As the lesions will respond to antiviral drugs such as acyclovir, gancyclovir, or foscarinet (Walling 2003) but not antifungals, treatment can be used as a diagnostic tool to distinguish OHL from candidiasis. Both diseases however respond well to ART, which has led to a significant decrease of these oral diseases (Triantos 1997, Ramirez-Amador 2003).

**Prurigo nodularis:** The stimulus for the development of Prurigo nodularis is Pruritus. Psyche-pruritus-scratch cycles support lesional proliferation of skin nerves for years. Nodules (0.5–3cm) develop at a local site in which persistent picking and scratching occur. Lesions appear as dome-shaped nodules, which often have an eroded surface with scale and crusts. Multiple lesions may be distributed throughout the extremities. The intervening skin shows scales, excoriations, lichenification, post-inflammatory pigmentary changes and scars, which can remain even after the healing process. Manifold underlying disorders were described along with HIV infection (Liautaud 1989). Psychiatric disorders and emotional tension are often associated with Prurigo nodularis. There is an affinity to Lichen simplex chronicus. Complications of the important dermatoses like atopic dermatitis or insect bites. Therapy: Local: Potent topical glucocorticoids (under occlusion) or intralesional injection. Polidocanol, calcipotriol, capsacin; phototherapy (UVB, UVA1) or PUVA therapy. Some patients have been successfully treated with cryotherapy, laser, electrosurgery and even with excisions. Systemic therapies with sedating antihistamines (interactions may occur), psychopharmacy (neuroleptics, antidepressives), corticosteroids and retinoids have been used. Good results have been shown with oral thalidomide up to 400 mg/day (be aware of possible neurotoxicity, teratogenicity) (Matthews 1998, Maurer 2004). Occlusive bandaging can protect against mechanical irritations.

**Pruritus:** Chronic, often unremitting pruritus is one of the most frequent clinical symptoms of HIV infection. One in three patients is affected. Etiology remains unclear in most patients, and therefore only symptomatic treatment can be offered
which may be unsatisfying (Moses 2003, Singh 2003). Pruritus in HIV-infected patients can be a complication of infectious diseases. Viral, bacterial, and fungal infections (e.g., *Malassezia furfur* folliculitis) and scabies can cause severe itching. Also, dry eczematous skin (xerosis), papulosquamous skin diseases, systemic lymphomas, renal insufficiency and hepatic disease are causative conditions. Finally, many antiretrovirals and other drugs given to the HIV-infected patient can cause pruritus (with or without rash).

To diagnose idiopathic pruritus it is necessary to exclude all skin and systemic diseases mentioned above. In patients on ART it can be useful to change the treatment regimen. Systemic antihistamines and topical corticosteroids are symptomatic treatment standards. If they are ineffective, or a prolonged systemic treatment is necessary, phototherapy (UVA-1, UVB 311nm) or photochemotherapy (PUVA) is an alternative or adjuvant therapy (Smith 1997, Gelfand 2001, Zirwas 2001, Singh 2003). Concerning the immunosuppressive effects of ultraviolet light, it seems that patients on ART are at less risk.

**Papular dermatoses:** Patients can present either with monomorphic skin colored to red papules (size 2–5 mm) or with combined eruptions consisting of papules and pustules (sterile eosinophilic pustulosis, Ofuji’s disease). There is no special predilection for any site. The etiology of papular eruptions is heterogeneous. According to the clinical presentation and laboratory findings (elevation of IgE, eosinophilia in peripheral blood and affected skin) they resemble the prurigo of atopic dermatitis found in adults. Autoimmune reactions against follicular antigens have also been discussed (eosinophilic folliculitis) (Fearfield 1999). These papules can be due to a hypersensitivity reaction to drugs, microbiological agents (viruses, bacteria, fungi), parasites or saprophytes (*Sarcoptes scabiei*, *Demodex folliculorum*, *Pityrosporum ovale* and others). A thorough history of drugs, microbiological and histological examinations (including special stains such as PAS) are required for a correct diagnosis. If possible, specific infectious agents are treated. In case of sterile eosinophilic pustulosis (Ofuji’s disease) or papular dermatosis of unknown origin, therapy is symptomatic. Depending on the clinical situation, antihistamines, itraconazole (200 mg/d for 2 weeks), isotretinoin, dapsone, mild PUVA or UVB (311=narrowband UVB is the most effective therapy) or 5% permethrin cream can be tried (Ellis 2004). Topical tacrolimus (0.1%) has also been shown to be effective (Kawaguchi 2004).

**Paronychia and ingrown nails:** Ingrown toenails and inflammatory reactions of the proximal nailfold are a well known complication in diabetics, but also in patients on beta-blockers or retinoid therapy. A few cases might be due to local pressure (wrong shoes) or occur spontaneously. Patients on ART are the latest group of patients to regularly develop ingrown nails. These are ascribed to retinoid-like side effects of several antiretrovirals, especially indinavir, but also 3TC (lamivudine). Usually, the large toenails are involved, but all other toenails and fingernails can be affected. Complete remission is often seen when indinavir or 3TC are replaced by other antiretrovirals. Surgical measures such as Emmert plasty or its modification after Hanneke, should only be performed when changing ART has not led to remission after 3 to 6 months (Tosti 1999, Alam 1999, Garcia-Silva 2002).

**Psoriasis vulgaris:** Today, psoriasis is regarded as an autoimmune disease and affects approximately 1% of the general population. It has multifactorial inheritance with variable penetrance. Physical stimuli such as friction and UV light or endogenous factors such as infections, drugs, and stress may trigger psoriatic flares. When HIV-infected persons are exposed to such factors, psoriasis may appear for the first time or can be aggravated. The incidence of psoriasis has been reported to be between 2.5% (Braun-Falco 1988) and 4.9% (Schöfer 1990). The use of antiretrovirals improves psoriasis.
Typical psoriatic plaques can be eruptive, guttate or chronic and stationary. Atypical findings include inverse localization on the palms or soles and in the genital region and axillae, exudative, pustular or erythrodermic manifestations. In general, the severity of psoriasis parallels the impairment of the immune system. Besides infection, drugs have to be considered as possible triggers. In the final stages of HIV infection, psoriasis can be generalized and extremely resistant to therapy. Alternatively, the disease may disappear completely.

The typical psoriatic plaque is a sharply demarcated, erythematous plaque covered with silvery scales. Clinically and histologically, it may be difficult to differentiate it from seborrheic dermatitis.

Triggering factors should be eliminated if possible. Treatment is more difficult if the immune system is impaired. Antiretroviral therapy should be initiated or optimized. Localized lesions can be treated topically with corticosteroids, anthralins, calcium-agonists (calcipotriol or tacalcitol) or the topical retinoid tazarotene. The scalp and nails can be treated topically with corticosteroids. Generalized or exudative eruptions are usually treated systemically: acitretin (25–75 mg/d) is not immunosuppressive. Methotrexate or cyclosporin are immunosuppressive and should be avoided. In some cases, however, it is necessary to use them. AZT has a beneficial effect on psoriasis, probably by improving the immune status. To treat refractory psoriasis, experimental therapies such as cimetidine (400 mg 4x/d) have been tried successfully.

The clinical relevance of immunosuppression by UV radiation is unknown. At present, it is believed that phototherapy or photochemotherapy have no real detrimental effect for HIV patients and that they are justifiable (Akarapathanth 1999, Schoppelrey 1999). These treatments are as effective as in patients without HIV infection. UVB 311 (narrowband UVB) is well tolerated and effective. Broadband UVB is an alternative. In case of treatment failure, photochemotherapy can be instituted (local = bath or cream PUVA, or systemic PUVA). Interactions of the mentioned antipsoriatics with antiretroviral agents are unknown. Recently, several biologics have been introduced for the therapy of psoriasis. These compounds specifically interact with certain elements of the inflammatory cascade in psoriasis such as TNF-alpha. Up until now, only case reports can be found in the literature regarding treatment in HIV-infected patients (Bartke 2004).

**Reiter’s syndrome:** Reiter’s syndrome is regarded as a variant of psoriasis in patients who carry HLA-B*27. This rare chronic-relapsing disease mainly affects young men, the incidence being higher in HIV-infected men than in the general population (0.6% to 6%) (Kaye 1989).

The classical triad consists of urethritis (sterile yellow urethral discharge), conjunctivitis (serous or purulent) and arthritis (mainly knee-, foot- or sacroiliac joints, causing pain and leading to immobility). The triad can be found in about 30% of patients. Furthermore, constitutional symptoms (attacks of fever, malaise, leukocytosis, elevated ESR) and skin lesions can be found. The skin lesions are characterized by erythema with sterile pustules on the palms and soles and later, hyperkeratotic, scaling, exudative lesions known as keratoderma blenorrhagicum. Psoriatic plaques can be seen as well as the typical circinate balanitis presenting as crusting, dessicated plaques in circumcised men and shallow, moist, serpiginous, painless ulcers with slightly raised borders in uncircumcised men.

The diagnosis depends on the typical pattern of arthritis plus one or more of the mentioned clinical symptoms. Gonorrhea or *Chlamydia urethritis* have to be excluded by microbiological methods. Psoriatic arthritis should have other clinical signs of psoriasis (nail changes) and lacks fever.

Initially symptomatic therapy with non-steroidal anti-inflammatory agents, or pos-
sibly corticosteroids (short-term, high-dose pulse therapy) should be given. Acitretin (25–75mg/d) in combination with topical fluorinated corticosteroids have also been shown to be effective. Alternatively, sulfasalazine has been used successfully. Arthritis is also treated with oral gold. There is one report on the successful use of infliximab in a patient with Reiter’s syndrome without negative effects on the HIV viral load (Gaylis 2003).

Scabies: Scabies can be found worldwide; prevalence varies from <1% to 30% depending on the socio-economic circumstances. Scabies is characterized by extreme pruritus, especially at night. In general, the clinical presentation does not differ from that seen in HIV-negative persons. In the interdigital areas (volar sides) of the joints of the hands, breasts, axillae, periumbilical region, or penile shaft, fine red burrows (S-shaped or straight lines) may be found. There may be a small papule or vesicle at one end. Excoriations and/or secondary infections make the identification of burrows difficult. Generalized eczematous eruption may be seen. Typically in the groin or on the genitals red-brown pruritic nodules can be found. These scabies granulomas can persist for months even after successful therapy. In the case of severe cellular immunodeficiency crusted scabies or Norwegian scabies can occur. Besides HIV-infected patients, persons with general physical or mental debilitation are affected. Over weeks or months, eczematous lesions covered with asbestos-like crusts extend over large areas and the plaques can be mistaken for psoriasis. Crusted scabies is extremely infectious and carries many more mites than regular scabies – up to 10,000 mites/g scales. The history of unremitting and intractable itching is suggestive of scabies. The diagnosis is made by the clinical picture and proven by the demonstration of the mites, their ova, or fecal droppings in the scales. On histology, the female mite can be seen in the stratum corneum. A single application of permethrin 5% cream is performed (whole body application from chin to toes, usually excluding the face; leave on skin for 8 hrs, then shower off). In cases of crusted scabies, the scales have to be removed over several days (salicylic ointments) and therapy has to be repeated over 3–4 days. Alternative therapies are hexachlorocyclohexane (lindane), benzoylbenzoate, pyrethrum extracts or allethrin/piperonyl butoxide, all applied for 3 days. It is important to treat all contact persons at the same time. Linens and bed clothes have to be changed daily. Depending on the clinical presentation another treatment one week later is sometimes recommended (as a safety). In cases of severe immunodeficiency the scalp has to be treated too. If more than 50% of the skin is affected or several recurrences have occurred a combination of keratolytic/topical therapy against scabies and systemic treatment with ivermectin is recommended. Hygienic measures to prevent contact infections are extremely critical. A single therapy with 2 tablets (6 mg each; or 200 µg/kg) is generally sufficient. Ivermectin is not licensed for this indication. There are no reports on complications after this therapy in HIV-infected patients (Dourmishev 1998).

Seborrheic dermatitis: The incidence in the general population is estimated to be 3–5%. The lipophilic yeast Malassezia furfur (formerly Pityrosporum ovale) is believed to be of pathogenetic relevance. Here the specific subtype appears to be more important than the density of colonization. In HIV infection 20–80% of untreated people are affected depending on the immune status (Chatzikokkinou 2008). Seborrheic dermatitis appearing de novo or exacerbation of mild seborrhetic dermatitis in an HIV-infected patient could indicate conversion from a latent state to a symptomatic state (Ippolito 2000). Areas rich in sebaceous glands, such as the scalp, forehead, eyebrows, nasolabial folds, over the sternum, between the shoulder blades, external ear canal and retroau-
ricular area, develop yellowish oily scales and crusts on mildly erythematous to very red plaques. The lesions may be pruritic.

The clinical picture is typical in most cases. Differentiation from psoriasis may be difficult both clinically and histologically. Initially other forms of eczema such as allergic contact dermatitis and atopic dermatitis may have similar presentations. Due to the pathogenic role of *Pityrosporum ovale*, topical antifungals such as ketoconazole cream, other topical imidazoles or triazoles, or alternatively selena disulfide, metronidazole, and low-dose dithranol or lithium succinate- and zinc-sulfate-creams are used. For the scalp antimycotic shampoos, zinc pyrithione or tar-containing products are used. In severe cases systemic antifungotics are given like ketoconazole (200 mg QD), itraconazole (100 mg QD) or terbinafine (250 mg QD).

**Syphilis:** see chapter on *HIV and Sexually Transmitted Diseases*.

**Tinea** (dermatophytosis, ringworm infections): Infections of the skin, hair or nails with dermatophytes (in Western Europe predominantly *Trichophyton*, *Microsporum* and *Epidermophyton* species). Tinea has a high prevalence in the general population. There is no significant difference between HIV-negative and HIV-positive adults. The prevalence depends upon climate, profession, clothing, and participation in team sports. Typical clinical findings are superficial, scaling, round or oval erythematous plaques that expand centrifugally with an inflammatory edge and central clearance. Deep infections with tissue destruction and abscess formation are rare in Europe and North America but common in tropical regions. According to Torssander (1988) onychomycosis due to dermatophytes is frequent in ART-naive patients and difficult to treat. Nails are discolored (white, yellow, green, black), thickened and show growth disturbances (onychodystrophy). Subungual hyperkeratosis and onycholysis are common.

Psoriasis, yeast infections and trauma can imitate onychomycosis so it is necessary to identify the causative organisms on KOH and fungal culture. Direct microscopic examination with the addition of 10–15% KOH solution shows translucent, septated hyphae (mycelium) and arthrospores. Calcofluor or Blankphor microscope slides can be used for diagnostic immunfluorescence microscopy. Culture on Sabouraud’s or Kimmig’s medium identifies different fungi by their growth characteristics.

Treatment of superficial fungal infections of the skin is best achieved with topical broad spectrum antifungals such as ciclopirox or -azoles applied twice daily. In severe inflammatory disease it is helpful to start with combination therapy including topical corticosteroids for 3 or 4 days to achieve quick relief. Deep infections and infections involving terminal hairs (tinea capitis, tinea barbae) require systemic treatment with griseofulvin (500–1000 mg/day), terbinafine (250 mg/day), fluconazole (50 mg/day), or itraconazole (100–400 mg/day) (Elewski 2001, Millikan 2001). There are different regimens to treat onychomycosis. Itraconazole and terbinafine are typically used for two months for fingernails and three months for toenails. Griseofulvin may be used for up to 9 months or longer, until the infection clears (Aly 1996, Myskowski 1997, Torssander 1988). If only the distal part of the nail plate is infected topical treatment with nail varnish containing antifungals, which are able to penetrate the nail plate, are advised to avoid drug interactions between systemic antifungals and antiretroviral medications (see chapter on *Drug Profiles*). If systemic therapy is necessary, fluconazole has fewer drug interactions in HIV-infected patients than the other antifungals mentioned.

**Xerosis/Dry skin:** Dry skin is a very frequent complication of any kind of immunodeficiency. In the pre-ART era, we diagnosed dry skin in one in three HIV-infected patients (Table 1). The patients complain of dry, itchy skin, which is exacerbated by any stimulus. Overall, these skin problems are very much like atopic dermatitis.
(Rudikoff 2002) and can culminate in acquired ichthyosis. The prevalence of dry skin in HIV-infected patients decreases after the introduction of ART but can sometimes be seen in patients on indinavir (Garcia-Silva 2000). Some years ago, we showed that the lipid film of the skin surface has a different composition in HIV-infected patients although not diminished in quantity (Semrau unpublished data).

Dry itchy skin is treated with the application of emollients that contain 5 to 10% urea, or 3 to 4% lactic acid, and dexpanthenol. Patients should be advised to take maximum one shower every (other) day. 1 to 2 oil baths per week should be recommended. In cases with severe inflammation and fissures (eczema craquele) topical Class 3 or 4 corticosteroids are very helpful in reducing symptoms. They should not be used for longer than 3 to 5 days.

References


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28. Sexual Dysfunction in HIV/AIDS
U. FRITZ BREDEEK, CHRISTOPH MAYR

Introduction
Sexual dysfunction (SD) is a common symptom of HIV infection. In 2007, a review of relevant literature estimated the overall prevalence at 51%, with 46% of HIV-infected men suffering from erectile dysfunction, 44% from reduced libido, and 39% reporting problems ejaculating (Collazos 2007). A recent survey of 1,017 European HIV infected men found 1/3 of all participants being unsatisfied with their sexual life (De Ryck 2012).
A variety of factors including age affect sexual function and satisfaction. HIV infection may lead to SD because of the well-known interactions between the immune and the reproductive, endocrine and the neuroendocrine systems. The impact of someone’s knowledge about their own HIV infection on sexual function cannot be overestimated, and long-term ART may have further negative psychological effects on sexual health. ART can cause lipodystrophy syndrome which shares characteristics of the classic metabolic syndrome. This syndrome is characterized by an increased insulin resistance, excess weight (waist circumference >94 cm according to the new definition of the International Diabetes Federation), dyslipidemia or hypertension (>130/85 mmHg). The clear association between metabolic syndrome and erectile dysfunction (ED) makes ED a predictive marker for metabolic syndrome (Shabsigh 2005, Tikkanen 2007).

Definitions
Erectile dysfunction (ED) or impotentia coeundi is defined as the “constant or repeated appearance of an inability to attain or maintain an erection sufficient for satisfactory sexual intercourse” (NIH 1993). The diagnosis requires a minimum of 6 months of ongoing problems with at least 70% of all attempts to engage in sexual intercourse being unsuccessful. This is an important difference between ED and libido disturbance or ejaculation disturbance. Libido disturbance is defined as a decreased to absent sexual drive or desire. The main signs of ejaculation disturbance is Ejaculatio praecox or Ejaculatio tarda.

Etiology of sexual dysfunction in HIV/AIDS
Causes of sexual dysfunction are plentifold. A paradigm shift has taken place since 1980: Improved diagnostic tests and increasing knowledge of the aging processes in men have led to the conclusion that 80% of ED cases have some organic component and 50% are exclusively organic in nature. A singularly psychological cause is responsible for just 20% of cases (NIH 1993). A disease-specific peculiarity of HIV is the fact that over the last years the incidence of sexual dysfunctions has increased. This is due to the chronicity of the infection and other factors related to the aging HIV population like increased rates of comorbidities, psychosocial stressors and polypharmacy (Crum 2005).

Age: The most important biological cause of ED is age. ED exists in variable degrees, from light (17%) to moderate (17–34%) to complete (5–15%) in 52% of all men aged 40 to 70 years (Feldman 1994). The overall prevalence of ED in men age 30 to 80 in is estimated at 19% (Braun 2000).
Incidence in HIV-infected men is likely to increase because of the increasing age of the HIV population. But besides age, both HIV and ART contribute to a declining testosterone production, decreasing erectile tissue sensitivity, secondary to decreasing neural or hormonal activity, and vascular problems. This will lead to an increasing incidence of ED in the future. A recent cohort study of HIV positive men older than 50 confirms that both sexual dysfunction as well as type-2 diabetes is more often encountered than in age matched HIV negative controls (German 50/2010). 50% of questioned HIV positive men report noticeable to severe impairments in sexual function in this cohort based on the Aging Male Scale (AMS; Mueck 2010). Of all variables tested HIV was the only ependent associated statistically significant factor for the finding.

Diseases and comorbidities: Important ED risk factors coexist frequently in HIV infected patients, including excessive alcohol consumption, smoking and other recreational drug use; metabolic disorders (hyperlipidemia, diabetes mellitus); and cardiovascular disease, with hypertension being of particular importance. Pathophysiologically, most cases of ED are caused by neuronal (polyneuropathy) and vascular (micro- and macroangiopathy) changes. However, ED can also be an early sign of a metabolic syndrome.

Other possible risk factors are endocrine disorders, various neurological problems (i.e., disc prolapse) or infectious diseases. Frequent causes of ED in young men are chronic kidney or liver dysfunction (hepatitis, cirrhosis). Psychosocial problems, relationship conflicts and psychiatric illnesses (e.g., depression) are frequently related to SD. As a consequence, HIV infected patients have an increased risk for ED.

Riding a bicycle over a period of three or more hours per week on a classic bike seat is seen as another risk factor for moderate to severe ED. Special bike seats can reduce the risk for ED (Huang 2005, Schrader 2008).

Medications: Many drugs have a negative impact on sexual function, mainly on libido and the arousability. Table 1 lists an overview of relevant drug classes in this context. In particular drugs used in the treatment of depression and hypertension are associated with an increased risk of erectile dysfunction (Hart 2012). Antiretroviral drugs are also associated with SD; both duration and combination of therapies have an accelerating effect. In a standardized survey on 78 HIV-infected men who have sex with men (MSM), conducted by Cove in 2004, 69% reported on at least one occasion dysfunction and 38% indicated ED. All antiretroviral drugs can potentially decrease sexual function. In particular PIs have been reported in this context, but published data remain controversial (Schrooten 2001, Colson 2002, Lallemand 2002, Asboe 2007). Even further, the overall effect of ART on ED is controversial, with one study (Guaraldi 2007) not finding such an association and another (Asboe 2007) reporting a strong relationship between duration of ART and prevalence of ED.

Ongoing research

An increased prevalence of SD of up to 50% was observed in HIV-infected men in the early 1990s (Tindall 1994). Similar results were seen in HIV-infected women (Goggin 1998). A clear increase in prevalence of both libido loss (48%) and ED (25%) was seen by Lamba in 2004 in HIV-positive MSM on ART, compared to HIV-positive MSM not on ART (both at 26%) or HIV negative MSM (2% and 10%, respectively). A European study (Schrooten 2001) on 904 HIV-infected men and women showed that libido loss and ED was significantly more common in patients on a PI containing ART regimen compared to patients not taking PIs (40% vs. 16% for LL and 34% vs. 12% for ED, respectively). In a multivariate analysis, the following factors were
identified for libido loss: Current or past use of a PI, symptomatic HIV infection, age, and MSM. Additionally, taking tranquilizers was found to be an independent risk factor for ED.

The impact of PIs in SD was also seen in a prospective study of 189 patients (Collazos 2002). No correlation could be found between sex hormone levels and incidence of SD. Interestingly, in subjects taking a PI-containing regimen, testosterone levels were significantly higher compared to NNRTI-containing regimens in which 17ß-estradiol levels were significantly elevated.

In a standardized questionnaire of 156 MSM, no role for PIs as the cause of SD could be ascertained (Lallemand 2002). 71% of the participants indicated signs of SD since initiation of ART; however, in groups stratified by therapy (PI: 71%, without PI: 65%, no PI in the last 4 weeks: 74%) there were no significant differences seen between patients taking or not taking a PI. 18% of the participants had already suffered from SD before the diagnosis of HIV infection, and 33% before the initiation of ART. The impact of psychological factors is highlighted by one study, in which the rate of HIV-positive MSM with ED rose from 38 to 51% with the use of condoms (Cove in 2004).


## Diagnosis of sexual dysfunction

A diagnostic work-up for the causes of SD is required before therapy. This includes a complete anamnesis with emphasis on sexual, social and family history as well as social (recreational drug use), familiar risk factors (i.e., diabetes mellitus), and a complete medication history. A thorough physical examination is obligatory. A diagnostic test of the morning blood level of testosterone is of central importance to determine the testicular endocrine function. The calculated index of free testosterone is the recommended parameter to follow, since this index reflects the real biological activity of testosterone. The direct determination of free testosterone by the lab has been identified as being unreliable (www.issam.ch). HIV-positive men often suffer from testosterone deficiency. A study of 1,317 HIV-positive subjects mostly with lipodystrophy found 16% being testosterone deficient. This was a finding seen in all age groups. Visceral fat accumulation and increased body-mass index were predictive of testosterone deficiency (Rochira 2011).

<table>
<thead>
<tr>
<th>Table 1: Laboratory diagnostics for erectile dysfunction</th>
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<tbody>
<tr>
<td><strong>Special hormone diagnostics</strong></td>
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<tr>
<td>Testosterone (free circulating testosterone)</td>
</tr>
<tr>
<td>Luteotropic hormone</td>
</tr>
<tr>
<td>Follicular stimulating hormone</td>
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<tr>
<td>Possible LHRH</td>
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<tr>
<td>Possible HCG</td>
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<td>Possible Prolactin, PSA</td>
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Low testosterone level requires measurement of LH and FSH. Further work-up may require an LH or FSH stimulating test, usually handled by an endocrinologist to exclude secondary hypogonadism. NPT (nocturnal penile tumescence measurement) is considered minimally invasive and measures nocturnal erections. 3–6 erections per
night of at least 70% rigidity, lasting 10 minutes, are considered normal values. The question of morning erections can serve as critical criterion for the sexual anamnesis. Further andrological diagnostics include sonography of the scrotum. If the mammary glands are enlarged or involvement of the hypophysis is suspected (i.e., by an increased prolactin or estrogen level), an MRI of the sella turcica is indicated. Other diagnostic tests used for the vascular work-up include Doppler sonography of the penis and pharmacocavernosography; and for the neurophysiological work-up a cavernosum EMG, vibrometry, sphincter- and N. pudendus-EMG. These are rarely necessary and left to the urologist.

**Therapy for sexual dysfunction**

Phosphodiesterase-5 inhibitors (PDE-5 inhibitors: sildenafil, vardenafil, tadalafil) have substantially improved the therapy of ED. They are simple to take, effective and, in general, relatively well-tolerated (Waldkirch 2005). In many countries, however, PDE-5 inhibitors are not covered by insurance plans and so must be paid by the patients themselves. With the introduction of PDE-5 inhibitors, intra-cavernous erectile tissue injection or the intra-urethral application of vasoactive prostaglandins has clearly receded into the background. Today, surgical interventions, such as penile vein surgery, revascularization surgery or prosthodontics, also no longer play a role.

For HIV physicians knowledge on the interactions between PDE-5 inhibitors and ART (particularly PIs) is important. Through the inhibition of the cytochrome p450 enzyme system (CYP3A4) plasma levels of PDE-5 inhibitors are increased. This needs to be discussed with the patient. In particular, for patients on a boosted PI regimen PDE-5 inhibitors need to be started at a lower dose. We specifically recommend a mini test dose at the beginning (e.g., 1/4 of a tablet of sildenafil 50 mg) and increase according to the success and side effects. Our experience indicates that a significant proportion of patients have the desired success with such a low dose. However, some patients do not achieve any effect with these low dosages (HIV infection of several years, multimorbidity, and psychological overlap). In these patients, the approved maximum dose should not be exceeded. Simultaneous administration of nitrate containing medications or agents containing nitrites (molsidomine; “poppers”) is contraindicated since it may cause severe dysfunctions of the circulatory system including therapy-resistant hypotension.

Sexual activity is physically tiring and can be a strain on the cardiovascular system. If it is not clear whether a patient has an underlying cardiovascular problem, it is advised to screen for it before prescribing ED drugs. This is particularly true if unstable angina is suspected.

Apomorphine is a centrally effective dopamine receptor agonist. It is less effective and so less important in the treatment of ED, but should be considered in patients with contraindications to PDE-5 inhibitors (APO-go ampullae, max. 100 mg s.c.). Apomorphine seems to be particularly helpful in psychogenic ED and light organic ED. Miscellaneous herbal agents (yohimbine, maca, Turnera diffusa) might have a positive effect on sexual function. However, systematic studies have not been performed. These agents have few side effects, but monitoring for possible interactions with ART is advisable. For psychosocial problems, relationship conflicts or depressive disorders, psychotherapeutic support and if necessary a sexual-medical discussion are advised. A review of studies looking into the relationship of psychosocial interventions and ED found that group therapy with or without sildenafil could significantly reduce the symptoms of ED (Melnik 2007).
**PDE-5 inhibitors**

**Sildenafil (Viagra®)** was the first licensed PDE-5 inhibitor. Sildenafil is available in dosages of 25, 50 and 100 mg. The first effects are seen between 12 and 40 minutes (mean 25 min.) after taking the medication. This can be delayed if a fatty meal or alcohol is consumed simultaneously. The maximum plasma concentration is reached after approximately one hour, the clinical time of effectivity lies within 8–12 hours. The response rate depends on the etiology of ED, but varies between 43 and 83%. The most frequent side effects seen are headaches (11%), flushes (11%), dyspepsia (3%), dizziness (3%), rhinitis (2%) and color blindness (1%). Epidemiologic studies have so far not shown a statistically increased likelihood of angina pectoris, myocardial infarction or deaths with sildenafil use.

**Vardenafil (Levitra®)** was licensed in 2003. Phosphodiesterase 5 or the hydrolysis from cGMP is restrained approximately tenfold greater than by sildenafil, but the bioavailability, at 15%, is low. Vardenafil is available in a dosage of 10 and 20 mg. First effects are seen 15 to 30 minutes after taking the medication; maximum plasma concentrations are reached after 1 hour. The clinical effect can last up to 12 hours. Placebo-controlled studies, evaluating satisfaction with the amount of erection, showed a response rate of between 48 and 80%. The response rate for successful sexual intercourse with ejaculation was approximately 75%. Vardenafil is well-tolerated by patients on antihypertensive therapy and is effective in these patients. There is a contraindication for the combination with nitrates. Adverse events include headache (10–21%), erythema (5–13%), dyspepsia (1–6%) and rhinitis (9–17%). A study comparing vardenafil to sildenafil (Rubio-Aurioles 2007) showed a slightly higher efficacy of vardenafil and a good safety profile.

**Tadalafil (Cialis®)** was licensed in 2003. Dosages of 10 and 20 mg are available. Compared to other PDE-5 inhibitors the maximum plasma concentration is reached at 2 hours, the first effect is noticeable after 15 to 20 minutes. Since the plasma half-life is approximately 17.5 hours, tadalafil is effective up to 36 hours after intake. Personal observations point to the fact that these circumstances promote the popularity of tadalafil in the gay scene (“weekend pill”). Headache (7–21%), dyspepsia and heartburn (1–17%), myalgia (3–7%), back pains (4–9%), rhinitis (5%) and flushes (1–5%) are the most frequently observed side effects. Clinical influences on the cardiovascular system could not be observed; an increased incidence of myocardial infarction was not seen in any study. Udenafil, a new selective PDE-5 inhibitor shows a good safety profile with high effectiveness in a phase III study (Ding 2012). Udenafil and the fifth PDE-5 inhibitor mirodenafil and are not yet licensed in the US or Europe. Studies with MSM suggest a connection between the intake of drugs and PDE-5 inhibitors and sexual risk behavior (Swearingen 2005, Jackson 2005, Spindler 2006). Based on a relative NO (nitric oxide) deficiency in certain conditions like type-2 diabetes and coronary heart disease PDE5-inhibitors have a limited success rate. Therapy alternatives like GC stimulators, rho-kinase inhibitors and new NO donators may play a greater roll in the conditions in the future (Lasker 2010).

**Testosterone**

Substitution therapy is indicated for a deficiency of testosterone with clinical symptoms. Options include intramuscular injections (testosterone depot 250 mg IM with an interval of 14 to 21 days) and application in the form of a gel (e.g., testogel 25 mg/50 mg daily). Oral substitution is possible (e.g., andriol testocaps), but has not proved itself in everyday clinical life. The depot injection of 1000 mg testoste-
rone undecanoate (Nebido®) has recently been recommended at intervals of 3 months with an increasing dose 6 weeks after the initial one. Advantages of the depot injection lies in the more even serum concentrations of testosterone. In times of limited resources it is advisable to document the testosterone deficit and the appropriate clinical symptoms precisely.

It has been pointed out that testosterone injections may promote growth of carcinoma of the prostate in situ. Yearly PSA measurement during therapy, and a baseline physical examination before starting substitution is recommended, although this may not be covered by health insurance plans. Moreover, with a positive family anamnesis, a urological consultation is advisable before testosterone substitution. Hair loss, skin irritation (with the gel), increase in serum liver enzymes and lipids, as well as water retention in tissues, have been described as relevant side effects.

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29. Traveling with HIV

THOMAS WEITZEL

About 10–15% of European and North American HIV-positive patients travel abroad at least once yearly. Such travel activities frequently include visits to tropical and developing countries (Kemper 1995, Salit 2005). Because of patients’ increasing ability to travel, related medical problems are of growing importance and have been subject of several reviews (Schuwerk 2006, Bhadelia 2007, Igreja 2008, Franco-Paredes 2009, Nelson 2011).

Travel preparations

Especially if CD4 T counts are below 200/µl, there is an increased risk of travel-associated infections and furthermore, the effectiveness of vaccinations is reduced. Therefore, patients should plan their trips together with their attending HIV physician at least 6 to 8 weeks in advance. In case of special health risks (e.g. tropical destinations), a travel medicine specialist should be consulted.

A general overview of travel recommendations can be accessed through different Internet sites (see Links). Long-term travelers should, in advance, clarify the treatment possibilities of HIV-related problems at their destination. A first-aid kit for HIV-infected travelers should contain, besides the usual (local antihistamines, disinfectants, sun protection, analgesics, antipyretics, antiemetics, and antidiarrheals), an antibiotic for the empirical treatment of acute diarrhea (see below).

Antiretroviral therapy (ART)

ART naïve patients with CD4 T cell counts <200/µl should postpone travel activities until their immune status has improved with ART. An ongoing antiretroviral regimen should be proven to be effective and well-tolerated for at least three months before traveling. Depending on the destination, planned activities and other individual factors such as compliance, a therapy interruption might be considered. If ART is continued during traveling, the following aspects should be considered:

- A sufficient amount of antiretroviral drugs should be packed, preferably in the hand luggage (checked suitcases might get lost…).
- The availability of ART at destination should be checked beforehand. If necessary, prescriptions and a medical letter in English should be taken along.
- Due to entry regulations (see below), it may be useful to pack antiretroviral drugs in neutral packages.
- Storage requirements for prescription drugs (e.g. refrigeration) must be checked in advanced.
- Steps to cope with unplanned therapy interruptions during travel should be discussed in advance.

General precautions

The HIV positive patients’ particular risk of gastrointestinal infections demands adherence to the principles of good food and water hygiene (Hayes 2003). The following foodstuff and drinks should be avoided:

- Raw fruit or vegetables that are not peeled
- Raw or undercooked meat or fish dishes
- Tap water, ice cubes from tap water, unpasteurized milk or milk products
- Food distributed under insecure hygienic circumstances (e.g. street vendors)
Even brushing teeth or swimming carries the risk of swallowing small amounts of potentially contaminated water. High risk patients should use bottled water for brushing teeth. If no safe drinking water is available, tap water should be boiled. In areas up to 2000 meters above sea level, a boiling time of one minute kills all potential pathogens; at higher altitudes, the boiling time should be prolonged to three minutes. Chemical treatment and filtration methods are less reliable. HIV infected patients should also carefully protect themselves against vector-borne infections. This includes:

- Wearing long-sleeves and bright clothes if outdoors.
- Using repellents (e.g. DEET-based with concentrations of 30–50%) on uncovered skin areas (apply sun protection before repellent).
- Avoiding outdoor stays at dawn or night.
- Sleeping in mosquito-safe areas (mosquito nets or air conditioned rooms).
- Treating clothes and mosquito nets with permethrin for additional safety.

Since condoms and lubricants abroad are not always available, a sufficient amount of these products should be brought along to guarantee safe sex during the holiday. Because of possible *Strongyloides stercoralis* infection (see below), direct skin contact to fecally contaminated soil should be avoided. It is wise to wear closed shoes and place a towel underneath when lying on the ground.

Precautions against zoonotic infections such as salmonella or cryptosporidiosis include proper hand washing following animal contact.

**Vaccinations**

A travel medicine consultation is an opportunity to check and complete routinely recommended immunizations such as tetanus/diphtheria/pertussis, pneumococcal disease, influenza, and hepatitis B vaccinations (see chapter on HIV and Vaccinations). It has to be kept in mind that the southern hemisphere influenza season is from April to September, while in the tropics influenza can occur all year long; if possible, the vaccine should cover the expected influenza types.

Additional immunizations have to be considered according to destination, duration, and travel style. In general, most travel vaccines are more generously indicated for HIV positive travelers than in healthy travelers. This affects for example the parenteral typhoid fever vaccine (since *S. typhi* infections in HIV positive patients are more severe and relapse more often) or the pre-exposure rabies vaccination (Chadwick 2007). According to US recommendations, immunocompromized travelers requiring hepatitis A vaccination shortly before departure (< 14 days) should receive passive immunization (ACIP 2007). Other immunization questions usually require the consultation of a specialized travel medicine institution.

**Malaria prophylaxis**

Interactions between antiretroviral drugs and drugs available for malaria prophylaxis, such as chloroquine, mefloquine, doxycycline, and Malarone® (atovaquone/proguanil) have been at best under-evaluated (Khoo 2005). In healthy volunteers taking mefloquine (Lariam®) together with ritonavir, a 30% reduction of the steady-state plasma level of ritonavir has been reported; however, mefloquine did not change the ritonavir level after a single dose of ritonavir (Khaliq 2001). The explanation is probably reduced bile production caused by mefloquine. No relevant interactions seem to occur if mefloquine is coadministered with nelfinavir or indinavir (Schippers 2000). Chloroquine is metabolized by CYP2D6 but is also significantly excreted by the kidneys. Explicit data on interactions of chloroquine with HIV drugs are lacking. *In*
vitro, chloroquine inhibits HIV replication and shows synergistic effects together with protease inhibitors (Savarino 2004). On the other hand, PIs display in vitro and in animals inhibitory effects on plasmodia as well as synergistic effects together with mefloquine and chloroquine (Andrews 2006, Skinner-Adams 2007). Still, a clinical impact of these effects is improbable (Porter 2012). Clinical interaction data on atovaquone/proguanil (Malarone®) are missing. Still, both components of this drug are reduced by PIs and NNRTIs and travelers should be informed about possible failures of malaria prevention (van Luin 2010). Atovaquone decreases the indinavir level by 20% and increases the acyclovir level by 30%. Doxycycline is not metabolized by the cytochrome p450 system; relevant interactions with antiretroviral drugs are not anticipated. A review by Skinner-Adams (2008) provides a comprehensive overview of interactions between antiretroviral and antimalarial drugs. Updated information can be checked at www.hiv-druginteractions.org.

Available data and clinical experience indicate that the routinely used drugs – chloroquine, mefloquine, Malarone®, and doxycycline can be safely and effectively used in patients taking antiretroviral therapy. Recommendations for malaria prophylaxis are not limited by concomitant HIV medication. However, mefloquine is often unfavorable because of frequent neurological comorbidity in HIV patients. The protective effect of cotrimoxazole against plasmodia is not sufficient for malaria prophylaxis. The German speaking countries recommend standby emergency treatment (SBET) for certain travelers to areas with low malaria risk. Common drugs used for this indication are chloroquine, mefloquine, Malarone®, and artemether/lumefantrine (Riamet®, Coartem®). The latter belongs to the ACT group (artemisinin combination therapy), which is considered first line treatment for uncomplicated malaria. Relevant interactions of these drugs with ART are hardly known but might be complex (Byakika-Kibwika 2011). A recent PK/PD study with 10 healthy volunteers demonstrated that co-administration of Riamet® and Kaletra® resulted in a significant 2.4-fold increase of lumefantrine and a non-significant decrease of artemether (German 2009). The authors concluded that the use of this combination might be safe, which seems premature in view of the limited number of participants and the missing data regarding possible cardiotoxic effects. Another study with five healthy participants taking efavirenz plus another artemisinin combination therapy (amodiaquine/artesunate) revealed hepatotoxic effects (German 2007); the same drug showed a high risk of neutropenia in African children under ART (Gasasira 2008). Therefore, up to now the WHO does not recommend ACT in patients taking PIs (WHO 2005).

**Entry regulations and travel insurance**

Entry restrictions for HIV-infected travelers violate internationally recognized basic human rights; furthermore, they are counterproductive as a measure of health policy and explicitly rejected by WHO and UNAIDS. Still, many countries refuse entry to HIV-infected individuals, which particularly affects long-term stays in connection to work or study. Since January 2010, the much criticized restrictions of HIV-positive travelers to the US were finally lifted. To avoid problems, information on entry regulations should be obtained beforehand. The brochure “Schnellfinder” by Deutsche AIDS-Hilfe (www.aidshilfe.de), which is available in various languages, provides a comprehensive overview on entry policies.

Travel insurance usually excludes existing illnesses and often refuses HIV-positive individuals explicitly. Still, few travel insurances do not follow that policy (e.g. World First).
Special risks

Enteric infections

Reduced immunological defense and diminished gastric acid production increase the risk for gastrointestinal infections in HIV patients. Furthermore, bacterial enteric pathogens such as *Salmonella*, *Shigella*, and *Campylobacter* bear a high risk of bacteremia and relapse (Angulo 1995). Infections caused by *Cryptosporidium*, *Isospora belli* and microsporidia are dangerous due to chronicity.

Prophylactic use of antibiotics, while it can reduce the prevalence of travel-associated diarrhea, is not generally recommended in HIV. In individual situations, e.g. HIV-positive patients with advanced immunodeficiency traveling under high risk conditions for gastrointestinal infections, prophylaxis with ciprofloxacin (500 mg per day) should be considered. In Southeast Asia, azithromycin or rifamixin should be used because of an increasing rate of quinolone resistance. Because of widespread bacterial resistance, cotrimoxazole and doxycycline are not sufficient.

Travel-associated diarrheal diseases should be empirically self-treated for three to five days with ciprofloxacin (500 mg bid) or the above mentioned alternatives.

Malaria

The interactions between HIV and malaria are alarming, especially in African areas where malaria is endemic (Korenromp 2005, Flateau 2011). In HIV patients, malaria episodes are more frequent and more severe (Patnaik 2005, Laufer 2006, Cohen 2005). HIV infection and CD4 counts below 200 are risk factors for malaria treatment failure (Shah 2006). Also, malaria leads to a long-term increase in HIV replication through proinflammatory cytokines (Kublin 2005) and might be associated with decreasing CD4 T cell counts (Mermin 2006). HIV/malaria coinfection has been subject to several recent reviews (Idemyor 2007, Herrero 2008, Skinner-Adams 2008). However, it has to be kept in mind that most probably the basic principle of the findings in is the waning malaria semi-immunity (“premunition”) caused by HIV infection and that these data are not transferable to imported malaria cases in travelers.

Up to now, recommendations for malaria therapy are not influenced by a concomitant HIV infection. As described above, drug interactions of antimalarial and HIV drugs are insufficiently established. The treatment of complicated malaria is especially problematic since the indicated drugs, quinine, quinidine, or artemisinin derivatives, are all metabolized by CYP3A4. The co-administration of these drugs with CYP3A4 inhibitors requires intensive monitoring, drug level monitoring (if possible) or an interruption of ART.

Measles

In 2002, more than 200 million annual cases of measles with about 600,000 deaths were reported by WHO. In HIV-infected patients, measles have a higher morbidity and mortality; furthermore, the virus is shed for prolonged periods of time (Moss 2002). This is especially problematic in (Moss 2006). American studies show a mortality rate of 40%, mostly due to giant-cell pneumonitis (Kaplan 1996). Non-immune HIV-positive patients should therefore receive active or passive immunization before traveling to areas with a high prevalence of measles (see chapter on HIV and Vaccinations).

Leishmaniasis

Visceral leishmaniasis (kala azar) is a life-threatening opportunistic infection with limited therapeutic options (see chapter on AIDS). In German travelers, most infections are acquired in Mediterranean countries. The infection is more frequent in
long-term travelers who have a higher risk if HIV-infected (Harms 2003, Weitzel 2005). Due to the infection's potentially extended latency period, symptoms can occur long after exposure in endemic areas. Diagnosis is challenging, requiring cooperation with a specialized center. Severely immunocompromised HIV-positive patients must be informed of the risk of leishmaniasis even when traveling to Mediterranean countries. Preventive measures against mosquito bites should be followed in order to avoid leishmania infections (see above); because of the vector's small size, the use of impregnated mosquito nets of small mesh size is advisable. Cutaneous leishmaniasis does not seem to occur more frequently in HIV patients.

Tuberculosis

Globally, tuberculosis is the most prevalent HIV-associated opportunistic infection (see chapter on Tuberculosis). In most tropical and subtropical regions, the risk of tuberculosis is higher than in . Before and after long-term travel to such areas, it is advisable to determine the TB reactivity by interferon-gamma release assay (IGRA) of PPD skin test (Rieder 2001). Patients with a positive reaction or with a known high-risk exposure and no further signs of active tuberculosis should receive a course of treatment for latent tuberculosis (see chapter on Tuberculosis). HIV-infected travelers should avoid risk areas such as hospitals, prisons or homeless shelters or wear adequate facemasks.

Endemic mycoses

Endemic mycoses outside endemic areas are rare. Nevertheless, they are able to cause life-threatening opportunistic infections in HIV-positive patients even years after a stay in an endemic area. Most agents of endemic mycoses are thought to enter the pulmonary tract after inhalation of infective spores. In areas endemic for Penicillium marneffei (South East Asia, Southern China) and Coccidioides immitis (south-west parts of the USA, parts of Central and South America), increased exposure to dust or soil should be avoided (e.g. construction sites, agriculture, garden work, excavations). Histoplasma capsulatum is prevalent worldwide in soil contaminated with bird and bat droppings. Exposure might happen during eco- or adventure-tourism and should be avoided by HIV-infected individuals. In certain cases, e.g. severely immunocompromised patients with a foreseeable contact with agents of endemic mycoses, primary prophylaxis can be considered. Depending on the expected pathogen, either fluconazole or itraconazole should be prescribed.

Another fungus that can cause severe infections in HIV-positive patients is Sporothrix schenckii. This pathogen, which occurs worldwide, enters the body through cutaneous lesions. Wearing gloves while working with plants, hay, or peat moss can reduce the sporotrichosis risk.

Sexually transmitted diseases

The risk of STDs is substantially increased in travelers (Richens 2006). In about 15% of HIV infections are acquired during holidays abroad (Rice 2012). HIV-positive travelers should be aware of the special risks that sexually transmitted diseases and HIV superinfection present to them.

Other parasites

The following parasitic pathogens are relevant to HIV-infected travelers:

- Strongyloides stercoralis is prevalent in most tropical and subtropical areas. The parasite is transmitted by cutaneous larval invasion after skin contact with contami-
nated soil. In HIV-infected patients, there is the risk of a “hyperinfection syndrome” with a high fatality rate (Gompels 1991). Besides HIV infection, corticosteroid therapy seems to be an important risk factor, as these drugs seem able to increase larval maturation triggering a cycle of massive autoinfection.

- **Trypanosoma cruzi** is endemic in large parts of Latin America. The protozoon that causes Chagas disease is transmitted by triatomine bugs but oral transmissions via contaminated fruit or sugarcane juice have also been reported. Chagas disease can persist asymptotically for many years and reactivate in severely immunocompromised patients. In these cases, lesions radiologically resembling cerebral toxoplasmosis are found in the central nervous system (Rocha 1994).

- **Babesia sp**, a worldwide cause of zoonotic infections, is transmitted by ticks. Severe infections, clinically mimicking malaria or manifesting as fever of unknown origin, mainly occur in patients after splenectomy, but have also been reported in severely immunocompromised patients (Falagas 1996).

- Free-living amoeba (**Acanthamoeba sp.** and **Balamuthia mandrillaris**) are ubiquitous, living in soil and water. In HIV-infected and other immunocompromised patients, these organisms are capable of causing severe infections of the central nervous system (granulomatous encephalitis) as well as local infections of the skin and cornea (Sison 1995).

- **Schistosoma sp.** cause long-lasting and dangerous helminthic infections. In HIV-positive patients, schistosomiasis treatment is less effective (Kallestrup 2006). It causes – like other helminthic infections – chronic stimulation of the immune system with a negative influence on HIV infection (Secor 2006). Therefore, HIV-positive travelers should avoid freshwater contact in endemic areas.

**Medical problems after traveling**

Every disease occurring during or after traveling should be checked in a timely manner. Because most tropical diseases are quite rare in temperate countries, diagnosis is often delayed. An analysis of imported visceral leishmaniasis in revealed a median time span of 85 days until the diagnosis was established (Weitzel 2005). Furthermore, tropical diseases often manifest atypically in HIV patients (Karp 1999). In any event, differential diagnoses of diseases in HIV-infected individuals are very broad. After traveling abroad the clinical and diagnostic situation can become even more complex, calling for a close cooperation of HIV and Tropical Medicine specialists.

**References**


Idemoyer Y. Human immunodeficiency virus (HIV) and malaria interaction in sub-Saharan Africa: the collision of two Titans. HIV Clin Trials 2007;8:246-53.


Links

http://wwwnc.cdc.gov/travel/
http://www.who.int/ith/
http://www.tropenmedicus.de/
http://www.crm.de/
http://dtg.org/
HIV-infected individuals have an increased morbidity and mortality due to various infectious diseases that are preventable by vaccinations. On the other hand, vaccinations might cause a higher rate of adverse effects in HIV-infected patients, who are also prone to a higher rate of failure in achieving a protective immune response. Indication and timing of vaccination should therefore reflect each patient’s individual situation – the better the immune status, the higher the chances for an appropriate immune response. Thus, indications should be checked as soon as a patient is diagnosed with HIV (see chapter Checklist: The new HIV patient). In severely immunocompromised patients, vaccinations are usually not successful and might even be contraindicated. In such cases, the immunization status of close contacts should be checked and, if necessary, completed information about exposure and exposure prophylaxis should be provided. In certain situations, passive immunoprophylaxis might be indicated. When ART leads to a sustained rise in CD4 counts, vaccinations should be reconsidered and/or repeated. Recent studies demonstrate that many HIV patients do not receive the vaccinations that are internationally recommended (Molton 2010, Mohseni-Sadar 2010).

Benefits of vaccination

Depending on their immune status, a poorer response to previous vaccines and an accelerated decline of protective immunity over time must be expected in HIV patients. Until recently, the rule of thumb was that:
- the response to vaccination is reduced if CD4 T cells are <300/µl,
- no vaccination response is expected if CD4 T cells are <100/µl (Rosseau 1999).

Newer data question this concept since in patients with sufficient viral suppression some vaccines (e.g. influenza) exhibited an immune response that was independent from CD4 counts (Evison 2009, Hatakeyama 2011). Still, re-vaccinations should be reconsidered if CD4 T cells rise to >200/µl. To evaluate possible benefits of vaccinations, the anamnesis should include the following factors:

<table>
<thead>
<tr>
<th>Current status of protection</th>
<th>Current risk of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior infections</td>
<td>• Sexual risks</td>
</tr>
<tr>
<td>• Prior vaccinations (problem: reduced</td>
<td>• Occupational risks</td>
</tr>
<tr>
<td>effectivity in severely immunocompromised</td>
<td>• Contacts with infected individuals</td>
</tr>
<tr>
<td>patients, consider antibody control)</td>
<td>• Contacts with children</td>
</tr>
<tr>
<td></td>
<td>• Traveling</td>
</tr>
</tbody>
</table>

Risks of vaccination

Some vaccinations might cause transient viral load increases. This effect reflects the stimulation of cellular immunity and does not occur in non-responders to the vaccine. The peak of this increased viral replication appears 1 to 3 weeks after the vaccination. Therefore, routine measurement of viral load should be avoided within four weeks after vaccinations. Numerous studies demonstrate that these transient elevations of the viral load are clinically and immunologically irrelevant. Still, genotyping before and after an influenza vaccine demonstrated in 2 out of 34 patients new mutations of the RT- or protease-gene (Kolber 2002). Furthermore, the elevated viral replication can (theoretically) increase the risk of materno-fetal transmission.
With inactivated vaccines, there is no higher rate of adverse events in HIV-infected patients. In live vaccines, however, the risk of complications caused by an infection with the vaccine strain is increased. Severe and even fatal complications have been reported following vaccinations for smallpox, tuberculosis, yellow fever, and measles. Nevertheless, there is no general contraindication for live vaccines in HIV-infected patients.

**Vaccination of contacts**

Whenever HIV-infected patients are susceptible to vaccine-preventable infections, particular care should be taken to vaccinate close contacts, who after gaining protective immunity will not transmit the disease. However, with certain live vaccines (e.g. oral polio vaccine) the HIV-infected patient might acquire vaccine-associated illness from the contact shedding the vaccine strain. Thus, oral polio and smallpox vaccinations of close contact persons are contraindicated. In contrast, MMR vaccination of contacts is possible. Varicella vaccination of contacts is suitable; if such a contact develops vaccine-associated varicella, the respective HIV-infected patient might receive prophylactic acyclovir (German recommendations: STIKO 2005).

**Vaccinations in HIV-infected children**

With few exceptions, HIV-infected children should be vaccinated according to national children vaccination schedules. BCG vaccination is generally not recommended in HIV-infected individuals. Children with severe immunodeficiency (relative CD4 T cell count <15%) should not receive MMR (measles, mumps, rubella) or varicella vaccine. Above this level, children should be vaccinated twice with MMR vaccine (second dose after 1 month). In Germany, varicella vaccine can be administered, if CD4 counts are >25% (STIKO 2005). The latest US recommendations state that this vaccine should also be considered in children aged 1–8 years with CD4 T cell counts >15% and children >8 years with CD4 counts >200 cell/µl (Mofenson 2009). Due to lack of data, quadruple MMRV vaccine should be avoided. If one of those four live vaccines can not be applied, then the family contacts (especially siblings) should be vaccinated if susceptible. A possible strategy to avoid unnecessary risks of live vaccines is to predict their success by measuring the response to inactivated vaccines. If there is no measurable vaccine response to diphtheria/tetanus, a benefit from live vaccines such as MMR or varicella is unlikely, even if CD4 counts are higher than the above-mentioned limits. In those cases, immunoglobulin prophylaxis may be useful (Tim Niehues, personal communication).

HIV-infected children should receive a routine series of pneumococcal conjugate vaccine (PCV), starting in the second month of life, and supplemented by polysaccharide vaccine (PPSV) after the second year of life (≥2 months after last PCV dose). PPSV should then be re-administered every 5–6 years. In Germany, revaccination is recommended every 3 years until the age of 10 years (STIKO 2011).

**Post-exposure prophylaxis**

With some infections, the risk of infection and/or disease severity can be reduced by post-exposure prophylaxis of susceptible individuals, which includes active and passive immunizations as well as chemoprophylaxis (Table 2). Usually, the time between exposure and the start of prophylactic measures is crucial and should be minimized.
Practical approach to vaccinations

**Informed consent:** The obligation to inform vaccines follows national recommendations, which were recently updated in Germany (STIKO 2004). HIV patients should be informed regarding the dangers of vaccine-preventable diseases and the risks and benefits of vaccines, with particular attention to HIV-related vaccination problems. Some countries might require patients to read written information and/or a written informed consent. Vaccine information statements in different languages are available via the Internet (e.g. www.immunize.org).

**Timing:** Vaccinations should be postponed when an acute infection is present; however, a mild afebrile infection is not relevant. Live vaccines such as MMR, varicella or yellow fever must be given either simultaneously or at least four weeks apart from each other. After treatment with immunoglobulin, live vaccines should not be administered within the following three months (exception: yellow fever vaccine). When exact viral load measurements are crucial (e.g. decisions about ART), vaccinations should be postponed as they might influence viral load.

**Booster vs. complete series:** As a rule of thumb, a complete series is necessary when no prior dose of the respective vaccination is reported or documented. That means that a past incomplete primary series can be completed independent of a time delay between the necessary shots (every shot counts!). This strategy does not take into account that vaccinations might be repeated if prior doses were given at a time when the patient was significantly immunosuppressed.

**Route of application:** Vaccination routes should follow the recommendations provided by the manufacturers of the respective vaccines. High immunogenicity and few complications make intramuscular injections the preferable application route for most vaccines (deltoid muscle, in infants also anterolateral thigh; gluteal applications are obsolete!). Many vaccines can also be administered subcutaneously (see respective product information). In hemophiliacs, subcutaneous vaccination followed by thorough compression (>2 minutes) usually allows vaccination without coadministration of clotting factors. Only a few vaccines have to be administered subcutaneously, including meningococcal polysaccharide, yellow fever, and some varicella vaccines. Intradermal rabies vaccination schedules, which are licensed in some countries, should not be administered to HIV-infected patients due to reduced immunogenicity (Tantawichien 2001).

**Combination vaccines:** In general, it is recommendable to combine vaccines to minimize patient discomfort (and sometimes costs).

**Documentation:** Vaccinations should be documented in the patient’s medical records as well as in a vaccination card kept by the patient. For the latter, a WHO recommended form can be ordered either through WHO or national providers. Documentation includes the brand, manufacturer, and lot number of the vaccine.

Details of selected vaccines

**Tetanus/Diphtheria/Pertussis:** Following a primary series during childhood, lifelong protection against tetanus/diphtheria should be maintained by boosters every 10 years. According to a Danish study (Kurtzhals 1992), protection against diphtheria in adult HIV-infected patients is often insufficient. Depending on their CD4 T cells, HIV-infected patients have a reduced response to boosting and an accelerated antibody waning (Moss 2003). Tetanus-diphtheria combination vaccines that are also available in some countries in combination with polio and/or pertussis (all suitable for HIV-infected patients) should be used. Recently, more and more countries recommend a single
booster of acellular pertussis vaccine for adults. Since adult pertussis vaccine is only available in combination (e.g. with tetanus/diphtheria), its use should be considered whenever tetanus and/or diphtheria vaccination might be indicated.

**Pneumococcal:** Even under highly active ART, there is an increased risk of invasive pneumococcal infections (Barry 2006) which can be reduced by vaccination (Breiman 2000, Grau 2005, Rodriguez-Barradas 2008). Older studies demonstrated that patients with CD4 T cells <500/µl have a decreased response to pneumococcal polysaccharide vaccine (Weiss 1995) even if followed by a double-dose booster (Rodriguez-Barradas 1996). A recent study in patients taking ART with CD4 cell counts >200/µl showed a vaccine response similar to healthy individuals (Falco 2006). Still, a cohort study demonstrated that patients with viral loads >100,000/ml did not benefit from the vaccine independent of their immune status (Teshale 2008). The pneumococcal conjugate vaccine seems to have no benefit over the polysaccharide vaccine in adults (Ahmed 1996, Mahdi 2005); the combination of both vaccines might be advantageous in patients who are not on ART (Chen 2008). Confusing data arose from a prospective randomized study in, which revealed an increased incidence of pneumococcal infections in the vaccine group (French 2000). Remarkably, long-term follow-up showed reduced mortality in the group that received the polysaccharide vaccine; therefore, the effectiveness of this vaccine in African patients without ART remains uncertain (Watera 2004). First results from indicate that in this setting the conjugate vaccine might be superior (French 2010).

According to current guidelines in developed countries, HIV-infected patients with CD4 T cells >200/µl should receive pneumococcal vaccination as early as possible after being diagnosed (Geretti 2008, Kaplan 2009, STIKO 2011); with CD4 T cells <200/µl, the efficacy of the vaccine is uncertain but vaccination should be considered especially if other risk factors related to smoking, alcohol, lung disease, etc. are present. Revaccination is recommended every 5–6 years or if CD4 T cells rise >200/µl. In developing countries, the vaccine is not recommended (WHO 2008).

**Influenza:** HIV-infected patients have an increased risk of severe manifestations of influenza infection and a higher influenza-associated mortality (Lin 2001). Although seasonal influenza vaccine is effective (Atashili 2006, Anema 2008) influenza remains a frequent cause of febrile respiratory infections (Klein 2007). Consequently, private and healthcare contacts of HIV-infected individuals should also be vaccinated. Yearly vaccination at the beginning of the influenza season is recommended for all HIV-infected patients older than six months (Geretti 2008, Fiore 2010, STIKO 2011). In children under 10 years of age, the first vaccination should include two doses at a 4-week interval. Intranasal live vaccines are not licensed for use in HIV-infected patients.

**Hepatitis B:** According to international standards, every HIV-infected patient with a negative HBV serology should be vaccinated, a recommendation that is not consistently followed in daily routine (Bailey 2008). A simultaneous hepatitis A and B vaccination should always be considered, since the combination vaccine is cheaper and might be more effective (van der Wielen 2006). The main problem is the reduced immune response to hepatitis B vaccination (van den Berg 2009). Depending on CD4 counts and other factors such as viral load, gender, and age (Fisman 2002, Overton 2005), only 20–70% of HIV-infected individuals will develop protective immunity measured by anti-HBs (Laurence 2005). Patients, even those with high CD4 counts, have higher vaccine responses if taking ART (Landrum 2009). Although the optimal vaccination strategy is still under debate, there is a broad consensus to:

- Vaccinate early after diagnosis
- Control immune response 4 weeks after the last shot
• Revaccinate if the immune response is lacking or suboptimal (\(<100, \ <10\) IU/mL) and/or if there is substantial immunoreconstitution

A normal vaccination schedule (3 doses of 10–20 µg) is recommended by most experts. Other strategies with multiple dosages, higher doses or more effective adjuvants were successfully tested (Fonseca 2005, Cooper 2008, de Vries-Sluijs 2008, Flynn 2011, Launay 2011). If the initial schedule fails to generate sufficient response, most experts recommend revaccination with a double dose vaccine (40 µg), which is commercially available for dialysis patients (e.g. HBVAXPRO® © 40). The use of hepatitis A/B combination vaccine (Twinrix®) in double dose was also very successful in a recent study (Cardell 2008). Intracutaneous vaccination provides no advantage in comparison to the normal i.m. route (Shafran 2007, Launay 2011). British guidelines recommend annual controls of anti-HBs levels (Geretti 2008). The optimal management of HIV-infected patients with “isolated” anti-HBc is uncertain (this might be due to a false positive result, a loss of anti-HBs after infection, or an occult HBV infection). Most experts recommend the vaccination and to monitor anti-HBs after the first vaccine dose. In the case of a positive result, further vaccinations might not be necessary (Ghandi 2005).

**Hepatitis A**: is common among HIV-infected patients (Fonquernie 2001). The vaccine is indicated in patients with chronic liver disease or increased risk of exposure, e.g. MSM, hemophilia or traveling to high-prevalence areas. Routine pre-vaccination serology (HAV IgG) is not generally recommended, but can be considered in patients with possible prior exposure. A combination with HBV is available and reduces costs. The reduced immune response in HIV-infected patients is enhanced if a three-dose schedule is used (Launay 2008).

**Measles**: As measles causes severe disease in HIV-infected patients (Kaplan 1992), patients without proven past infection or vaccination should be vaccinated (two doses with one month in between). The status of protection should be checked prior to trips to endemic areas (see chapter on Traveling with HIV). It is possible to vaccinate patients with CD4 T cells >200/µl (different age-specific values in children) or >15% who are mildly symptomatic or asymptomatic. Commonly, the MMR combination vaccine is used. For susceptible patients, immunoglobulin administration is indicated as post-exposure prophylaxis (in certain high-risk situations also pre-exposure prophylaxis).

**Yellow fever**: Available data in around 170 HIV-infected individuals (all with CD4 T cells >200/µl) indicates good tolerability of yellow fever (YF) vaccination, but reduced rates of seroconversion (Veit 2011, Thomas 2012). One asymptomatic patient with a low CD4 count developed fatal encephalitis caused by the vaccine strain (Kengsakul 2002). Vaccination is possible in asymptomatic patients with adequate immune function if possible exposure to YF virus can not be avoided (Staples 2010). In this context, most experts define adequate immune function as CD4 T counts >200/µl. In general, older individuals (>60 years) have a higher risk for severe adverse events caused by YF vaccination (Khromava 2005). This should also be taken into account. British guidelines disapprove YF vaccination in HIV-infected patients >60 years of age (Geretti 2008). Recently, concerns about a (theoretical) risk of severe side effects of the YF vaccine in patients treated with maraviroc have been raised (Roukens 2009). Due to reduced response rates, titer controls are often recommended. Another, possibly better, approach is the documentation of seroconversion in a paired serum sample (before and 2–3 weeks after vaccination). If vaccination is contraindicated, a medical waiver should be issued to patients traveling to countries where yellow fever vaccination is mandatory. Such waiver should always be used in HIV-positive travelers, if the vaccine is only indicated for entry regulations without a real risk of YF exposure.
**Human papilloma virus (HPV):** In any countries, HPV vaccination of juvenile girls is part of the routine vaccination schedule. In 2011, the recommendations also included boys and young adults, especially MSM. The benefit in HIV patients, who have a higher risk of HPV-associated neoplasias, is subject of ongoing studies. Since complications of the inactivated vaccine are improbable, both vaccines may be used on an individual basis (Kaplan 2009). In developing countries with their high incidences of HPV-associated cancers, the high price of the vaccine will be a major obstacle to its widespread use.

**Varicella:** Similar to measles, chickenpox is potentially life-threatening for HIV patients (Perronne 1990). Patients without a history of VZV infections (chickenpox or herpes zoster) or vaccination should be screened for antibodies. If susceptible and with CD4 T counts >200/µl, patients should be vaccinated (Kaplan 2009, Geretti 2008); although German recommendations are more restrictive (CD4 >25%, STIKO 2005). Vaccine complications should be treated with acyclovir. Zoster-like reactivations of the vaccine strain are possible but very rare. The zoster vaccine, which is licensed since 2006, contains a higher dose of the vaccine strain and was therefore initially contraindicated (Kimberlin 2007). New recommendations by ACIP permit its use, if CD4 T counts are >200/µl (CDC 2011).

The following tables summarize current recommendations.
Table 1: Vaccinations in HIV-infected individuals.

<table>
<thead>
<tr>
<th>Vaccinea</th>
<th>Type of vaccine</th>
<th>Indicationsb</th>
<th>HIV-specific recommendations / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera</td>
<td>Inactivated + toxoid</td>
<td>Stay in endemic areas with increased risk of exposure</td>
<td>B Partly protects against some forms of travelers’ diarrhea</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Toxoid</td>
<td>Generally recommended</td>
<td>B Age 6 years or older: reduced dosage</td>
</tr>
<tr>
<td><em>Haemophilus influenzae b</em> (HiB)</td>
<td>Polysaccharide</td>
<td>Children: generally recommended Asplenia</td>
<td>B Might be offered to unvaccinated HIV patients (CDC 2006, Geretti 2008)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated</td>
<td>Chronic liver disease, hemophilia, increased risk (e.g., MSM, travel to endemic areas)</td>
<td>B British recommendations: in HIV patients booster every 5 years (Geretti 2008)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recombinant antigen</td>
<td>Children: generally recommended Chronic diseases, increased risk (e.g., healthcare workers, sexual behavior, drug addiction, stay in endemic areas)</td>
<td>A In HIV patients double dose vaccines might be used (see text)</td>
</tr>
<tr>
<td>Human Papilloma Virus (HPV)</td>
<td>Recombinant (2- or 4-valent)</td>
<td>Girls aged 12–17: generally recommended USA: both genders</td>
<td>B</td>
</tr>
<tr>
<td>Influenza</td>
<td>I. Inactivated/ fractionated antigen II. Live intranasal</td>
<td>Chronic diseases, age &gt;60, and others (USA: all individuals &gt;6)</td>
<td>I. A II. D Yearly different antigen combination</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Inactivated</td>
<td>Stay in endemic areas with risk of exposure</td>
<td>B Since 2009 new vaccine: Ixiaro®</td>
</tr>
<tr>
<td>Measles</td>
<td>Live</td>
<td>Children: generally recommended Susceptible individuals who work in healthcare, have contact with kids or immunocompromised patients, travel to endemic areas</td>
<td>C Vaccinate susceptible HIV-patients if possible (see text) MMR combination vaccine</td>
</tr>
<tr>
<td>Meningococcal (groups A, C, W135, Y)</td>
<td>I. 2-/4-valent polysaccharide II. 1-/4-valent conjugate</td>
<td>Children: generally recommended (group C) Complement deficiency, hypogammaglobulinemia, asplenia, travel to endemic areas</td>
<td>B GB: HIV+ age &lt;25 y (Geretti 2008) USA: HIV+ juveniles (4-val. conjugate vacc. 2x) WHO: advanced HIV infection (WHO 2011)</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Vaccine¹</th>
<th>Type of vaccine</th>
<th>Indications²</th>
<th>HIV-specific recommendations¹ / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumps</td>
<td>Live</td>
<td>Children: generally recommended Susceptible individuals⁴ with contact with children</td>
<td>C MMR combination vaccine</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Pertussis</td>
<td>Acellular antigens</td>
<td>Children: generally recommended Adults: 1 booster in many countries recommended</td>
<td>B For adults only available in combination with tetanus/diphtheria + polio</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Pneumococcal</td>
<td>I. 23-valent polysaccharide II. 7-valent conjugate</td>
<td>I. Chronic diseases, immunodeficiencies, age &gt;60 years (US: 65) II. In many countries recommended for all children up to age 2</td>
<td>A I. After 2 years of age II. 2nd months to 5th year of life</td>
</tr>
<tr>
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</tr>
<tr>
<td>Poliomyelitis</td>
<td>I. Inactivated (IPV) II. Live (OPV)</td>
<td>Children: generally recommended Booster if indicated (e.g. stay in endemic areas)</td>
<td>I. B II. D</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Rabies</td>
<td>Inactivated</td>
<td>Risk of animal contact in endemic areas, travel to endemic areas with risk of exposure</td>
<td>B HIV: often poor response, serological testing, no intradermal schedules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Live</td>
<td>Children: generally recommended Susceptible women⁴ of child-bearing age, susceptible individuals⁴ with frequent contact with children</td>
<td>C MMR combination vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxoid</td>
<td>Generally recommended</td>
<td>B</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Tick-borne encephalitis (German: FSME)</td>
<td>Inactivated</td>
<td>Risk of tick bite in endemic areas (usually April to November)</td>
<td>B German and European areas of risk: see <a href="http://www.rki.de">www.rki.de</a></td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tuberculosis</td>
<td>Live (BCG)</td>
<td>Depending on national guideline (Germany: not recommended)</td>
<td>D</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>I. Polysaccharide II. Live</td>
<td>Stay in endemic areas with risk of exposure</td>
<td>I. B II. D</td>
</tr>
</tbody>
</table>

¹ Vaccine
² Indications
³ HIV-specific recommendations
⁴ Comments
Table 1 (continued)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type of vaccine</th>
<th>Indications</th>
<th>HIV-specific recommendations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>Live</td>
<td>Children: generally recommended Susceptible women(^4) of child-bearing age, susceptible individuals(^4) with frequent contact to children or immunocompromised patients, before immunosuppressive therapy</td>
<td>C Vaccinate susceptible HIV+ patients if possible (see text)</td>
<td></td>
</tr>
</tbody>
</table>

| Yellow fever | Live | Stay in endemic areas, travel requirements in some countries | C Vaccination only by authorized institutions | |

1 Use combination vaccines, if available (exception MMR+Varicella, see above)  
2 Indications mainly adapted to German standards. Strategies in other countries may vary.  
3 A, recommended in HIV patients; B, usable in HIV patients independent of immune status; C, usable in HIV patients dependent on immune status; D, contraindicated for HIV patients  
4 Susceptible: No documented history of disease or vaccination, no specific antibodies in serological testing

Table 2: Post-exposure vaccines and chemoprophylaxis in HIV-infected individuals.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of prophylaxis(^1)</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>VAC CH</td>
<td>Close contact (face-to-face) with diphtheria patient VAC: if last vacc. &gt; 5 y CH: independent of prior vaccinations</td>
<td>CH: oral macrolide x 7–10 d</td>
</tr>
<tr>
<td>Haemophilus influenzae b</td>
<td>CH</td>
<td>Immunocompromised patients or their contacts after close contact with patient with invasive infection</td>
<td>Rifampicin 600 mg qd x 4 d (alternative: ciprofloxacin)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>VAC IG</td>
<td>Exposure of susceptible individuals(^2) Within 14 (maybe even 28) d after exposure</td>
<td>Immunocompromised patients: IG might be more effective than VAC (Victor 2007) HIV: IG recommended in USA (CDC 2007), VAC/IG simultaneously recomm. in GB (Geretti 2008)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>VAC IG(^3)</td>
<td>Depending on susceptibility and vaccination status</td>
<td>German recommendations: STIKO 2009</td>
</tr>
<tr>
<td>Disease</td>
<td>Type of prophylaxis</td>
<td>Indication</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Influenza</td>
<td>VAC CH</td>
<td>VAC: contact or outbreak with strain covered by vaccine</td>
<td>CH (Influenza A or B); Oseltamivir (Tamiflu®) 75 mg qd x 10 d; Alternative: Zanamivir (Relenza®) 10 mg qd x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH: exposure of unvaccinated or insufficiently protected HIV patients</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>VAC IG</td>
<td>IG: exposure of HIV patient (independent of vaccine history or serology)</td>
<td>IG: within 6 d after exposure (consider active vaccination history or serology) 6 months later</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VAC: Exposure of a susceptible individual without immunity suppression</td>
<td>VAC: within 72 h after start of exposure, if later: IG Never VAC + IG simultaneously!</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Following an index case: VAC: according to health authorities</td>
<td>CH: if possible, within 24 h, up to 14 d (index case contagious 7 d before onset of symptoms)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH: all household members; persons in contact with oropharyngeal secretions;</td>
<td>Rifampicin 600 mg bid x 2 d or ciprofloxacin 500 mg once or ceftriaxone 250 mg i.m. once</td>
</tr>
<tr>
<td></td>
<td></td>
<td>close contacts in child-care centers, dormitories etc.</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>VAC</td>
<td>Exposure of susceptible individuals</td>
<td>Within 3 (–5) d of exposure Consider contraindications</td>
</tr>
<tr>
<td>Pertussis</td>
<td>VAC CH</td>
<td>VAC: exposure and incomplete immunization</td>
<td>CH: within 7 d of exposure Oral macrolides, e.g., clarithromycin 500 mg bid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH: close contacts, e.g., household contacts</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>VAC</td>
<td>Any exposure independent of immunization status</td>
<td>Avoid any delays!</td>
</tr>
<tr>
<td>Rabies</td>
<td>VAC IG (simultaneous)</td>
<td>Depending on vaccination status, exposure, and national guidelines (German recommendations: STIKO 2011)</td>
<td>HIV patients: VAC: consider double dose on day 0 IG: if CD4 &lt;400/μl use more liberally (even if vaccinated before exposure or minor exposure)</td>
</tr>
<tr>
<td>Rubella</td>
<td>VAC</td>
<td>Exposure of susceptible individuals</td>
<td>Within 5 d of exposure Consider contraindications</td>
</tr>
<tr>
<td>Tetanus</td>
<td>VAC IG (simultaneous)</td>
<td>Depending on vaccination status, wound, and national guidelines</td>
<td>German recommendations: STIKO 2011</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>CH</td>
<td>HIV patients after close contact with open TB case</td>
<td>Treat as latent TB (see chapter on TB)</td>
</tr>
<tr>
<td>Disease</td>
<td>Type of prophylaxis</td>
<td>Indication</td>
<td>Comments</td>
</tr>
<tr>
<td>---------</td>
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<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>Varicella</td>
<td>VAC, IG, CH</td>
<td>IG/CH: exposure(^4) of susceptible immuno-compromised individual</td>
<td>VAC: exposure(^4) of susceptible individual(^2) without immunosuppression</td>
</tr>
<tr>
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</tbody>
</table>

1 VAC, vaccination (active immunization); IG, immunoglobulin (passive immunization); CH, chemoprophylaxis
2 Susceptible: No documented history of disease or vaccination, no specific antibodies in serological testing
3 Specific hyperimmunoglobulin might be available in some countries
4 Chickenpox exposure: >1 h in the same room, face-to-face contact, household contact; herpes zoster exposure: direct contact with skin lesions or their secretions, but indication for immunoprophylaxis under debate (data lacking)

References


HIV-1-associated neurocognitive disorder (HAND)
Terminology, epidemiology, and etiology

The primary cause of HIV-1-associated neurocognitive disorder (HAND) is an infection of the CNS caused by HIV. In untreated HAND there is a high level of replication of HIV in the macrophages and microglial cells of the brain. Neuronal cells have not consistently been shown to be infected. However, different immunopathological mechanisms lead to functional and structural damage of these cells. With respect to viral replication and viral quasispecies, the CNS is partially independent from the hematolymphatic compartment (Eggers 2003). In 2007 an international panel (Antinori 2007) devised three categories of HAND in the order of descending severity: HIV-1-associated dementia (HAD), HIV-1-associated mild neurocognitive disorder (MND), and HIV-associated asymptomatic neurocognitive impairment (ANI). This replaces the older terms HIV encephalopathy, AIDS dementia complex, and HIV-associated cognitive motor complex.

Table 1: The classification system of HAND (Antinori 2007)

| HIV-associated asymptomatic neurocognitive impairment (ANI) | Neuropsychological* testing with impairment (≥ 1 standard deviation) in cognitive function in ≥ 2 functional domains**. The impairment does not interfere with everyday functioning. |
| HIV-1-associated mild neurocognitive disorder (MND) | Cognitive results as in ANI. At least mild interference in daily functioning (at least one of the following): a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning. b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning. |
| HIV-1-associated dementia (HAD) | Marked acquired impairment in cognitive functioning. Cognitive results as in ANI, but most times in multiple domains and impairment ≥ 2 standard deviations. Marked interference with day-to-day functioning (work, home life, social activities). |

For all categories, delirium must be excluded, and there must be no alternative plausible cause. * considering age- and education-adjusted norms. ** cognitive domains are: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.

As the life expectancy of HIV-infected individuals in the developed world comes close to that of the general population, the prevalence of HAND has risen to some 20 to 50% (Sacktor 2002). Recent work has shown some 50% of HIV-infected subjects to be neurocognitively impaired. With ART, the prevalence of severe cases has decreased while that of the minor variants has increased (Heaton 2010, Heaton 2011). Among individuals in the WHO/CDC clinical stage A, however, a slight to moderate impairment is more frequent than in the pre-HAART era. HAND is associated with a shortened survival (Sevigny 2007).
It is generally accepted that HAND, occurring in an untreated patient, is a treatable condition. However, the extent and sustainability of the effects of ART on cerebral function are still unclear. There is accumulating evidence of chronically progressive and, at times, fluctuating neurocognitive impairment in patients on suppressive ART (Brew 2004, Antinori 2007, Canestri 2010). A five-year longitudinal observation of treated patients with no cognitive impairment at baseline, yielded stable cognitive function in the majority of patients (Cole 2007). Another study of treated subjects with initially low but increasing CD4 T cell counts, showed some improvement of cognitive function, but this remained worse than that of an HIV-negative control group (McCutchan 2007). Frequent subjective complaints of reduced cognitive performance in combination with the objective correlates on formal neuropsychological testing, have been found in many patients with longstanding suppression of plasma viral load (Simioni 2010). Thus, severe HAND manifestations are now rare in HIV-infected subjects on ART (Price 2008). However, more subtle but, with regard to working performance, significant dysfunction may be seen in everyday clinical practice, and it now occurs at earlier stages of HIV-induced immunosuppression (Sacktor 2001, Dore 2003).

In the pre-ART era, the time course of the CSF and plasma viral load and the CD4 T cell count were predictors of HAND, but this has now changed. Longitudinal studies in ART-treated subjects without dementia show low nadir CD4 T cell counts, previous AIDS, longer duration of HIV infection, low educational status, older age, and plasma levels of TNF-alpha and MCP-1 as predictors in the development of HAND (Sevigny 2004, Robertson 2007, Tozzi 2007, Bhaskaran 2008). The occurrence and/or persistence of HAND, despite effective suppression of plasma viral replication might be associated with chronic immune activation within the CNS, as suggested by persistently elevated levels of neopterin and anti-MOG antibodies in the CSF (Eden 2007, Lackner 2010). This observation might suggest some “uncoupling” of mechanisms within the CNS from those in the hematolymphatic compartments. Other known risk factors for the development of HAND are ongoing illicit drug use, and possibly, HCV coinfection.

Cases of severe HAND with high levels of CSF viral load were observed in ART-treated patients with well-suppressed plasma viral load (Venkataramana 2006, Canestri 2010). Histopathologically numerous CD8-positive lymphocytes were found in the perivascular spaces and the parenchyma, partly in close spatial association with neurons. This condition may be interpreted as an immune reconstitution phenomenon directed against HIV itself (Venkataramana 2006).

**Clinical manifestation**

HAND is considered to be a subcortical dementia. In the HAART era, signs of cortical involvement and memory impairment have become more prominent, while motor signs have become less important (Heaton 2011).

HAND emerges over the course of weeks and months. Acutely developing symptoms point to another etiology. Fever, exhaustion, the effects of tranquilizers, reduced physical condition and even major depression may all mimic dementia. In these cases, diagnosis of HAND can only be made after repeated examinations when the condition mimicking dementia has improved.

Symptoms are occasionally noted earlier by relatives than by the patient. This is why a history given by these persons is important. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy, mild depressive symptoms and emotional blunting (Tables 2 and 3). Impairment of alertness, neck stiffness and focal or lateralizing neurological signs (e.g., hemiparesis, aphasia) are not
typical for HAND. Psychotic symptoms without cognitive or motor disturbance do not warrant a diagnosis of HAND. The coincidence of psychosis with HAND is rare. Focal and generalized epileptic seizures are rare manifestations of HAND. The severity of HAND may be functionally categorized according to the Memorial Sloan Kettering scale (Table 4) (Price 1988).

Table 2: Symptoms of HAND including history given by close relatives or companions

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Forgetfulness, difficulties concentrating, mental slowing (apprehension, processing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional</td>
<td>Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative aspects of one's life. Depressive mood, emotional blunting</td>
</tr>
<tr>
<td>Motor</td>
<td>Slowing and impairment of fine movements (e.g., typing, buttoning up) and disturbance of gait</td>
</tr>
<tr>
<td>Autonomous</td>
<td>Impaired micturition (urgency), loss of sexual libido, erectile dysfunction</td>
</tr>
</tbody>
</table>

Table 3: Signs of HAND

| Neurological findings                                                                                                                                   |
| Early stages: impaired gait, slowing of rapidly alternating movements, hypomimia, occasionally tremor and short-stepped gait |
| Later: brisk tendon reflexes, positive Babinski sign, slowing of gaze saccades, sphincter impairment including incontinence. Palmomental, grasp and glabella reflexes. Occasionally accompanying polyneuropathy |
| In the terminal stages: spastic tetraplegia and dual incontinence |

| Neuropsychological findings                                                                                                                             |
| Slowing of psychomotor speed (e.g., naming the months in reverse), impairment of short term memory (recall of verbally presented items, digit span), and mental flexibility (spelling simple words backwards) |

| Psychological findings                                                                                                                                  |
| Early stages: emotional blunting, disappearance of strong personality traits, distractability, loss of initiative |
| Later: problems with recalling events in the correct time order, disorientation to time, space and situation. Finally mutism |

Table 4: Severity of HAND. (Memorial Sloan-Kettering Scale, MSK scale, [Price 1988])

| Stage 0 (normal) normal mental and motor function.                                                                                     |
| Stage 0.5 (equivocal/subclinical) no impairment of work or capacity to perform activities of daily living (ADL); normal gait; slowing of ocular movements and movements of extremities may be present |
| Stage 1 (mild) able to perform all but the more demanding aspects of work or ADL, but with unequivocal signs or symptoms of functional, intellectual or motor impairment; can walk without assistance |
| Stage 2 (moderate) able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life; able to walk, but may require a single prop |
| Stage 3 (severe) major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable psychomotor slowing); motor disability (cannot walk without assistance, usually manual slowing and clumsiness) |
| Stage 4 (end stage) almost mutistic. Intellectual and social comprehension and output are at a rudimentary level; almost or completely mute; paraparetic or paraplegic with urinary and fecal incontinence |
Diagnostic workup

Making a HAND diagnosis requires a synopsis of clinical information and laboratory tests. No laboratory test result on its own can warrant a diagnosis of HAND. Rather, the diagnosis requires the exclusion of other conditions (Table 3). Clinically, the cognitive deficits prevail. Psychological and behavioral, as well as motor signs and symptoms may be subtle in the early stages, but these are invariably encountered in the late stages (Table 2). The HIV dementia scale (Morgan 2008) is an easy-to-use bedside instrument for the detection and quantification of the cognitive impairment of HAND.

Laboratory tests are mainly employed to exclude differential diagnoses. MRI is preferred to CT. The MRI may show patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. In addition, atrophy with enlargement of the ventricles and the extraventricular CSF spaces may be seen. However, none of these findings are specific for HAND, and the disease may evolve with a normal MRI. Unlike in PML, the white matter lesions do not affect the cortical U-fibers, i.e., they do not reach the cortical ribbon. Edema and space occupying lesions are not typical for HAND and should raise suspicion of other conditions.

CSF analysis mostly shows a normal white cell count, and with severe immunosuppression, this may even be decreased. In patients with an at least partially effective antiretroviral treatment, CSF pleocytosis may be seen, suggesting an immunological response to HIV in the context of immune reconstitution. Total protein and albumin concentrations may be slightly elevated (blood-brain barrier disruption). Oligoclonal bands and increased IgG-index indicate autochthonous immunoglobulin production within the CNS. However, these findings are non-specific and are frequently present even in the asymptomatic stages of HIV infection.

In untreated patients there is a weak but statistically significant correlation of (higher) CSF viral load with HAND. However, this association is no longer true for individuals on ART (McArthur 2004, Heaton 2011). Abnormally low levels of Aß42 (a cleavage product of the amyloid precursor protein, APP) have been seen in the CSF of HAND patients, a finding known from Alzheimer’s disease. In contrast to Alzheimer’s, the CSF concentration of the protein τ (tau) is not elevated. Thus, the combined measurement of Aß42 and τ in the CSF might provide a new diagnostic tool (Clifford 2009).

The electroencephalogram (EEG) shows no or only mild signs of generalized slowing. Moderate or severe slowing or focal arrhythmic delta activity are atypical for HAND. With a large part of the HIV-infected population growing old, other types of dementia such as Alzheimer’s disease, vascular dementia, Lewy body dementia etc. need to be differentiated by appropriate diagnostic steps.

Treatment

According to the pathogenesis of HAND, treatment should aim at suppressing viral replication in the CNS. Although the CNS is a separate compartment of viral replication, the initiation of ART leads to a generally rapid decline of viral load in the CSF (Eggers 1999) with clinical improvement of neurocognitive performance occurring by 3 to 9 months (Cysique 2009).

ART may lead to significant clinical improvement of HAND including restoration of working ability in patients previously dependent on caregivers. During the first months of treatment and despite clinical improvement, the radiological signs of leukoencephalopathy may become more prominent, but eventually will regress over the following one or two years.
It is largely unknown what antiretroviral compounds and in what combination these are best suited for the treatment of HAND. The extent of penetration into the CSF and the brain parenchyma is generally assumed to be essential, and this view is supported by findings of little suppression of the CSF viral load by regimens containing only PIs (Gutmann 2010). A CNS penetration score (CPE), composed of the relative values of CNS penetration of the substances, comprises four categories, where lower scores indicate lower CNS penetration (Table 6) (Letendre 2009). Although the results are not uniform, the majority of studies assessing the CPE scores of antiviral regimens found better CSF viral suppression and better neurocognitive performance with higher CPE scores (Letendre 2008, Cysique 2009). One group, in a non-controlled and small study, found better suppression of CSF viral load with higher CPE scores; however, these patient’s cognitive performance was significantly worse than that of patients with less penetrating regimens (Marra 2009). Another study on long-term virologically suppressed subjects showed only a non-significant trend towards better performance with higher CPE scores (Simioni 2010). Our own work shows no association between the CSF viral load and the time course of CSF viral elimination with the measured CSF levels of the antiviral agents (Eggers 2003). These diverging results are likely due to the differing methodology and the uncertainty of how to measure and define CNS penetration. Recently, a small randomized controlled study comparing efavirenz, atazanavir/r, and AZT/abacavir on the backbone of TDF+FTC found a significantly better neurocognitive performance in the AZT/abacavir treated group (Winston 2010). The notion of the importance of suppressing the CNS viral replication is supported by case series that describe patients with long-standing suppression of the plasma viral load, but detectable viral replication in the CSF (viral escape). These subjects had clinically overt neurological disease, and on optimization of their ART according to the CPE score and resistance testing, all improved clinically and in terms of CSF viral load (Canestri 2010). It is therefore recommended that antiviral regimens contain CNS-penetrating compounds, and this is even more important with symptomatic CNS involvement of HIV. A further argument for achieving high enough levels of antiviral compounds in the CNS, is its role as a viral reservoir and the finding of resistant viral strains in the CSF (Smit 2004, Canestri 2010).

Several non-antiviral substances have been tried as an adjunctive treatment for HAND (minocycline, memantine, selegiline, lithium, valproate, lexitropfin, CPI-1189, peptide T, nimodipine, and psychostimulants). Although all proved to be safe, none exhibited any meaningful clinical effect (Uthman 2008, Sacktor 2011).

Non-pharmacological interventions include the treatment of concomitant conditions such as hepatitis C, major depressive disorders, the management of cardiovascular and metabolic risk factors, and the improvement of drug adherence (Ettenhofer 2010, Foley 2010).

Neurotoxic effects of antiretroviral substances may be considered in patients developing or maintaining neurocognitive and psychiatric dysfunction. Neuropsychiatric side effects are best documented for efavirenz, but these are mostly transient. Some authors reported on cognitive dysfunction with suppressive ART that resolved with withdrawal of ART, but these results have been questioned by others (Munoz-Moreno 2010, Robertson 2010). In view of its systemic effects, however, treatment interruptions are not recommended. If neurotoxicity is suspected, the ART regimen might be altered.

While there used to be a discussion about the optimal time point to start antiviral treatment in relation to cognitive impairment, in some guidelines ART is now recommended in any HIV-infected subject irrespective of the stage of the disease (Thompson 2012). The guidelines of the European AIDS Clinical Society consider
HAND for the choice of the antiviral compounds (europeanaidsclinicalsociety.org; accessed 9/12).

We recommend that all HIV-infected patients be screened for HAND, and this should ideally be carried out before initiation of ART in order to generate baseline data. Screening should be done every 6 to 24 months, according to the risk profile of the patient. The HIV dementia scale may be employed as screening instrument (Morgan 2008). When results are abnormal, further neuropsychological testing should be done encompassing the domains verbal/language, attention/working memory, abstraction/executive function, learning/recall, speed of information processing, and motor skills. Some evidence suggests an early initiation of ART for the prevention of HAND (Ellis 2011), but the value of CNS-penetrating compounds is unclear.

Table 5: Differential diagnoses of HIV encephalopathy and diagnostic workup

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adequate diagnostic step (commentary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosyphilis</td>
<td>Antibody testing and CSF analysis (pleocytosis &gt;15/μl) (serological findings may be atypical for active neurosyphilis)</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>CSF (pleocytosis, potentially granulocytic; decreased glucose elevated total protein)</td>
</tr>
<tr>
<td></td>
<td>PCR for CMV in CSF, CMV antigen (pp65) in blood antibody testing in blood and CSF (IgG and antibody index may be increased)</td>
</tr>
<tr>
<td></td>
<td>MRI (potentially subependymal hyperintensity and contrast enhancement) Occurs mostly in association with manifestation of other organs (retinitis, colitis, pneumonitis, esophagitis)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>CT / MRI (single or multiple lesions found most frequently in basal ganglia or thalamus, space occupying effect, edema, frequently with contrast enhancement [patchy or ring-shaped])</td>
</tr>
<tr>
<td></td>
<td>Presence of toxoplasma specific IgG in blood and CSF (rarely total seronegativity). PCR for Toxo DNA in CSF has low sensitivity (Disease may rarely run as diffuse microglial nodule encephalitis)</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>CT / MRI (single or multiple lesions most frequently adjacent to ventricles, space occupying effect, edema, contrast enhancement)</td>
</tr>
<tr>
<td></td>
<td>CSF cytology</td>
</tr>
<tr>
<td></td>
<td>EBV PCR in CSF (HIV-associated CNS lymphomas EBV induced)</td>
</tr>
<tr>
<td></td>
<td>PET or SPECT (tracer enhancement in lesion)</td>
</tr>
<tr>
<td>VZV encephalitis</td>
<td>CSF (marked inflammatory signs)</td>
</tr>
<tr>
<td></td>
<td>VZV specific IgG in blood and CSF (IgM may be absent)</td>
</tr>
<tr>
<td></td>
<td>VZV PCR in CSF</td>
</tr>
<tr>
<td></td>
<td>Mostly antecedent or accompanying cutaneous zoster lesions</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>CSF (opening pressure frequently elevated, cell count and protein may be normal), India ink stain</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal antigen in blood and CSF, fungal culture</td>
</tr>
<tr>
<td>Tuberculous meningitis and other bacterial infections</td>
<td>CSF, culture, PCR for mycobacteria appropriate tests</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy (PML), classical form</td>
<td>MRI (single or multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement)</td>
</tr>
<tr>
<td></td>
<td>CSF (no signs of inflammation but PCR for JC virus positive)</td>
</tr>
</tbody>
</table>
**Table 5 (continued)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adequate diagnostic step (commentary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intoxication</td>
<td>Determination of drug levels / screening for illicit drugs</td>
</tr>
<tr>
<td>Metabolic encephalopathy and impaired general physical condition</td>
<td>Determination of electrolytes, renal and hepatic markers, hormones (thyroid, cortisol), blood count</td>
</tr>
<tr>
<td>Depression with “pseudo-dementia”</td>
<td>Psychiatric examination</td>
</tr>
<tr>
<td>Other forms of “subcortical” dementia</td>
<td>Normal pressure hydrocephalus, Parkinsonian syndromes, other neurodegenerative conditions, subcortical arteriosclerotic encephalopathy</td>
</tr>
</tbody>
</table>

**Table 6: CNS penetration effectiveness score (CPE) (Letendre 2009)**

<table>
<thead>
<tr>
<th>CPE rank</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>AZT</td>
<td>Abacavir FTC</td>
<td>DDI 3TC D4T</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Nevirapine</td>
<td>Delavirdine Efavirenz</td>
<td>Etravirine</td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>Indinavir/r</td>
<td>Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r</td>
<td>Atazanavir Atazanavir/r Fosamprenavir</td>
<td>Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r</td>
</tr>
<tr>
<td>Entry Inhibitors</td>
<td></td>
<td></td>
<td>Maraviroc</td>
<td>T-20</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td></td>
<td>Raltegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HIV-associated myelopathy**

**Clinical characteristics**

HIV-infected patients may develop myelopathy without the neuropsychological signs and symptoms of HAND, called HIV-associated myelopathy (HIVM). The histopathological hallmarks are prominent vacuoles in the cervical and thoracic parts of the spinal cord and lipid-laden macrophages, hence the term “vacuolar myelopathy” (Petito 1985). These changes are reminiscent of severe combined degeneration and may occur with HIV-negative patients. As HIV viral products have only inconsistently been shown to be part of the lesions, the role of the virus in the disease is uncertain. Pathogenetically, a disturbance of cobalamin-dependent trans-methylation has been discussed. Like HAND, HIVM occurs mainly with advanced immunosuppression. Not all patients with the autopic finding of vacuolar myelopathy show clinically apparent myelopathy during life (dal Pan 1994).

A patient may be suspected of having HIVM if he has a spastic-atactic gait, hyperreflexia with positive Babinski sign, disturbance of sphincter control, erectile dys-
function, and slight signs of sensory dysfunction in a glove and stocking distribution. The diagnosis of an independent HIVM should only be made when the concomitant cognitive impairment is significantly less prominent than the myelopathy. Electrophysiological tests that show increased latencies of somatosensory-evoked potentials (SEP) and motor-evoked potentials on transcranial magnetic stimulation, are compatible with the diagnosis. CSF, microbiological and spinal imaging studies are inconspicuous or non-specific, and they have their importance in the exclusion of other diagnoses, as listed in Table 7. Spinal imaging should include MRI of the cervical and, possibly the thoracic cord.

**Diagnostic workup**

Table 7: Differential diagnoses of HIV myelopathy and diagnostic workup

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adequate diagnostic step (commentary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanic compression of the myelon (cervical myelopathy, disk herniation)</td>
<td>Degenerative changes of the cervical spine MRI shows reduced CSF spaces around the spinal cord with hyperintense lesions of the cord parenchyma</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Antibody testing and CSF analysis (pleocytosis &gt;45/3) (serological findings may be atypical)</td>
</tr>
<tr>
<td>CMV myelopathy</td>
<td>CSF (signs of inflammation), PCR for CMV in CSF Antibody testing in blood and CSF (IgG and antibody index may be increased)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Contrast enhancing cord lesion on MRI</td>
</tr>
<tr>
<td>HZV myelitis</td>
<td>CSF (marked inflammatory signs) HZV specific IgG in blood and CSF (IgM may be absent) HZV PCR in CSF Mostly antecedent or accompanying cutaneous zoster</td>
</tr>
<tr>
<td>HZV myelitis</td>
<td>CSF (inflammatory signs may be absent), HSV PCR in CSF</td>
</tr>
<tr>
<td>HTLV-1 (tropical spastic paraparesis)</td>
<td>Travel to the Caribbean, West Africa or East Asia Slow evolution of symptoms, bladder dysfunction characteristic, CSF inflammation, HTLV-1 specific antibodies</td>
</tr>
<tr>
<td>Severe combined degeneration</td>
<td>Vitamin B12 levels, increased erythrocyte volume</td>
</tr>
<tr>
<td>Heredo-degenerative diseases (hereditary spastic paraparesis, adrenoleukodystrophy, Friedreich ataxia, etc.)</td>
<td>Appropriate tests</td>
</tr>
</tbody>
</table>

**Treatment**

Early observations of significant improvement with AZT monotherapy (Oksenhendler 1990) were later confirmed with ART. Any patient with HIVM should be offered ART. A controlled trial showed L-methionine to bring about improvement on electrophysiological but not clinical parameters.

**References**


Brew B. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS 2004;18 Suppl 1:S75-78.


32. Neuromuscular Diseases

THORSTEN ROSENKRANZ, CHRISTIAN EGGERS

Polyneuropathy and polyradiculopathy

Peripheral neuropathy is the most common neurologic complication of HIV infection. Even in the era of modern antiretroviral therapy neuropathic signs and symptoms are found in about 30% of patients (Evans 2011). Neuropathies can be classified as primarily HIV-associated or as secondary diseases caused by neurotoxic agents or opportunistic infections. Distal symmetrical sensory polyneuropathies (DSSP) related to HIV infection have been on the decline since the introduction of ART, but there has been an increase in the prevalence of medication-related toxic neuropathies (Gonzalez-Duarte 2008). Even though the incidence rate of the other types of neuropathies is low, they require a precise and rapid diagnosis because many of them do benefit from specific therapies.

Clinical features

Acute, inflammatory, demyelinating polyneuropathy (AIDP), Guillain-Barré syndrome (GBS)

AIDP usually occurs at seroconversion or during the asymptomatic stages of HIV infection. It seems to be rarely associated with immune reconstitution. Typical clinical signs are areflexia, symmetrical ascending weakness and relative sparing of sensory nerve fibers. Involvement of cranial nerves and cervical and thoracic spinal nerves leads to respiratory insufficiency, dysarthria and dysphagia. Parasympathetic and sympathetic nerve involvement may cause life threatening cardiac arrhythmias and severe arterial hypo- or hypertension. CSF typically shows a raised concentration of protein caused by the dysfunction of the blood-brain barrier. In contrast to HIV-negative patients with AIDP, a moderate pleocytosis of up to 50 leucocytes/µl CSF is found in most HIV-infected patients. The progressive stage is followed by a few days or weeks of stable disease until recovery begins. If secondary axonal damage has occurred, recovery can last up to two years. A persistent disability of varying degrees develops in about 30%.

Chronic, inflammatory, demyelinating polyneuropathy (CIDP)

Whereas AIDP is a monophasic, self-limiting disease, the course of CIDP is chronic progressive or relapsing-remitting. Weakness and sensory disturbances commonly develop over several months. In some cases relapses, incomplete remissions and periods of stable disease alternate with each other. In CIDP, as in AIDP, the CSF is abnormal with an elevated protein level. A moderate pleocytosis is often found instead of the classical acellularity. CIDP is a rare complication of seroconversion or the early stages of infection before AIDS.

Vasculitic neuropathy

Necrotizing vasculitis with involvement of the peripheral nerves is a rare cause of neuropathy in HIV infection. Most patients develop a mononeuritis multiplex characterized by acute relapsing dysfunction of individual peripheral nerves. Prognosis of the disease is determined by involvement of other organs such as heart, kidneys or muscles in the vasculitic process. An immune complex attack associated with hepatitis C virus infection or cryoglobulins appears to play an essential role in the pathological mechanism.
Table 1: Polyneuropathies and polyradiculopathies in HIV infection.

<table>
<thead>
<tr>
<th>Type</th>
<th>HIV infection</th>
<th>Clinical features</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary HIV-associated polyneuropathies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute, inflammatory, demyelinating polyneuropathy (Guillain-Barré syndrome, GBS)</td>
<td>Seroconversion, asymptomatic, no or early immunosuppression</td>
<td>Symmetrical weakness &gt; sensory loss, areflexia</td>
<td>ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (&lt;50 c/μl)</td>
</tr>
<tr>
<td>Chronic demyelinating inflammatory polyneuropathy (CIDP)</td>
<td>Asymptomatic early immunosuppression, rarely AIDS</td>
<td>Distal and proximal weakness &gt; sensory loss, areflexia</td>
<td>ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (&lt;50 c/μl)</td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>Asymptomatic no or early immunosuppression, rarely AIDS</td>
<td>Mostly asymmetric, acute loss of function of single nerves, rarely distal symmetrical sensory and motor disturbances</td>
<td>Elevation of ANA, cryoglobulinemia, HCV coinfection; vasculitis in nerve biopsy but also in muscle, kidney and other organs</td>
</tr>
<tr>
<td>Neuropathy in diffuse, infiltrative leukocytosis syndrome (DILS)</td>
<td>Early immunosuppression</td>
<td>Mostly asymmetrical weakness and sensory loss, rarely distal symmetrical</td>
<td>Disease resembling Sjögren’s syndrome; CD 8 T cells &gt;1200/μl</td>
</tr>
<tr>
<td>Distal symmetrical sensory polyneuropathy (DSSP)</td>
<td>AIDS or advanced immunosuppression</td>
<td>Distal symmetrical sensory loss, paresthesia and pain of the legs</td>
<td>ENG with axonal features predominantly involving sensory nerves of the legs</td>
</tr>
<tr>
<td><strong>Secondary polyneuropathies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-related toxic neuropathy</td>
<td>Early or advanced immunosuppression</td>
<td>Distal symmetrical sensory loss, paresthesia and pain of the lower legs</td>
<td>Treatment with ddl, ddC, d4T, vincristine, dapsone</td>
</tr>
<tr>
<td>Acute neuromuscular weakness syndrome</td>
<td>Early or advanced immunosuppression</td>
<td>Acute progressive tetraparesis</td>
<td>Lactic acidosis (NRTIs) axonal nerve damage, additional myopathy</td>
</tr>
<tr>
<td>Mononeuritis multiplex in CMV-infection or non-Hodgkin lymphoma</td>
<td>AIDS</td>
<td>Asymmetric, acute loss of function of single nerves</td>
<td>CMV infection of other organs, CMV DNA detection in plasma; non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Polyradiculitis in CMV or M. tuberculosis infection or due to meningeal lymphoma</td>
<td>AIDS</td>
<td>Flaccid paraparesis, sensory loss, bladder dysfunction</td>
<td>CMV or mycobacterial infection at other sites, detection of mycobacteria in CSF, malignant cells in CSF</td>
</tr>
</tbody>
</table>
Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS is a rare cause of distal symmetrical, often painful neuropathy. It resembles Sjögren’s syndrome, but has multivisceral infiltration characterized by CD8 hyperlymphocytosis (CD8 T cell count >1000/µl). Sicca syndrome with parotidomegaly, lymphadenopathy, splenomegaly, pneumonitis and renal dysfunction may occur in association with axonal neuropathy (Gherardi 1998).

Distal symmetrical sensory polyneuropathy (DSSP)

DSSP is still the most common neuropathy in HIV-positive patients and becomes symptomatic in the later stages of infection. Risk factors are older age, diabetes mellitus, HTLV-1 coinfection and hypertriglyceridemia (Banerjee 2011, Evans 2011, Silva 2012). The clinical course is predominated by slowly progressive sensory symptoms such as numbness, dys- and paresthesia of the feet and lower legs (Table 2). Approximately 30–50% of patients complain of burning, lacerating or stabbing pain. It mainly involves toes and soles of the feet and sometimes makes walking difficult. The most important clinical findings are depressed or absent ankle reflexes, an elevated vibration threshold at toes and ankles and a decreased sensitivity to pain and temperature in a stocking distribution, whereas proprioception is usually normal. Weakness and atrophy of intrinsic foot muscles are mild and are not features of the disease. The fingers and hands are rarely involved. Involvement of the upper legs and trunk, significant weakness of leg muscles or decreasing proprioception are not typical for DSSP and should raise suspicion of other disorders, for instance a conjoined myelopathy. Loss and dysfunction of small sympathetic and parasympathetic nerve fibers may cause postural hypotension, erectile dysfunction, gastroparesis and alterations of skin or nails in many DSSP patients.

<table>
<thead>
<tr>
<th>Table 2: Clinical features of distal symmetrical sensory polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness, pain, dys- and paresthesia of the feet and lower legs</td>
</tr>
<tr>
<td>Decreased or absent deep ankle tendon reflexes</td>
</tr>
<tr>
<td>Decreased or absent vibratory sense of the toes and ankles</td>
</tr>
<tr>
<td>No or only minimal motor dysfunction</td>
</tr>
<tr>
<td>No or only minimal involvement of the hands and arms</td>
</tr>
<tr>
<td>Slowly progressive course</td>
</tr>
<tr>
<td>Electrodiagnostic studies with features of axonal nerve damage</td>
</tr>
<tr>
<td>Autonomic dysfunction: orthostatic hypotension, erectile dysfunction</td>
</tr>
</tbody>
</table>

Medication-related toxic neuropathy

A distal symmetrical sensory peripheral neuropathy occurs in about 10–30% of patients treated with ddI, d4T or ddC. It is indistinguishable from HIV-induced DSSP on clinical examination or in electrodiagnostic studies. The only difference is in the exposure to neurotoxic nucleoside antiretroviral medication. Brew (2003) found an elevation of serum lactate in over 90% of patients with d4T-related neuropathies. NRTI neuropathy develops after a mean of 12–24 weeks of treatment. After withdrawal, there can be a temporary worsening for 2–4 weeks and improvement usually begins after 6–12 weeks. In several cases the restitution remains incomplete. In these cases there may have been an additional pre-existent damage to the peripheral nerves due to HIV infection itself. Subclinical disturbance of peripheral nerve function confirmed by pathological findings in electrodiagnostic studies elevates the risk of developing NRTI-related neuropathy. PIs seem to have a very low additional neurotoxicity. In combination with d4T, ddI or ddC they seem to be an additional risk factor for neuropathy (Ellis 2008, Evans 2011).
The instruction leaflets of many PIs list peripheral neuropathy as a possible side effect, because neuropathic symptoms were slightly more often reported in the PI arms of clinical trials. But there are no reports of cases of neuropathy that developed while on PI treatment that resolved after withdrawal. In clinical experience, the risk of PI-induced neuropathy is very low.

Table 3: Neurotoxic drugs frequently used in HIV medicine

<table>
<thead>
<tr>
<th>NRTI</th>
<th>ddI, d4T (ddC no longer manufactured)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>dapsone, metronidazole, isoniazid</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>vincristine, etoposide</td>
</tr>
</tbody>
</table>

Acute neuromuscular weakness syndrome

In the course of an NRTI-induced lactic acidosis a life threatening tetraparesis resembling AIDP may occur. In most cases axonal peripheral nerve damage is found, but in a few patients demyelination is also detected. In addition, muscle biopsy reveals myositis or mitochondrial myopathy in some cases (Simpson 2004).

Polyneuropathy and polyradiculopathy due to other diseases

In patients with advanced HIV disease, mononeuritis multiplex may be caused by CMV infection or lymphoma. Acute or subacute polyradiculopathies of the cauda equina with rapidly progressive flaccid paraparesis of the legs, bowel dysfunction and sensory disturbances occur in the course of opportunistic infections (CMV, M. tuberculosis) or meningeal Non-Hodgkin lymphoma. Other important causes of polyneuropathy are alcohol abuse, diabetes mellitus, malnutrition in patients with long-lasting gastrointestinal diseases, neoplastic diseases or cachexia.

Diagnosis

A diagnosis of neuropathy can usually be made based on medical history and clinical examination. Electrodiagnostic studies may be performed for confirmation and for differentiation from other diseases such as myelopathy. Cerebrospinal fluid analysis may be necessary if there is a suspicion of infection with, for example, CMV or syphilis. Sural nerve and muscle biopsy may be necessary only in atypical cases – for instance, painful DSSP with a high CD4 cell count and low viral load and without neurotoxic medication or other risk factors. Table 4 gives some recommendations for clinical practice.

Table 4: Diagnostic work-up.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Findings</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic examinations (recommended for all cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>Drugs, Opportunistic diseases, Alcohol abuse</td>
<td>Medication-related toxic PNP Neuropathy associated with CMV infection or lymphoma Alcoholic PNP</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Clinical type of PNP (distal symmetrical, mononeuritis multiplex, etc.)</td>
<td>Symptoms not due to myelopathy or myopathy</td>
</tr>
<tr>
<td>Electromyography</td>
<td>Confirmation of neuropathy Demyelinating features Axonal features</td>
<td>Symptoms not due to myelopathy or myopathy AIDP, CIDP DSSP, Multiplex Neuropathy, DILS</td>
</tr>
</tbody>
</table>
Table 4 (continued)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Findings</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>HbA1c, glucose</td>
<td>Diabetic polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Vit B12, B1, B6, Fe, ferritin</td>
<td>PNP due to malnutrition or malassimilation</td>
</tr>
<tr>
<td></td>
<td>ANA, cryoglobulins, HCV-serology, circulating</td>
<td>Vasculitic neuropathy</td>
</tr>
<tr>
<td></td>
<td>immune complexes, ANCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPHA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD8 cells &gt;1200/μl lactate</td>
<td>Neuropathy associated with DILS</td>
</tr>
<tr>
<td></td>
<td>CMV DNA (if CD4 cells &lt;100/μl)</td>
<td>NRTI-induced toxic neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mononeuritis multiplex due to CMV-infection</td>
</tr>
<tr>
<td>Additional tests (necessary only in particular cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Elevated total protein</td>
<td>AIDP, CIDP</td>
</tr>
<tr>
<td></td>
<td>Pleocytosis (granulocytes), CMV DNA</td>
<td>Polyradiculitis due to CMV infection</td>
</tr>
<tr>
<td></td>
<td>Lymphoma cells, EBV DNA</td>
<td>Lymphomatous meningitis</td>
</tr>
<tr>
<td></td>
<td>Elevated IgA, acid fast bacilli, mycobacterial DNA</td>
<td>Tuberculous polyradiculitis</td>
</tr>
<tr>
<td>Autonomic tests (sympathetic skin reaction, heart rate variability)</td>
<td>Involvement of sympathetic or parasympathetic nerves</td>
<td>Additional autonomic neuropathy</td>
</tr>
<tr>
<td>MRI (lumbar spine)</td>
<td>Compression of the cauda equina</td>
<td>Spinal lymphoma</td>
</tr>
<tr>
<td></td>
<td>Spinal toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Nerve and muscle biopsy</td>
<td>Necrotizing vasculitis</td>
<td>Vasculitic neuropathy</td>
</tr>
<tr>
<td></td>
<td>Perivascular CD8 infiltration without necrosis</td>
<td>DILS-associated neuropathy</td>
</tr>
</tbody>
</table>

Occasionally, patients report complaints of burning feet, aches, pain and tingling but clinical examination and nerve conduction studies are unremarkable. In these cases symptoms might be due to an isolated small fiber neuropathy exclusively affecting the small unmyelinated vegetative nerve fibers. Diagnosis requires a punch skin biopsy with histological assessment of intraepidermal nerve fiber density or pain-related evoked potential conduction testing (Obermann 2007).

**Treatment**

Causative treatment options only exist for some of the rare neuropathies or polyradiculopathies. Intravenous immunoglobulins and plasmapheresis have proven effective in the therapy of AIDP. Corticosteroids are also effective in CIPD. In clinical trials on the treatment of CIDP, no difference in the efficacy of immunoglobulins, plasmapheresis or corticosteroids has been shown. However, an individual patient may only respond to one of the three options. In patients who only respond to higher dosages of corticosteroids, other immunosuppressive agents such as azathioprine, low dose weekly methotrexate or cyclosporine may replace long-term steroid therapy. We have seen CIDP patients who were in partial remission after temporary steroid therapy and who have remained stable for years with ART alone.
In medication-related neuropathy the offending agent needs to be withdrawn. The intake of 2 g L-acetyl-carnitine significantly reduced pain in HIV patients with neurotoxic neuropathy (Youle 2007).

A causative treatment for DSSP does not exist. ART might improve the function of sensory nerves in a few cases, and therefore starting ART or optimizing a current ART should be considered in newly diagnosed DSSP. In most cases the neuropathic symptoms still persist.

Symptomatic treatment is directed at irritative symptoms such as pain and paresthesia. It is not effective against deficits of nerve function including sensory loss or weakness. The agents listed in Table 6 are recommended because they have proven useful in daily practice and because they interfere only slightly and in a predictable way with ART. A controlled study showed that lamotrigine was effective in reducing the symptoms of neurotoxic neuropathy (Simpson 2003). The drug is well tolerated if one adheres to the slow dose escalation regimen and stops treatment or reduces the dose when a skin reaction occurs. In a small study, gabapentin was shown to be effective in reducing DSSP-induced pain (Hahn 2004). The advantages of this agent are good tolerability and lack of interference with ART. Pregabalin, an anticonvulsant drug similar to gabapentin, effectively relieves pain in studies of patients with painful diabetic peripheral neuropathy (Rosenstock 2004). Like gabapentin, it does not interfere with ART and is well tolerated. It is commonly used in DSSP, although a recent trial in HIV patients did not show efficacy (Simpson 2010).

Table 5: Causative treatment of polyneuropathies and polyradiculopathies.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>Intravenous immunoglobulins 0.4 g/kg daily for 5 days or: plasmapheresis (5 x in 7–10 days)</td>
</tr>
<tr>
<td>CIDP</td>
<td>Intravenous immunoglobulins 0.4 g/kg daily for 5 days or: plasmapheresis (5 x in 7–10 days) or: prednisone 1–1.5 mg/kg daily for 3–4 weeks with subsequent tapering for 12–16 weeks</td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>Prednisone 1–1.5 mg/kg daily for 3–4 weeks with subsequent tapering for 12–16 weeks</td>
</tr>
<tr>
<td>Neuropathy due to DILS</td>
<td>Starting or adjusting ART plus prednisone 1–1.5 mg/kg daily for 3–4 weeks with subsequent tapering for 12–16 weeks</td>
</tr>
<tr>
<td>Distal symmetrical sensory polyneuropathy</td>
<td>A causative treatment is not known, ART may improve nerve function, for symptomatic treatment. See Table 6</td>
</tr>
<tr>
<td>Medication-related toxic neuropathy</td>
<td>Withdrawal of the neurotoxic agents, if possible.</td>
</tr>
<tr>
<td>Mononeuritis multiplex or polyradiculitis due to CMV-infection</td>
<td>Intravenous foscarnet 2 x 90 mg/kg daily plus intravenous ganciclovir 2 x 5 mg/kg daily.</td>
</tr>
<tr>
<td>Lymphomatous meningitis</td>
<td>Starting or adjusting ART plus intrathecal methotrexate (intraventricular shunt or lumbar puncture) 12–15 mg 2 x/weekly until CSF is free of malignant cells, subsequently 1 x/week for 4 weeks and subsequently 1 x/month plus 15 mg oral folinate after each injection plus systemic treatment of lymphoma (see chapter on Malignant Lymphoma)</td>
</tr>
<tr>
<td>Polyradiculitis due to infection with M. tuberculosis</td>
<td>Treat tuberculosis (see chapter on OIs)</td>
</tr>
</tbody>
</table>
The tricyclic antidepressants amitriptyline and nortriptyline both have significant anticholinergic side effects. The dose necessary for reducing neuropathic pain is in the same range as for treating depression and many patients cannot tolerate these dosages. However, lower dosages have proved ineffective in DSSP. Nortriptyline has no sedative side effects. We use this agent with good success rates, although clinical trials for its use in HIV-associated neuropathy are lacking. The antidepressant duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been approved for the treatment of painful diabetic neuropathy. In our experience it is also useful in reducing pain in DSSP and toxic neuropathy in HIV patients. The anticonvulsant carbamazepine is widely used for the treatment of neuropathic pain. However, it induces some enzymes of the CYP450 system and interferes significantly with ART. Thus, its use in HIV medicine is very limited.

A high-concentration capsaicin patch has recently been shown to be effective in the treatment of pain in DSSP patients (Simpson 2008). The patch is now available in Europe and in US, where it is OTC. The responsiveness varies considerably from patient to patient, but the somewhat laborious application is worth a try. In two recent trials smoked cannabis has proven effective against neuropathic pain in DSSP (Abrams 2007, Ellis 2009). However, the effect was rather short-lived. Oral cannabinoids have not been tested yet in painful HIV-neuropathy. Potent opioids may be used to manage moderate or severe pain if a slow dose escalation of an antidepressant or anticonvulsant is not possible and an immediate analgesic effect is desired (Sindrup 1999). Even in cases of substituted or non-substituted drug abuse, opioids can be used (Breitbart 1997). Sometimes, the dosage of methadone only needs to be moderately increased for a sufficient analgesic effect.

Table 6: Symptomatic treatment of painful neuropathy.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
</tr>
<tr>
<td>Physical therapy, supporting measures (wide shoes, etc.), L-acetyl-carnitine 2 x 2–4 g</td>
<td>Rarely allergy, rarely mild diarrhea</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
</tr>
<tr>
<td>Temporary trial of 3–4 x 1000 mg paracetamol or 2–3 x 50 mg diclofenac or 4 x 40 drops novaminsulfone for 10–14 days or 8%-capsaicin patch</td>
<td>Nausea, vomiting, allergy (rarely), Transient skin irritation</td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
</tr>
<tr>
<td>Gabapentin 300 mg at night, dose escalation of 300 mg a day every third day up to a maximum of 1200 mg TID or Pregabalin 2 x 75 mg for 1 week, dose escalation to 2 x 150 in the 2nd week, possible escalation up to 2 x 300 mg or Lamotrigine 25 mg at night, dose escalation of 25 mg every 5 days up to 300 mg</td>
<td>Sedation, nausea, dizziness, rarely pancreatitis, Nausea, vomiting, diarrhea, allergic drug rash, Allergy, sedation, cephalgia, nausea</td>
</tr>
</tbody>
</table>
Table 6 (continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>or Amitriptyline 25 mg at night, dose</td>
<td>Sedation, orthostatic hypotension, constipation,</td>
</tr>
<tr>
<td>escalation of 10–25 mg every 2–3 days</td>
<td>dizziness, dry mouth, dysrhythmia, retention of urine,</td>
</tr>
<tr>
<td>up to 3 x 50 mg</td>
<td>except for: glaucoma</td>
</tr>
<tr>
<td>or Nortriptyline 25 mg in the mornings</td>
<td>Orthostatic hypotension, constipation, dizziness,</td>
</tr>
<tr>
<td>dose escalation of 25 mg every 2–3 days</td>
<td>dry mouth, dysrhythmia, retention of urine, except</td>
</tr>
<tr>
<td>up to 2–3 x 50 mg</td>
<td>for: glaucoma</td>
</tr>
<tr>
<td>or Duloxetine 1 x 60–120 mg</td>
<td>Nausea, diarrhea, agitation</td>
</tr>
</tbody>
</table>

Step 4

| Flupirtine 3 x 100, dose escalation   | Sedation, constipation, nausea                      |
| up to 3 x 600 mg                     |                                                      |
| or Retarded morphine 2 x 10 mg       |                                                      |
| gradual escalation up to 2 x 200 mg   |                                                      |

General practice

Proceed to the next step if symptoms persist.

Agents within step 3 may be combined (for instance an anticonvulsant and an antidepressant), agents of step 3 and step 4 may also be combined (for instance flupirtine and an anticonvulsant).

If a rapid relief of symptoms is necessary, treatment should be started with step 4 agents and a low dose step 3 drug should simultaneously be started with slow escalation.

The slower the escalation the greater the possibility of reaching an effective dosage.

---

**Myopathy**

Myopathies occur in 1–2% of all HIV-positive patients. They may appear at any stage of disease.

Table 7: Most important myopathies in HIV infection

<table>
<thead>
<tr>
<th>Primary HIV-associated</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyositis</td>
<td>AZT myopathy</td>
</tr>
<tr>
<td>Nemaline (rod body) myopathy</td>
<td>Vasculitic myopathy</td>
</tr>
<tr>
<td>Vacuolar myopathy</td>
<td>Lymphomatous muscle infiltration</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Infectious myositis</td>
</tr>
<tr>
<td></td>
<td>Medication-related toxic rhabdomyolysis</td>
</tr>
</tbody>
</table>

Polymyositis mediated by cytotoxic T cells is the most common HIV-associated myopathy. AZT-induced myopathy occurs very infrequently with the dosages used today (500–600 mg/day). Other agents such as ddI, co-trimoxazole, pentamidine, sulfadiazine, lipid-lowering drugs and the integrase inhibitor raltegravir (Zembower 2008) may rarely cause acute rhabdomyolysis with tetraparesis and marked elevation of serum CK levels. Notably, PIs raise the serum concentration of statins, increasing the risk of myopathy and rhabdomyolysis (Hare 2002). An elevated serum CK activity is frequently observed during treatment with TDF, especially in patients with HBV/HCV coinfection. This is due to a type 2 macroenzyme creatine kinase (Macro
(CK) and must not lead to suspicion of ischemic heart or of muscular disease. The accumulation of this liver-derived isoenzyme seems to be the result of an insufficient Macro CK2 clearance capacity mediated by TDF (Schmid 2005).

**Clinical features**

Myopathy in HIV infection usually presents with exercise-induced myalgia of proximal muscles followed by slowly progressive, symmetrical weakness and atrophy of proximal muscles. Limb girdle muscles are most commonly involved, but distal muscles and muscles of the trunk, neck, face or throat may also be affected.

**Diagnosis**

Myalgia, fatigue and elevated serum CK levels are frequently found in HIV infection. Some of the antiretroviral substances, mainly AZT, nevirapine and maraviro, may cause myalgia. But these unspecific symptoms and signs on their own do not warrant the diagnosis of myopathy. The diagnosis of probable myopathy requires weakness, muscle atrophy or myopathic features demonstrated by electromyography. A muscle biopsy confirms the diagnosis and may give some additional clues to the classification and pathogenesis of the muscle disease.

**Treatment**

Moderate myalgia may respond to non-steroidal anti-inflammatory drugs. Prednisone (100 mg daily for 3–4 weeks, subsequent tapering) or intravenous immunoglobulin (0.4 g/kg for 5 days) have been shown to be effective in treatment of polymyositis (Johnson 2003, Viard 1992). The treatment of AZT myopathy is cessation of the drug. Myalgia usually resolves within 1–2 weeks. If symptoms persist beyond 4–6 weeks, prednisone as described above may be effective.

**References**


The initial interview

Should be spread over several appointments at short intervals.

What the patient should know after their first appointment

- In general terms, how the virus causes illness.
- The difference between being HIV-infected and having AIDS.
- The importance of CD4 T cells and viral load.
- How others can become infected and how this can be avoided.
- That additional venereal diseases (STDs) should be avoided, as these can worsen the course of HIV infection.
- That it is theoretically possible to become infected with another more pathogenic or resistant strain of HIV (re-, super-infection).
- Where HIV therapy comes in and how helpful it can be.
- A healthy balanced diet and regular physical exercise can help improve the prognosis.
- Smoking increases the risk of countless complications.
- Where to find further information.
- The self-help groups and facilities (NGOs, community-based organizations) available in the area for the support of HIV patients.
- What tests are planned and their usefulness for future treatment.

What the doctor should know afterwards

Infection and risk

- When, where and why was the HIV test performed? Was there a negative test prior to this? What risks did the patient take in the meantime? These questions can help to identify potential areas of concern for the patient. In the case of no recognizable risk, the test result may be held in doubt until confirmation (see below).
- Family history of diabetes, coronary heart disease, cancer, tuberculosis or other infectious diseases
- Has the patient traveled recently? Prevalence of infections may vary by region. For example, someone who has lived in Hollywood has a risk of histoplasmosis (which is very rare in Europe).
- What drugs does the patient consume regularly? Large amounts of alcohol are not only toxic, but also may make adherence more difficult. For smokers, the cardiovascular complications are very real. Cocaine abuse may worsen cardiac and lung diseases. Injection drug users have a high risk for bacteremia and endocarditis or abscess complications; drug use reduces safer sex aspects.
- Tuberculosis among contacts of the patient.

Concomitant illnesses

- What previous illnesses, what concomitant illnesses?
- Formerly treated or untreated infections, tuberculosis, STDs, including syphilis and hepatitis B/C?
- What medications are taken regularly/occasionally?
- Is there a history of allergic reactions?
- Check the vaccination status (vaccination card?). Did the patient take part in disease screening programs?
Social

- What about partners? Is the partner tested for HIV and STDs? What about children or plans for pregnancy?
- What is the social background of the patient? What do they do professionally? Differing working schedules over the month? Think about therapy side effects at day and night. What duties do they have to fulfill? What are their priorities? Is it possible to pay for some medical aspects due to local medical care insurances?
- What about migration aspects? What about the resident status, legal and insurance aspects?
- What about the religious background? Are there any restrictions to take ART or to talk about risk factors and sexual orientation?
- Who knows about the infection? Who will help when/if they become ill? Who do they talk to about problems? Do they have friends who are also infected? Are they interested in getting in touch with social workers or self-help groups?
- Is psychotherapeutic support necessary?
- Is there an aspect of statutory care?

The laboratory

- The HIV test is checked in a cooperating laboratory. Reactive Quick and Elisa antibody tests have to be checked with a Western Blot (WB) or Immunoblot test (see Test Chapter)
- Complete blood count: 30–40% of all HIV patients suffer from anemia, neutropenia or thrombocytopenia
- CD4 T cell count and CD4/CD8 ratio. Allow for variations (percentage with less fluctuation; HTLV-1 co-infection leads to higher counts despite existing immunodeficiency),
- Plasma HIV RNA (viral load) and HIV resistance test (genotype)
- HLA-B*5701 testing is recommended before starting abacavir, tropism test before maraviroc therapy
- Electrolytes, creatinine, calculated creatinin clearance, urine status (proteinuria is often a sign of HIV-associated nephropathy), GOT, GPT, γGT, AP, LDH, lipase, total protein, protein electrophoresis
- Fasting blood glucose determination in order to assess the probability of metabolic side-effects when undergoing ART
- Lipid profile, as a baseline determination to check the course of metabolic side-effects while on antiretroviral therapy
- Hepatitis serology: A, B, C, D (vaccination? B also in order to choose an ART that might also be useful for hepatitis B)
- TPHA test and cardiolipin when TPHA positive
- STDs – Screening of chlamydia, gonorrhea with tissue swaps (oral, urethral, anal if necessary) and PCR testing
- Toxoplasmosis serology IgG. If negative: important for differential diagnosis, if CD4 T cells <200/µl – prevention of infection (no raw meat). If positive: medical prophylaxis if necessary
- CMV serology (IgG). If negative: important for differential diagnosis, inform well about prevention (i.e., safe sex). In cases of severe anemia, transfusion of CMV-negative blood only. If positive and CD4 <100, PCR test or pp65 Antigen for CMV Viral load; eye check for retinitis
- Varicella, measles, rubella serology; If negative: active vaccination with attenuated pathogens is contraindicated, but at >400 CD4 T cells/µl you should refer to the vaccination guideline
- Blood culture in acute diseases
The examination

- Physical diagnosis, including an exploratory neurological examination (including vibration sensitivity and mini-mental test)
- If neurological impairment CT or MRT Scan of the brain should be done for Toxoplasmosis or other brain infections / lymphomas
- If CD4 T cells are above 400/µl a tuberculin skin test (TST, PPD) should be done. A negative test does not exclude active or latent tuberculosis. T cell interferon gamma release tests (TIGRA, e.g., ELISpot or QuantiFERON®) can be an alternative to TST and are more specific and sensitive than skin tests
- Chest X-ray. Contradictory recommendations, probably only makes sense in case of positive TST or TIGRA or clinical indications of disease of the thoracic organs
- Sonographic scan of the abdomen. A harmless, informative examination as a baseline finding (liver, kidney, lymphoma)
- ECG and pulmonary function test. Simple tests to rule out any cardiovascular and pulmonary disease; n-BNP in cardiac diseases; risk scores for CHD
- For women, a PAP smear upon initial diagnosis, after 6 months and then, if negative, once a year
- Some experts recommend for homosexually active males an anal PAP smear for AIN Screening, proctologic investigation should be offered
- Funduscopy (ophthalmological consultancy), especially at low CD4 T cells (<100/µl) in order to rule out active CMV retinitis or scars
- Nutritional advice and/or treatment of malnutrition
- Check for Vitamin D / osteoporosis risk
- Verifying vaccinations (see chapter on Vaccinations)
- Checking for necessity of OI prophylaxis
- Checking the indication for an antiretroviral therapy

The result

- Patient overview to check the local guidelines for antiretroviral therapy, OI Prevention, OI therapy
- Development of a strategic medical care plan for long term care
The risk of HIV transmission is present if an HIV-negative person comes into contact and incorporates the blood, semen or vaginal fluids of an HIV-positive source person. Exposure of intact skin to HIV-contaminated body fluids (e.g., blood) is not sufficient to transfer the virus. Besides vertical HIV transmission, HIV transfer is possible if HIV-containing material enters the body by:

- needlestick injury or incision by surgical instruments
- exposure of damaged skin or mucosal membranes
- unprotected sexual intercourse with an infected person (including sexual accidents, i.e., broken condom...)
- IDU needle or equipment sharing
- transfusion of HIV-contaminated blood or blood products

**Transmission risk**

Overall, HIV is a low contagious pathogen. The transmission rate via one of the methods above ranges between 1:100 and 1:1000. Compared with HIV, the transmission rate for hepatitis C is 10 times higher, and 100 times higher for hepatitis B. Factors for the probability of transmission include the amount of source-incorporated virus transmitted and the length of exposure time. Contact with body fluids of a patient with a high viral load theoretically holds a greater risk of contagion than a similar contact with body fluids of a patient on ART with a suppressed viral load. Additionally, rapid removal of infectious material, e.g., from damaged skin or mucosal membrane by washing or disinfection, presumably decreases the risk of transmission.

For percutaneous contact with HIV-containing blood, an infectiousness of 0.3% on average is assumed. According to retrospective data, calculations have been established to assess the transmission risks of accidental exposure more precisely (Table 1).

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep needlestick injury or cut</td>
<td>16:1</td>
</tr>
<tr>
<td>Fresh blood on the penetrating instrument</td>
<td>5:1</td>
</tr>
<tr>
<td>Penetrating needle previously placed in blood vessel</td>
<td>5:1</td>
</tr>
<tr>
<td>Source person with high viral load</td>
<td>6:1</td>
</tr>
<tr>
<td>Exposition of mucosal membrane</td>
<td>1:10</td>
</tr>
<tr>
<td>Exposition of inflammatory damaged skin</td>
<td>1:10</td>
</tr>
</tbody>
</table>

* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2008

For information about assumed transmission risk of other types of exposure, please see Table 1 on page 5 of this book (Introduction) or the latest UK guidelines (Benn 2011).

Simian models show that in mucosal membranes, HIV primarily infects the local immunocompetent cells such as Langerhans cells. These cells and/or their sibling cells migrate to regional lymph nodes; detection of HIV in the blood occurs days later. The process of local infection and migration of the cells to the lymph nodes takes approximately 24–48 hours (Spira 1996, Otten 2000). Theoretically, immediate treatment may avert a systemic infection.
Effectiveness and limitations of PEP

Early reports on the use of AZT after occupational needlestick injuries date from 1989. An analysis of retrospective case-control studies shows that even prophylaxis with a single antiretroviral (ARV) agent after exposure reduces the probability of an infection by approximately 80% (Tokars 1993). The combination of multiple drugs seems to be – theoretically – even more potent. Unfortunately, transmission of HIV cannot always be prevented. There have been reports of HIV infections despite the use of PEP. Many of the described cases of PEP failure were treated with AZT alone. But there are also reports of failures of ARV combination therapies (Roland 2005). Furthermore, transmission from patients on ARV therapy may lead to transfer of resistant virus strains. The rate of primary resistances in naïve patients varies by region and country, but over the years it stabilized at approximately 10 to 15% for at least one agent or drug class. How to deal with this issue concerning PEP initiation still remains unclear since resistance testing takes some days or more. Results would arrive too late to avoid the spread of HIV using the appropriate antiretrovirals.

When is PEP indicated?

The decision to provide PEP should be made by a physician experienced in HIV treatment. It is important to ascertain whether the source person has a supposed or confirmed HIV infection. Unclear HIV status should be clarified. Presupposing the approval of the index person for an HIV test, a rapid test may be helpful in such a situation, but confirmation of the result should be performed by established laboratory-based methods. However, the sooner the PEP patient starts therapy, the better the chances to avoid transmission, regardless of the serostatus of the source. In case of a negative result, the medication can be stopped in any case.

For source persons with confirmed HIV infection, the current HIV viral load, stage of disease, former and current ART, have to be taken into consideration. Optimally, a resistance test would also be available (Puro 2003). The exposed person should also be asked about any first aid procedures that have already been performed. After clarification of these queries, the exposed person has to be informed about the possible risks of PEP. It should also be emphasized that none of the antiretroviral agents is approved for use in this setting (although Truvada® is approved for PrEP in the US, it is not licensed for PEP!). Besides the legal responsibility of the prescribing physician, these facts are also important with regard to the coverage of cost, especially after sexual exposure. For example, in Germany, although some regional and national plans will cover a limited program of PEP, the medication cannot be prescribed at the expense of health insurance companies; however, PEP for occupational exposure is usually covered by statutory accident insurance.

Table 2 gives an overview of situations in which PEP is recommended. But it should be mentioned that the risk assessment has changed in the last years: following the statement of the Swiss Federal Commission for HIV/AIDS (EKAF 2008), declaring that the risk of transmission is negligible in the case of an index person with viral suppression below 50 copies/ml who has been on ART for at least 6 months (see chapter on ART and Prevention), the newest UK guidelines for the use of post-exposure prophylaxis for HIV following sexual exposure have modified their recommendations: in case of a confirmed positive source person without detectable viral load, PEP should only be provided after receptive anal intercourse. In cases of detectable viral load, PEP is recommended in direct homo- or heterosexual intercourse. In case of unknown serostatus of the source person, the use of PEP is very restrained (Benn 2011). The overview of recommendations for PEP usage should serve as an orientation, although alterations may be necessary in individual cases.
Table 2: Overview of recommendations for usage of PEP

<table>
<thead>
<tr>
<th>Occupational Exposure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous needlestick injury with hollow needle (body fluids with high viral load: blood, liquor, material from biopsies, cultured virus)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Deep injury (e.g., cuts), apparently blood-stained</td>
<td>Recommended</td>
</tr>
<tr>
<td>Intravenous injection with a previously used needle</td>
<td>Recommended</td>
</tr>
<tr>
<td>Superficial injury (e.g., with surgical needle)</td>
<td>Considered</td>
</tr>
<tr>
<td>- if source person has AIDS or high viral load</td>
<td>Recommended</td>
</tr>
<tr>
<td>Contact of mucosal membrane or damaged skin with fluids with high viral load</td>
<td>Considered</td>
</tr>
<tr>
<td>Percutaneous contact with body fluids other than blood (e.g., urine, saliva)</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Contact of intact skin with blood (including high viral load)</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Contact of skin or mucosal membranes with body fluids such as urine or saliva</td>
<td>Not Recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-occupational Exposure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion of HIV-containing blood products (or if HIV contamination is highly probable)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Unprotected insertive or receptive sex with an HIV-infected person</td>
<td>Considered or Recommended*</td>
</tr>
<tr>
<td>Sharing contaminated needle or equipment with IDUs</td>
<td>Recommended*</td>
</tr>
<tr>
<td>Unprotected receptive oral sex with ejaculation with an HIV-infected person</td>
<td>Considered</td>
</tr>
<tr>
<td>Kissing and other sexual contacts without semen-/blood-mucosal membrane contact</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Needlestick from a discarded needle in the community</td>
<td>Not Recommended</td>
</tr>
</tbody>
</table>

Sources: CDC Guidelines for the management of occupational exposure to HIV 2005; UK guidelines for the use of post-exposure prophylaxis for HIV following sexual exposure 2011

* Only recommended if source person has detectable viral load. Consider if serostatus of source is unknown and person belongs to or comes from high prevalence group/area

**Potential risks of PEP**

The risks of PEP are primarily connected with the adverse effects of the antiretrovirals used, most frequently gastrointestinal symptoms such as nausea, vomiting or diarrhea. Changes of hematology, transaminases or creatinine are also possible. Additionally, there have been reports of elevated triglycerides and cholesterol levels, and insulin resistance even with short-term use of PIs (Parkin 2000).

It is unknown whether the temporary use of antiretroviral agents may lead to long-term side effects, but this seems to be secondary since the main emphasis is to prevent a chronic and potentially life-threatening disease. For pregnant women, particular caution is required since data concerning teratogenicity are lacking.

**Initial interventions**

According to current guidelines, different procedures are recommended following exposure to HIV, depending on the type of exposure. Following needlestick or cut injuries with HIV-contaminated instruments, fluid should be expressed by squeezing the tissue surrounding the wound and striking out proximal blood vessels towards the wound. Too intense massage or contusions should be avoided. The wound should be flushed with an alcoholic virucidal antiseptic for a minimum of 10 minutes. For
skin that has been in contact with blood or body fluids removal of the infectious material and subsequent extensive disinfection with a skin antiseptic appears sufficient. After contamination of an eye, immediate flushing with water or antiseptic solutions is recommended. The oral cavity should be washed several times (about 10–15 seconds each) with an aqueous solution or alcohol after contact with potentially infectious material.

Persons who, through sexual exposure, have had contact with anal or genital mucosae from infectious material, should wash the penis with soap and water; genital mucosae should be flushed with water after urination in order to wash contaminated material from the urethra. Intense deep washing of the vagina or enemas are not recommended due to an elevated risk of injuries. Following these initial interventions, an expert in HIV treatment and antiretroviral therapy should be consulted for the decision on whether pharmaceutical PEP needs to be initiated.

Comprehensive evaluation and accurate documentation of the course of the accident is very important, especially for occupational exposure. The process of informing the patient about the risks of PEP needs to be documented carefully and the patient should sign an informed consent.

**Initiation of PEP**

Timing is the most crucial factor for initiation of PEP. The best chance to prevent transmission is within the first 24 hours of exposure, preferably within 2 hours after exposure. A deferred initiation leads to the risk of systemic spread of the virus increases. Initiating PEP after more than 72 hours following exposure does not seem reasonable.

In this short time frame, if consultation with a physician experienced in HIV treatment is not possible, it might be advantageous to just initiate PEP. Interrupting a regimen that is not indicated is always an option.

Actual recommendations prefer a regimen with a combination of antiretroviral agents given for 4 weeks, preferably consisting of two NRTIs and one PI (Table 3). NNRTIs, especially nevirapine, should not be used for PEP because of the risk of severe adverse effects (hepatotoxicity) (CDC 2001). For efavirenz, such severe adverse effects have not been reported but the impact of possible CNS effects, particularly in the first weeks of intake, limits its use for PEP.

Recent publications discuss the possibility to use only a two-drug therapy for PEP if the potential risk of transmission is low (Landovitz 2009, IAS 2010). This practice may be of interest in well-observed populations but it seems to be too early to be established as a general recommendation.

When starting PEP, knowledge of viral resistance against antiretroviral agents of the source person should be taken into account as far as possible; in many cases, this

<table>
<thead>
<tr>
<th>Needlestick or cut injury</th>
<th>Contamination of damaged skin, eye or oral cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressing fluid by squeezing the tissue surrounding the wound (≥1 minute)</td>
<td>Intensive washing with easily accessible liquid: water or isotonic saline solution, possibly PVP iodine solution</td>
</tr>
</tbody>
</table>

**Figure 1.** Recommended initial interventions after HIV exposure (Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2008)
information will not be available. Therefore use of standard regimens for PEP has proven practical. Recommended combinations are shown in Table 3. Except for nelfinavir, all PIs are recommended to be boosted with ritonavir.

Beside the standard drugs, other agents such as enfuvirtide (Fuzeon®), raltegravir (Isentress®) and maraviroc (Selzentry® or Celsentri®) have been approved for HIV therapy more recently. These agents with their new mechanisms of inhibiting viral cell entry or integration might also be interesting with regard to increasing efficiency of PEP. Due to these facts and its good tolerability profile raltegravir has been recently included in the latest UK guidelines as an alternative to protease inhibitor use, in special cases. Experience with the use of integrase inhibitors in PEP is limited and the high costs currently prevent routine use.

During pregnancy, PEP should only be used after careful consideration of the benefits, since there are only limited data on the teratogenic effects. In any case, advice of a physician experienced in HIV treatment and pregnancy should be obtained.

After contact with potentially infectious material, not only HIV, but other diseases might be transmitted. Hepatitis B/C testing should also be performed. Persons exposed to HBV should receive hepatitis B immunoglobulin and a vaccine series simultaneously if they have no sufficient vaccination status.

Unprotected sexual contacts should highlight the possibility of transmissions of other STDs such as syphilis or gonorrhea. STD testing is recommended between 2–4 weeks after exposure.

Table 3: Recommended antiretroviral combinations for HIV Post-Exposure Prophylaxis*.

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + FTC (Truvada®)</td>
<td>lopinavir/r (Kaletra®) or</td>
</tr>
<tr>
<td>AZT + 3TC (Combivir®)</td>
<td>other boosted PI (atazanavir/r, darunavir/r) or</td>
</tr>
<tr>
<td></td>
<td>raltegravir (Isentress®) or</td>
</tr>
<tr>
<td></td>
<td>efavirenz (Sustiva® or Stocrin®)</td>
</tr>
</tbody>
</table>

* Sources: CDC Guidelines for the management of occupational exposure to HIV 2005; UK guidelines for the use of post-exposure prophylaxis for HIV following sexual exposure 2011; German-Austrian Recommendations for PEP against HIV infection 2008

Note: Efavirenz often causes CNS side effects in the first few weeks of use and it is contraindicated in pregnancy

Management of PEP

After initiation of PEP, the patient should not be discharged without a follow-up consultation. Persons exposed to HIV are under high psychological pressure. In addition to talking with and listening to the patients, it should be emphasized to them that there is generally a low risk of transmission and no need to over-worry. If there is a patient organization in the area that works on prevention and PEP, the person may be given their telephone number for further consultation.

Adverse effects often include gastrointestinal symptoms. Changes in hematology, liver enzymes, and/or creatinine are less frequent. However, tests for these side effects should be conducted after 14 days and at the end of the course of PEP. Despite close monitoring, different studies report discontinuation rates of 15–30% (Lancombe 2006, Sonder 2005+2007).

At the end of a completed course or discontinued PEP, HIV testing should be performed after 6 weeks and 3 months. An HIV PCR which may indicate an early infection before seroconversion would only be helpful if there is reasonable suspicion of transmission of HIV infection.

In any case, the patient should be counseled to always practice safer sex.
References


PART 6

Drugs
35. Drug Profiles

CHRISTIAN HOFFMANN

3TC (lamivudine)

Manufacturer: ViiV Healthcare.

Indication and trade names: as component of a combination ART for both naïve and pretreated HIV-infected patients. Of note, the lower dosage of 3TC which is approved for Hepatitis B is not recommended in HIV patients. 3TC is a component of the following:

- Epivir® tablets, 150 mg or 300 mg 3TC.
- Epivir® oral solution, 10 mg per ml 3TC.
- Combivir® film-coated tablets, 150 mg 3TC+300 mg AZT.
- Trizivir® film-coated tablets, 150 mg 3TC+300 mg AZT+300 mg ABC.
- Kivexa® (USA: Epzicom®) film-coated tablets, 300 mg 3TC+600 mg ABC.
- Zeffix® film-coated tablets, 100 mg 3TC. Caution: Only for HBV, never for HIV!
- Zeffix® oral solution, 5 mg per ml. Only for HBV, never for HIV (lower dosage!)

Standard dose: 300 mg QD or 150 mg BID. Children receive 4 mg/kg with a maximum of 150 mg BID. Dose adjustment is required with reduced creatinine clearance. For patients with creatinine clearance of between 30–49 ml/min, a dose of 150 mg QD is recommended. Below 30, only the oral solution should be used.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Initial Dose</th>
<th>Maintenance dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50, 30–49</td>
<td>150 mg (15 ml)</td>
<td>150 mg (15 ml) QD</td>
</tr>
<tr>
<td>15–29</td>
<td>150 mg (15 ml)</td>
<td>100 mg (10 ml) QD</td>
</tr>
<tr>
<td>5–14</td>
<td>150 mg (15 ml)</td>
<td>50 mg (5 ml) QD</td>
</tr>
<tr>
<td>&lt;5</td>
<td>50 mg (5 ml)</td>
<td>25 mg (2.5 ml) QD</td>
</tr>
</tbody>
</table>

Side effects: mild and uncommon. Fatigue, nausea, vomiting, diarrhea, headache, insomnia and myalgia may occur, but are usually due to the other drugs in the combination (see AZT and ABC). Polyneuropathy, pancreatitis, anemia and lactic acidosis are rare.

Comments: Usually well-tolerated, 3TC remains an often-prescribed NRTI, even fourteen years after the date of its first registration in 1996. 3TC is available in different dosages and several fixed dose combination drugs. Resistance to 3TC develops quickly but enhances the viral susceptibility to AZT and impairs viral fitness. 3TC is also effective against hepatitis B (attention: development of HIV resistance can be quite fast when used as an HBV monotherapy. In addition, there is a risk of HBV rebound upon 3TC discontinuation in an ART regimen). The dose required for HBV treatment is lower than that approved for HIV and should never be used in HIV infected patients.

For detailed information see page: 69

Abacavir (ABC)

Manufacturer: ViiV Healthcare.

Indications and trade name: as component of a combination ART for both naïve and pretreated HIV patients. Abacavir is a component of the following:

- Ziagen® film-coated tablets, 300 mg ABC.
- Ziagen® oral solution, 20 mg per ml.
• **Kivexa®** (USA: Epzicom®) film-coated tablets, 600 mg ABC+300 mg 3TC.
• **Trizivir®** film-coated tablets, 300 mg ABC+150 mg 3TC+300 mg AZT.

**Standard dose**: 300 mg BID or 600 mg QD, with or without food. Although mainly metabolized by the liver, abacavir should be avoided in patients with severe renal insufficiency (GFR <20 ml).

**Side effects**: abacavir causes a hypersensitivity syndrome (HSR) in about 2 to 8% of patients. HSR usually occurs within the first six weeks after initiation of treatment. Pruritus and rash are common, but may also be absent. HSR may present as just fever and slowly developing malaise. Gastrointestinal complaints (nausea, diarrhea, abdominal pain) and fatigue are also possible, but not necessarily linked to the HSR. Elevated liver function tests, insomnia, dizziness, breathlessness, sore throat or cough are rare. Before starting abacavir, a test for the HLA-B*5701 allele is strongly recommended. HLA testing reduces the HSR risk considerably, but not completely. Rechallenge after suspected HSR may be fatal and is contraindicated. It is also contraindicated after treatment interruption if HSR cannot be definitively ruled out in retrospect. A slightly elevated risk of myocardial infarction is discussed controversially. The mechanism for this is not clear.

**Comments**: Abacavir is an NRTI (guanosine analog) with good CNS penetration which is mainly used in the fixed dose combination with 3TC. Abacavir is usually well-tolerated and has little mitochondrial toxicity. The main problem with abacavir is a hypersensitivity reaction (HSR) which can be avoided by prior HLA testing. For detailed information see page: 67

**Acyclovir**

**Manufacturer and trade names**: diverse manufacturers, therefore several trade names such as Aciclobeta®, Aciclostad®, Aciclovir®, Zovirax®.

**Indications**: herpes zoster, as well as prophylaxis of serious herpes simplex infections in immunosuppressed adults.

**Dose**: depends on herpes lesions.

For **herpes zoster** 800 mg orally five times a day for one week. In cases of disseminated or complicated herpes zoster, 10 mg/kg IV TID. Reduce dosage in having patients with renal insufficiency at a creatinine clearance of 25–10 ml/min, 800 mg TID, and at <10 ml/min, 800 mg BID.

For **genital HSV infection**, 400 mg five times a day. In severe cases (ulcerating genital herpes) intravenous treatment with 5–10 mg/kg IV TID. For HSV encephalitis or HSV esophagitis 10 mg/kg IV TID.

**Side effects**: uncommon. Headache, nausea and elevation of creatinine may occur. Phlebitis can occur with intravenous dosing.

**Comments**: approved and well tolerated HZV/HSV medicine. Generics are significantly cheaper than the originally introduced formulation, Zovirax®. Initiation of treatment for HSV infections should be within the first 24 hours after appearance of symptoms and when possible, for HZV infection within the first 4 days. Adequate fluid intake is important. Newer studies reported on a moderate but significant effect on HIV replication.

For detailed information see page: 247, 378

**Agenerase®**, see Amprenavir.

**Ambisome®**, see Amphotericin B.
Amphotericin B

Manufacturer: Bristol-Myers Squibb (Amphotericin B®), Gilead (Ambisome®), Dermapharm (Ampho-Moronal®).

Indications and trade names: diverse. Amphotericin B® is indicated for organ mycoses and generalized mycoses, primarily candidiasis, aspergillosis, cryptococcosis and histoplasmosis. AmBisome® (more as twice as expensive) is indicated only if conventional Amphotericin B® is contraindicated due to kidney dysfunction or intolerance. The indication also applies to visceral leishmaniasis. Suspension and tablets are only licensed for oral candidiasis. Amphotericin is a component of the following:

- Amphotericin B® injection vial, 50 mg of powder.
- AmBisome® injection vial, 50 mg of dry agent.
- Ampho-Moronal® suspension, 100 mg/ml.
- Ampho-Moronal® lozenges, to 10 mg.

Dosage (per day): when using Amphotericin B®, always apply test dose first (see below). For aspergillosis 1.0–1.5 mg/kg, for other mycoses 0.5–1 mg/kg usually suffices. Maximum dose is 1.5 mg/kg. In case of over-dosage, respiratory and cardiac arrest can occur. Dose of Ambisome®: initial 1 mg/kg QD, if necessary may be gradually increased to 3 mg/kg.

Side effects: nephrotoxicity, hypokalemia and gastrointestinal complaints. Frequent: fever, chills, and hypotension approximately 10–20 min after starting infusions. Thrombophlebitis (non-liposomal amphotericin B only via a central venous line). Side effects are generally less severe with Ambisome®.

Comments: daily monitoring of electrolytes, creatinine, BUN, ALT, blood count. A central venous line is always necessary due to hypokalemia and the usually required potassium substitution. Sodium should be kept at normal levels. Do not combine with other nephrotoxic drugs.

Always prehydrate with 1000 ml 0.9% NaCl. Always first test dose with 5 mg in 250 ml 5% glucose over 30–60 min with strict monitoring of blood pressure and pulse for the first hour. If the test dose is tolerated, then half of the planned maintenance dose may subsequently be given on the same day. In cases of fever or chills (can be very impressive), the following may be repeated after 30 min: 50 mg pethidine (e.g., Dolantin®) IV plus 1 ampule clemastine (e.g., Tavegil®), steroids only if complaints persist (prednisolone 1 mg/kg).

If side effects are severe, then switch to Ambisome®, which is probably not more effective than conventional amphotericin B but significantly better tolerated and less nephrotoxic (no test dose, no prehydration, no central line necessary). Never mix amphotericin infusions, and always protect from light. Infuse slowly. The longer the infusion time (>3 hours), the better the tolerability. Always use 5% glucose as a diluting agent.

Amprenavir (Agenerase®), replaced by fosamprenavir in 2008. See below.
Atazanavir

**Manufacturer:** Bristol-Myers Squibb.

**Indications and trade name:** Indicated for treatment of HIV-infected adults as part of a combination. Since 2008, it has been used for both pretreated and ART-naïve patients. Atazanavir is a component of the following:

- Reyataz® capsules, 150 mg, 200 mg, 300 mg.

**Dosage:** 300 mg atazanavir QD combined with 100 mg ritonavir. If ritonavir is not tolerated, atazanavir can be given 400 mg OD, without booster (combination with tenofovir should then be avoided). If atazanavir is combined with efavirenz (even if boosted), increase dosage to 400 mg. The capsules should be swallowed (not chewed) and taken with a meal.

**Side effects:** very often hyperbilirubinemia (up to 50%), also with jaundice; rarer elevated transaminases. Diarrhea, nausea, vomiting, headache, insomnia and abdominal pain are also relatively rare. In contrast to other PIs, there is less dyslipidemia. The effect on lipodystrophy remains unknown. Rarely nephrolithiasis.

**Interactions, warnings:** Do not combine with indinavir. Caution with impaired liver function. Atazanavir is contraindicated in patients with Child-Pugh B and C. Be careful with proton pump inhibitors (PPI) and antacids! Combinations with the following pharmaceuticals are contraindicated: cisapride, midazolam, triazolam, simvastatin, lovastatin, ergotamines, calcium antagonists. Life-threatening interactions may occur with concomitant administration of amiodarone, lidocaine (systemic dosing), tricyclic anti-depressants and quinidine (measure plasma levels). Do not combine boosted atazanavir with clarithromycin. It should not be given with rifampin (reduces plasma levels of atazanavir by 90%). Reduce the rifabutin dose by 75% (instead of 300 mg daily, give only 150 mg every other day or three times per week).

**Comments:** PI with a favorable lipid profile and a low pill burden which can be taken once daily. Should be boosted with ritonavir. The most important side effect is hyperbilirubinemia, which often presents as jaundice. There are some relevant interactions – primarily with proton pump inhibitors and antacids, but also with tenofovir, efavirenz, nevirapine and ddI.

For detailed information see page: 87

Atovaquone

**Manufacturer:** GlaxoSmithKline.

**Indications and trade name:** Acute treatment of mild or moderate PCP in cases of hypersensitivity to cotrimoxazole; in combination with proguanil for the treatment and prophylaxis of malaria. Off-label, can be used as PCP prophylaxis (as reserve) and as acute treatment of cerebral toxoplasmosis.

- Atovaquone is a component of the following:
  - Wellvone® suspension, 750 mg atovaquone/5 ml.
  - Malarone® film-coated tablets, 250 mg atovaquone and 100 mg proguanil.

**Dose:** as therapy for acute PCP (or toxoplasmosis): 750–1500 mg BID (i.e., 1–2 measuring spoons of 5 ml BID) for 21 days. For prophylaxis 750 mg BID (i.e., 1 measuring spoon of 5 ml BID) or 1500 mg QD.
Side effects: gastrointestinal complaints such as nausea, vomiting and diarrhea are frequent (but often mild), as are rashes, which occur in approximately 20% of patients. Less common are headache and insomnia. Elevated liver enzymes, amylase. Anemia, leukopenia (rare).

Interactions, warnings: Atovaquone should be taken with meals, ideally with fatty dishes, as this improves absorption. Rifampin and possibly also rifabutin lower plasma levels of atovaquone by approximately 50%. Fluconazole probably increases levels.

Comments: Nowadays, used only rarely. Atovaquone is considerably more expensive than other drugs for PCP prophylaxis.

Atripla®

Manufacturer: co-produced by Gilead Sciences, Bristol-Myers Squibb and MSD.

Indications and trade name: adult HIV-infected patients. It should be noted that in Europe, approval for Atripla® is more strict than in the US. The EMA has only approved the use of Atripla® in patients who have already achieved virologic suppression to below 50 copies/ml on their current antiretroviral regimen for at least three months. Furthermore, patients must not have experienced virologic failure with an earlier treatment combination or be known to have resistance to any of the drugs in Atripla®.

- Atripla® film-coated tablets with 600 mg EFV, 200 mg FTC, 300 mg TDF.

Dose: one tablet daily in the evening, unchewed, on an empty stomach.

Comments: the first complete ART in one single tablet per day; a convenient simplification. In Europe, the above-mentioned limitation of the indication applies. For side effects, see sections on tenofovir (caution with renal function), efavirenz (CNS side effects) and FTC.

For detailed information see page: 177

Azithromycin

Manufacturer and trade names: diverse, therefore several trade names, such as Azithromycin®, Zithromax®, Utreon®.

Indications: treatment and prophylaxis of MAC infection. Infections of the upper and lower respiratory tract, otitis media. Uncomplicated gonorrhea, uncomplicated genital infections with Chlamydia trachomatis, chancroid. Azithromycin is a component of the following:

- Utreon® film-coated tablets, 600 mg.
- Zithromax® film-coated tablets, 250 mg and 500 mg.
- Zithromax® dry suspension, 200 mg per 5 ml.

Dose: primary prophylaxis of disseminated MAC infection: 1200 mg azithromycin once weekly (2 tablets Utreon® 600 mg per week). MAC treatment: 1 tablet Utreon® 600 mg QD, only in combination with ethambutol and rifabutin. Infections of the respiratory tract: 500 mg QD for 3 days. Uncomplicated gonorrhea, uncomplicated genital infections or chancroid with Chlamydia trachomatis: 1000 mg azithromycin may be given as a single dose.

Comments: This macrolide antibiotic has a long half-life and good tissue penetration. In patients with genital infections, a single dose is sufficient. For respiratory tract infections, azithromycin should be given for 3–5 days. In HIV infection, azithromycin has been often used as (permanent) prophylaxis or treatment of MAC infections.

AZT (zidovudine)

Manufacturer: Viiv Healthcare.

Indications and trade name: as component in a combination ART for both naïve or pretreated HIV patients. Prevention of maternal-fetal HIV transmission. AZT is a component of the following:

- Retrovir® hard capsule, 100 mg AZT and 250 mg AZT.
- Retrovir® film-coated tablets, 300 mg AZT.
- Retrovir® oral solution, 100 mg AZT per 10 ml.
- Retrovir® concentrate, 10 mg AZT per ml (5 injection vials 200 mg each).
- Combivir® film-coated tablets, 300 mg AZT+300 mg 3TC.
- Trizivir® film-coated tablets, 300 mg AZT+150 mg 3TC+300 mg abacavir.

Dose: 250 mg BID (in Combivir® and Trizivir® 300 mg BID). In patients with serious renal impairment (creatinine clearance below 20 ml/min, hemodialysis) 300 mg daily. With severe hepatic impairment 100 mg TID.

Side effects: nausea, vomiting, abdominal discomfort, headache, myalgia, and dizziness. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Elevations in LDH, CPK and transaminases may occur. Episodes of lactic acidosis are rare.

Interactions, warnings: do not combine with d4T. There is increased myelotoxicity if used with other myelosuppressive drugs, especially gancyclovir but also co-trimoxazole, dapson, pyrimethamine, interferon, sulfadiazine, amphotericin B, ribavirin and various other chemotherapeutic agents. Ribavirin antagonizes the antiviral activity of AZT in vitro (combination should be avoided). Initially monthly monitoring of blood count, transaminases, CPK and bilirubin. Gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks. Anemia can develop even after months. AZT should always be a component of transmission prophylaxis.

Comments: The first NRTI (thymidine analog) on the market and the oldest HIV drug of all (registered in 1987). Still partner in some ART therapies. However, due to numerous toxicities (myelotoxicity, mitochondrial toxicity) AZT is prescribed considerably less frequent than previously. Remains important in transmission prophylaxis. Comprehensive data, good penetration of the blood-brain barrier. Generics to be expected.

For detailed information see page: 68
Boceprevir

Manufacturer: MSD.

Indications and trade name: Patients with chronic hepatitis C, genotype 1. Boceprevir should only be used in combination with peginterferon alfa and ribavirin (PEG+RIBA), usually after a lead-in phase of four weeks with PEG+RIBA. Treatment duration (24–44 weeks) depends on treatment response, previous HCV therapy and on preexistent cirrhosis.

- Victrelis® hard capsules, 200 mg.

Dose: 800 mg administered orally TID (four capsules every 7–9 hours) with food (a meal or light snack). A dose reduction is not recommended. In patients with renal impairment, no dose adjustment is required.

Side effects: Nausea, fatigue, headache, dysgeusia (specific! Alteration of taste – patients should be informed). In particular, anemia and neutropenia seem to become more frequent and severe when boceprevir is added to PEG+RIBA. Anemia seems to be the main reason for discontinuation of therapy.

Interactions, warnings: do not use in other HCV genotypes than genotype 1. Boceprevir is a strong CYP3A inhibitor, and numerous interactions must be considered prior to and during therapy. Do not combine with lopinavir/r and darunavir/r as levels of both PIs and of boceprevir are markedly reduced. Concomitant administration of boceprevir and atazanavir/r resulted in reduced exposures to atazanavir/r but not to boceprevir (individual decision, TDM of atazanavir). Limited or no interactions with efavirenz and raltegravir. Do not combine with carbamazepine, midazolam, rifampin, atorvastatin, simvastatin, triazolam, amlodipin.

Comments: New HCV drug which was approved by the FDA in May 2011. In Europe, the first HCV-PI on the market (approval July 2011). Limited but promising data in HIV-infected patients with HCV genotype 1 coinfection. Due to numerous toxicities of the triple HCV therapy, the use of boceprevir is only recommended in experienced centers.

For detailed information see page: 509

Caelyx®, see Doxorubicin, liposomal.

Cidofovir

Manufacturer: Gilead Sciences.

Indications and trade name: CMV retinitis in patients without renal dysfunction, mainly in cases of resistance/contraindications to gancyclovir or foscavir. Some experts use cidofovir for PML (off-label use), although efficacy is uncertain.

- Vistide® injection vial, 375 mg per 5 ml (= 75 mg/ml).

Dose: induction dose 5 mg/kg IV weekly, by day 21 maintenance therapy with 5 mg/kg IV every two weeks. A precise treatment plan (see below) is necessary.

Side effects: renal failure, which can occur even after 1 dose of cidofovir. Less frequent: neutropenia, dyspnea, alopecia, decreased intraocular pressure, iritis, uveitis. Fever, chills, headache, rash, nausea and vomiting are usually caused by probenecid and should subside within 12 hours. Complaints may be lessened with food intake, antipyretics, or antiemetics.
**Warnings:** renal function (serum creatinine, electrolytes, proteinuria) should be checked before each dose of cidofovir. If serum creatinine increases by more than 0.3 mg/dl, reduce dose to 3 mg/kg. If serum creatinine increases by more than 0.5 mg/dl above levels prior to treatment, discontinue cidofovir. Cidofovir is always contraindicated at serum creatinine levels >1.5 mg/dl or creatinine clearance below 55 ml/min or proteinuria >100 mg/dl. Always ensure sufficient hydration. Cidofovir should be given according to the following scheme:

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>–3 h</td>
<td>2 g probenecid (4 tablets of 500 mg), prior poss. 20 drops metamizole plus 50 mg prednisolone</td>
</tr>
<tr>
<td>–3 to –1 h</td>
<td>1000–2000 ml 0.9% NaCl</td>
</tr>
<tr>
<td>0 to + 2 h</td>
<td>Cidofovir in 500 ml 0.9% NaCl over 1–2 h. Concurrently 1000 ml 0.9% NaCl.</td>
</tr>
<tr>
<td>+4 h</td>
<td>1 g probenecid (2 tablets of 500 mg), prior 20 drops metamizole</td>
</tr>
<tr>
<td>+10 h</td>
<td>1 g probenecid (2 tablets of 500 mg), prior 20 drops metamizole</td>
</tr>
</tbody>
</table>

Potentially, nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, IV pentamidine or vancomycin must be avoided or discontinued at least 7 days prior to treatment with cidofovir. Probenecid is necessary to reduce nephrotoxicity. Probenecid has drug interactions with acetaminophen, acyclovir, angiotensin converting enzyme inhibitors, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide and theophylline.

**Comments:** Reserve drug in severe CMV infections. Rarely used due to considerable nephrotoxicity. The effect in PML is more than questionable.

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**Clarithromycin**

**Manufacturer and trade names:** diverse manufacturers, therefore several trade names, such as Clarithromycin-CT®, Klacid®, Mavid®.

**Indications:** prophylaxis and treatment of MAC disease. Infections of the respiratory tract, ENT area and the skin. Clarithromycin is a component of the following (selection):

- Mavid® film-coated tablets, 500 mg.
- Klacid® film-coated tablets, 250 mg.

**Dose:** with MAC 500 mg BID, both for primary prophylaxis and for maintenance therapy. 50% dose reduction if creatinine clearance is below 30 ml/min. At respiratory tract infections 250 mg BID will suffice.

**Side effects:** mainly gastrointestinal complaints such as nausea, vomiting, abdominal discomfort and diarrhea; in addition, allergic skin reactions, headache, elevated transaminases, alkaline phosphates and bilirubin.

**Interactions, warnings:** no concurrent treatment with rifampin, carbamazepine, cisapride, terfenadine, pimozide and other macrolide antibiotics such as erythromycin or azithromycin. Lopinavir and ritonavir increase clarithromycin levels. If administered concurrently, oral treatments with clarithromycin and AZT should be taken 1–2 hours apart.

**Comments:** Macrolide antibiotic with a shorter half-life than azithromycin. The daily dose should not exceed 500 mg BID.
Clindamycin

**Manufacturer and trade name:** diverse manufacturers, therefore several trade names, such as Aclinda®, Clindabella®, Clindamycin-ratiopharm®, Sobelin®.

**Indications:** for HIV-infected patients, mainly cerebral toxoplasmosis. Also for serious infections by anaerobes, staphylococci (because of good tissue and bone penetration also used in dentistry).

**Dose:** 600 mg IV QD or 600 mg oral QD (always with pyrimethamine and leucovorin). Half dose for (oral) maintenance therapy. In renal failure, reduce dose to a quarter or a third of the normal dose.

**Side effects:** diarrhea in 10–30% of patients. Allergies are also frequent and often require discontinuation. In cases of infection with *Clostridium difficile* “Pseudomembranous colitis”, the clinical spectrum ranges from mild watery stool to severe diarrhea with blood and mucous, leukocytosis, fever and severe abdominal cramps which may progress to peritonitis, shock and toxic megacolon.

**Warnings:** Clindamycin is contraindicated in inflammatory bowel disease and antibiotic-induced colitis. Caution with reduced hepatic or renal function and in asthma. No concurrent administration of antiperistaltics. For every occurrence of diarrhea on clindamycin, discontinue and give metronidazole (or vancomycin).

**Comments:** Still used in patients with cerebral toxoplasmosis. Several side effects, caution with colitis.

Combivir®

**Manufacturer:** ViiV Healthcare.

**Indications and trade name:** as a component in combined therapy for ART naïve or pretreated HIV patients.

- Combivir® film-coated tablets, 300 mg AZT+300 mg 3TC.

**Dose:** 1 tablet BID. In cases of reduced renal function (creatinine clearance below 50 ml/min) and anemia, Combivir® should be replaced with the individual drugs to allow for adjustment of 3TC and AZT doses.

**Comments:** the first fixed-dose combination in HIV medicine (1998). For a long time one of the most used drugs. While it is prescribed less, it remains an alternative in certain circumstances. See AZT for side effects.

For detailed information see page: 73

Complera® (Europe: Eviplera®)

**Manufacturer:** Gilead Sciences and Janssen-Cilag.

**Indications and trade name:** For ART naïve HIV patients with less than 100,000 copies/ml.

- Complera® film-coated tablets with 25 mg RPV, 200 mg FTC, 300 mg TDF.

**Dose:** 1 tablet per day. Should be taken with a meal. In cases of reduced renal function (creatinine clearance below 50 mL/min), Complera® should be avoided.

**Side effects:** Usually well tolerated. Rash, mostly mild. For side effects, see sections on tenofovir (caution with renal function, Fanconi syndrome), rilpivirine and FTC.
Interactions, warnings: For interactions, see also sections on tenofovir, rilpivirine and FTC. Complera® should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, proton pump inhibitors (PPIs), St. John’s wort (Hypericum perforatum). In patients with HIV-1 RNA greater than 100,000 copies/mL, the observed virologic failure rate conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to Atripla®.

Comments: The second complete ART (fixed dose combination, FDC) in one single tablet per day, approved in 2011. In highly viremic patients, resistance rates with this well-tolerated FDC are higher than seen with Atripla®. Approval is limited to naïve patients with low viremia. As increase in gastric PH decreases rilpivirine plasma concentrations, caution is needed with antacids and PPIs.

For detailed information see page: 81

Co-trimoxazole (Trimethoprim-sulfamethoxazole)

Manufacturer and trade names: diverse manufacturers, therefore several trade names, such as Cotrimratiorpharm®, Cotrimstada®, Eusaprim®.

Indications: Prophylaxis and treatment of Pneumocystis pneumonia (PCP). Prophylaxis and treatment (reserve drug) of cerebral toxoplasmosis. Also for other infections, for example urinary tract infections.

• Cotrim 960® tablets, 160/800 mg TMP/SMX.
• Cotrim forte® tablets, 160/800 mg TMP/SMX.
• Cotrim 480® tablets, 80/400 mg TMP/SMX.
• Bactrim® liquid suspension, adults (16/80 mg/ml), children (8/40 mg/ml).
• Bactrim® ampule, 80/400 mg TMP/SMX.

Dose: As PCP prophylaxis: 80/400 mg QD or 160/800 mg TMP/SMX 3 x/week. As PCP therapy: 5 mg/kg (based on TMP) orally or IV q 8 h x 21 days, therefore usually 5 to 6 ampules each 80/400 mg TID. Toxoplasmosis prophylaxis: 1 tablet (160/800 mg) QD. With reduced renal function, use half-dose with creatinine clearance of 15 to 50 ml/min. Co-trimoxazole is contraindicated below 15 ml/min.

Side effects: allergies. High intravenous doses also cause myelotoxicity (anemia, neutropenia), nausea, vomiting, headache, raised transaminases. Treatment can often be continued in cases of mild allergy.

Comments: caution with sulfonamide allergy. Co-trimoxazole oral suspension for children can be used for desensitization. Increase the dose slowly over six days from 12.5, 25, 37.5, 50 and 75 to 100% of the 480 mg tablet dose. Co-trimoxazole can increase levels of anticoagulants and phenytoin and reduce the efficacy of oral contraceptives.

Crixivan®, see Indinavir.

Cymeven®, see Gancyclovir.
**d4T (stavudine)**

**Manufacturer:** Bristol-Myers Squibb.

**Indications and trade name:** HIV infection. In view of the side effects seen with the drug, the EMA recommended in February 2011 that the marketing authorisation for d4T should be renewed with restrictions. The drug “should only be used when there are no appropriate alternatives, and for the shortest possible time”.

- Zerit® hard capsule, 20, 30 and 40 mg.
- Zerit® powder for preparation of an oral solution, 1 mg/ml.

**Dose:** 40 mg BID for body weight >60 kg, 30 mg BID for body weight <60 kg. On empty stomach or with a light meal. In renal failure:

<table>
<thead>
<tr>
<th>Weight</th>
<th>CrCl 26-50 ml/min</th>
<th>CrCl below 26 ml/min (incl. dialysis patients)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 kg</td>
<td>15 mg BID</td>
<td>15 mg QD</td>
</tr>
<tr>
<td>&gt;60 kg</td>
<td>20 mg BID</td>
<td>20 mg QD</td>
</tr>
</tbody>
</table>

* Hemodialysis patients should take d4T after dialysis, and at the same time on the other days.

**Side effects:** more than other NRTIs, mitochondrially toxic, lipoatrophy. Peripheral neuropathy, especially in combination with ddI (up to 24%). The following are less frequent: diarrhea, nausea, headache, hepatic steatosis and pancreatitis. Very rare, but potentially fatal are lactic acidosis, which occurs mostly in combination with ddI (especially in pregnancy).

**Comments:** This thymidine analog was long-considered an important alternative to AZT. Due to the mitochondrial toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy), the use of d4T is no longer recommended. Since 2011, use is severely restricted in both adults and children.

*For detailed information see page: 69*

**Dapsone**

**Manufacturer:** Fatol.

**Indications:** rarely used reserve drug for prophylaxis of PCP and cerebral toxoplasmosis. Other (rare) areas of application are in dermatology (bullous pemphigoid), rheumatology and leprosy.

- Dapson-Fatol® tablets, 50 mg.

**Dose:** 100 mg daily. Alternative: 50 mg QD + pyrimethamine 50 mg/week + folinic acid 30 mg/week.

**Side effects:** allergies (pruritus, rash), fever. Frequently hemolytic anemia (with almost obligatory elevation of LDH), hepatitis.

**Comments:** dapsone is contraindicated in severe anemia and must be used with caution in G-6-PD deficiency. Not to be taken simultaneously with ddI, antacids and H2 blockers (to be taken at least two hours apart). Rifabutin and rifampin lower dapsone levels.

**Daraprim®,** see Pyrimethamine.
Darunavir

**Manufacturer:** Janssen-Cilag.

**Indications and trade name:** to be used in either ART-naïve or pretreated HIV patients.

- Prezista® tablets, 400 and 600 mg.
- Prezista® tablets, 75 and 150 mg (pediatric formulation).

**Dose:** 800 mg QD (2 tablets of 400 mg) + 100 mg ritonavir QD. In patients with extensive pretreatment (or/and limited resistance mutations), it is recommended to use 600 mg BID (1 tablet of 600 mg) + 100 mg ritonavir BID.

In 2009, darunavir was also approved for children aged 6 years and older. Recommended dosage is 375/50 mg BID (Wt ≥20 kg to <30 kg), 450/60 BID (Wt ≥30 kg to <40 kg). At ≥40 kg, adult dosage is recommended.

**Side effects:** the usual PI side effects, with (moderate) gastrointestinal complaints and dyslipidemia. The dyslipidemia may not be as pronounced as with other PIs. Data on lipodystrophy is lacking. Rash (7%) within the first 2 weeks, usually mild.

**Interactions, warnings:** darunavir should be taken with or shortly after meals. Caution for sulfonamide allergy. Since darunavir is metabolized by the cytochrome P450 system, some interactions have to be taken into account. Lopinavir and saquinavir lower the plasma levels of darunavir so should be avoided in combination. Also do not combine with St. John’s wort, astemizole, terfenadine, cisapride, pimozide, midazolam, triazolam, erythromycin, rifampicin, phenobarbital, phenytoin, and carbamazepin. Use atorvastatin instead of pravastatin at the lowest dose (10 mg). Dosage adjustments may be required with efavirenz (decreased darunavir levels and increased efavirenz levels), rifabutin (dose should be reduced to 150 mg every two days), calcium antagonists (increased levels), methadone (reduced levels). Interactions with contraceptives may occur. Maximum doses of PDE5 inhibitors when combined with darunavir, 10 mg Cialis® in 72 hours; 2.5 mg Levitra® in 72 hours; 25 mg Viagra® in 48 hours. For further information (azoles, cyclosporine, SSRIs and others) see product information.

**Comments:** Well-tolerated and broadly applicable protease inhibitor that has considerable activity against PI-resistant viruses. Needs to be boosted with ritonavir. Different dosages as well as interactions have to be taken into account.

*For detailed information see page: 88*

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Daunorubicin (liposomal)

**Manufacturer:** Gilead Sciences (Galen Limited), Fresenius.

**Indications and trade name:** AIDS-associated Kaposi sarcoma with <200 CD4 T cells/µl and severe mucocutaneous or visceral involvement.

- DaunoXome® injection vial, 50 mg (25 ml).

**Dose:** 40 mg/m² in 250 ml 5% glucose solution intravenously over 30–60 minutes. Repeat after 2–3 weeks.

**Side effects:** during infusion: back pain, flushing (up to 14%). Symptoms usually occur during the first minutes and resolve when the infusion is slowed or stopped. Fatigue, headaches, chills. Myelosuppression, cardiomyopathy. Beware of paravasation!
Interactions, warnings: liposomal doxorubicin is contraindicated in decompen-sated cardiomyopathy, severe myelosuppression (neutrophils <1,000/µl, platelets <50,000/µl). Cardiological examination is important (ECG, echocardiography: left ventricular ejection fraction, LVEF) before initiation of treatment and at periodic intervals during treatment.

Comments: Compared to pegylated liposomal doxorubicin, treatment with liposomal daunorubicin yields to slightly lower remission rates of KS. However, as capacity constraints for Caelyx® were seen in 2011/2012, DaunoXome® represents an important alternative for KS treatment.

ddc (zalcitabine), manufacturing and distribution was stopped in 2006.

ddI (didanosine)

Manufacturer: Bristol-Myers Squibb.

Indications and trade name: HIV infection.
- Videx® hard capsules, 125, 200, 250 and 400 mg.
- Videx® powder, 2 g.

Dose: 400 mg QD (body weight >60 kg) or 250 mg QD (body weight <60 kg). ddI must be taken on an empty stomach, at least 2 hours after or 1 hour before meals.

Side effects: diarrhea, nausea, headache. Pancreatitis, even after longer periods of treatment. Peripheral polyneuropathy. Rarely lactic acidosis, especially in combination with d4T and ribavirin.

Interactions, warnings: acute and chronic pancreatitis are contraindications, as well therapy with ribavirin. The following drugs should be used with caution: d4T, ethambutol, cisplatin, disulfiram, INH, vincristine, etc (peripheral neuropathy). Concurrent dosing with tenofovir should be avoided because it increases the AUC of ddI by 44%. The ddI dose should be reduced to 250 mg. Tenofovir must be taken two hours before or one hour after ddI. Treatment with indinavir, dapsone, ketoconazole, itraconazole, or tetracyclines should be given 2 hours before or after ddI. Initially, monthly monitoring of amylase, blood count, transaminases and bilirubin. Patients should be informed about the symptoms of pancreatitis. ddI should be discontinued if there is clinical suspicion for pancreatitis with no future rechallenge.

Comments: An early NRTI. Due to considerable toxicity (pancreatitis, polyneuropathy, mitochondrial toxicity) today only used in certain resistance situations. The dose has to be adjusted according to bodyweight. Combinations with tenofovir and d4T should be avoided.

For detailed information see page: 69

Diflucan®, see Fluconazole.
**Delavirdine**

**Manufacturer:** ViiV Healthcare (Pfizer).

**Indications and trade name:** HIV infection. Not licensed in Europe.

- Rescriptor® tablets, 100 mg and 200 mg.

**Dose:** 400 mg TID. The tablets can be dissolved in water.

**Side effects:** rash, usually occurring within the first six weeks of treatment. In uncomplicated cases, give antihistamines. Discontinue if systemic effects such as fever, conjunctivitis, and myalgia occur. Nausea, elevated transaminases.

**Interactions, warnings:** delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

Delavirdine interacts with numerous drugs via reduction of CYP3A activity. It increases the AUC of some PIs (saquinavir, nelfinavir), sildenafil, dapsone, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by ddI, H₂ blockers, carbamazepine, phenytoin and antacids.

**Comment:** delavirdine is rarely used due to high pill burden and drug interactions. This NNRTI was never approved in Europe.

For detailed information see page: 79

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**Doxorubicin (liposomal)**

**Manufacturer:** Janssen-Cilag (Johnson & Johnson).

**Indications and trade name:** AIDS-associated Kaposi’s sarcoma with <200 CD4 cells/µl and severe mucocutaneous or visceral involvement.

- Caelyx® (or Doxil®) injection vial, 10 ml (20 mg) and 25 ml (50 mg).

**Dose:** 20 mg/m² in 250 ml 5% glucose solution intravenously over 30 minutes. Repeat after 2–3 weeks.

**Side effects:** myelosuppression, cardiomyopathy, stomatitis (rarely severe), palmar-plantar erythrodysesthesia (PPE or hand-foot syndrome – erythematous rash which may be very painful. Treatment: cool affected areas). Be careful with extravasations (never SC or intramuscular, never give a bolus).

**Interactions, warnings:** liposomal doxorubicin is contraindicated in decompensated cardiomyopathy, severe myelosuppression (neutrophils <1,000/µl, platelets <50,000/µl).

Cardiological examination is important (ECG, echocardiography: left ventricular ejection fraction, LVEF) before initiation of treatment and at periodic intervals during treatment. If the cumulative dose of 450 mg/m² is exceeded, then an echocardiography is necessary before each further cycle. It is important to inform patients of PPE (may be induced by sweating, pressure, friction – i.e., no tight gloves, no sun, no long warm showers). Cool drinks are favorable. This drug is expensive.

**Edurant®,** see Rilpivirine.
Efavirenz

**Manufacturer:** BMS (Sustiva®); MSD (Stocrin®); Gilead/BMS/MSD (Atripla®).

**Indications and trade name:** HIV infection.

- Sustiva® film-coated tablets, 600 mg, in some countries known as Stocrin®.
- Sustiva® hard capsules, 50 mg, 200 mg.
- Sustiva® solution for oral administration as 30 mg/ml (180 ml = 5.4 g).
- Atripla® film-coated tablets, 600 mg efavirenz +200 mg FTC +300 mg tenofovir.

**Dose:** 600 mg daily preferably before going to bed on an empty stomach.

**Side effects:** CNS symptoms occur frequently in the first weeks. Nightmares, confusion, dizziness, depression, somnolence, impaired concentration, insomnia and depersonalization. A generally mild rash (15%) may also occur in the first weeks, and continued treatment is usually possible. Elevation of liver function tests and biliary enzymes. Dyslipidemia. Occasionally painful gynecomastia.

**Interactions, warnings:** contraindicated in pregnancy. Caution with women of childbearing age. Efavirenz should not be taken with fatty meals (possibly higher absorption and side effects).

Contraindicated for concurrent administration with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptives. Dose increases may be necessary for lopinavir/r (to 3 tablets BID), atazanavir/r (400/100mg), rifabutin (450 mg), methadone (20–30%) and maraviroc (600 mg BID if no boosted PI is given).

**Comments:** Efavirenz is a frequently used and very effective NNRTI. However, it has some CNS side effects. Further disadvantages as with the other members of this drug class include drug interactions, a low resistance barrier and cross-resistance.

For detailed information see page: 79

**Elvitegravir,** see Stribild®.

Emtricitabine (FTC)

**Manufacturer:** Gilead (Emtriva®, Truvada®, Stribild®); Gilead+BMS+MSD (Atripla®); Gilead+Janssen-Cilag (Complera®).

**Indications and trade name:** HIV infection.

- Emtriva® hard capsules, 200 mg FTC.
- Emtriva® solution, 10 mg FTC per ml.
- Truvada® film-coated tablets, 200 mg FTC + 300 mg tenofovir.
- Atripla® film-coated tablets, 200 mg FTC + 300 mg tenofovir +600 mg efavirenz.
- Complera® film-coated tablets with 25 mg RPV, 200 mg FTC, 300 mg TDF.
- Stribild® film-coated tablets with 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 300 mg TDF.

**Dose:** 200 mg QD (solution recommended dose 240 mg = 24 ml). At reduced creatinine clearance, FDCs should be avoided. FTC is adapted as follows:

<table>
<thead>
<tr>
<th>Cr Cl (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–49</td>
<td>200 mg every 2 days</td>
</tr>
<tr>
<td>15–29</td>
<td>200 mg every 3 days</td>
</tr>
<tr>
<td>Below 14 or dialysis</td>
<td>200 mg every 4 days</td>
</tr>
</tbody>
</table>
**Side effects:** Most commonly mild headache, nausea, diarrhea, rash. Possibly hyperpigmentation.

**Comments:** FTC is a well-tolerated cytidine analog comparable to 3TC. FTC has the same resistance profile but has a significantly longer half-life than 3TC. The single preparation is rarely prescribed. FTC is mainly used as a component in different fixed dose combinations. Effective against HBV, beware of viral rebounds after discontinuing FTC.

For detailed information see page: 70

Emtriva®, see Emtricitabine.

Enfuvirtide®, see T-20.

Epivir®, see 3TC.

Eremfat®, see Rifampicin.

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**Ethambutol**

**Manufacturer:** among others Riemser, Fatol.

**Indications and trade names:** tuberculosis, MAC infection.

- EMB-Fatol® tablets, 100 mg.
- EMB-Fatol® film-coated tablets, 250 mg, 400 mg and 500 mg.
- EMB-Fatol® injection solution, 1 g in 10 ml.
- Myambutol® film-coated tablets, 100 mg and 400 mg.
- Myambutol® injection solution, 400 mg/4 ml and 1000 mg/10 ml.

**Dose:** 15 to 25 mg/kg (maximum 2 g) daily, usually 3 x 400 mg tablets QD. Ethambutol should only be given as combination therapy. Dose reduction in renal failure as follows:

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 75 ml/min</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>40–75 ml/min</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>30–40 ml/min</td>
<td>15 mg/kg every second day</td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>Measurement of serum levels required (should be within the range of minimal inhibitory concentration 2–5 μg/ml after 2–4 hours)</td>
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</tbody>
</table>

**Side effects:** ethambutol can lead to optical neuritis with impaired vision (decreased acuity, restricted fields, loss of red-green color discrimination). It is usually reversible if ethambutol is discontinued immediately. Other side effects: nausea, vomiting, abdominal pain, headache, dizziness, pruritus, arthralgia, elevated serum uric acid (possible acute gout attacks), abnormal liver function tests.

**Interactions, warnings:** ethambutol is contraindicated with pre-existing optical nerve damage.

Ophthalmologic examination before initiation of treatment and subsequently at 4-week intervals (color discrimination, field of vision, acuity). Immediate discontinuation to prevent optical atrophy if drug-related impairment of vision occurs.
Patients should be informed that impairment of vision may occur and to immediately report this to the treating physician. Aluminum hydroxide reduces absorption of ethambutol; ethambutol should therefore be taken at least one hour before antacids. Monitor liver values and uric acid levels at monthly intervals.

**Etravirine**

**Manufacturer:** Janssen-Cilag.

**Indications and trade name:** in combination with a boosted protease inhibitor and other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients.

- Intelen® tablets, 200 mg.

**Dose:** 200 mg (2 x 1 pill) BID after a meal. The tablets are soluble in water.

**Side effects:** Mostly mild rash, nausea is rare. With mild exanthema, which usually appears in the second week, treatment can usually be continued, immediately stopping at a serious exanthema. Rarely Stevens-Johnson syndrome. In October 2009, the company published a Dear Doctor letter, reporting on three cases of TEN.

**Interactions, warnings:** Etravirine is a substrate of the CYP450 enzyme system as well as an inducer of CYP3A4 and an inhibitor of CYP2C9, therefore, some interactions are to be anticipated. Etravirine reduces the serum concentrations of atazanavir, maraviroc and raltegravir and increases fosamprenavir levels. On the other hand, the etravirine levels are considerably reduced by tipranavir, efavirenz and nevirapine (moderately by darunavir, saquinavir and tenofovir). Lopinavir and delavirdine increase the levels of etravirine.

Etravirine should not be combined with the following: Atazanavir, fosamprenavir, tipranavir, unboosted PIs or other NNRTIs. Avoid rifampicin, carbamazepine, phenobarbital, phenytoin and St. John’s wort as well. For further details, see product information.

**Comments:** Etravirine is the first second-generation NNRTI that was licensed in 2008 for pre-treated patients. It is well-tolerated and effective against NNRTI-resistant HIV strains with classic NNRTI mutations like K103N. Should be combined with a boosted PI (preferably darunavir, due to the lack of data with other PIs).

For detailed information see page: 80

**Fluconazole**

**Manufacturer and trade name:** Pfizer and many other companies, therefore several trade names, such as Diflucan®, Fluconazole CT®/Stada, or Flucobeta®.

**Indications:** Candida infection, cryptococcal meningitis and some rare mycoses.

- Fluconazole® capsules, 50 mg, 100 mg, 200 mg.
- Fluconazole® suspension, 50 mg per 10 ml.
- Fluconazole® IV for injections, 100, 200 and 400 mg.

**Dose:** for oral candidiasis, 100 mg QD orally; for *candida esophagitis* 200 mg QD for 7–10 days. Double the dose on the first day. An attempt with a higher dose (up to 800 mg daily) may be made if there is persistent candidiasis after 10 days.

Cryptococcal meningitis: Initially, 400–800 mg daily, combined with flucytosine and amphotericin B if possible. After completion of acute therapy – usually after 6 weeks – maintenance therapy with 200 mg fluconazole daily.
Renal insufficiency: half the dose with creatinine clearance of 10 to 50 ml/min; reduce to 25% below 10 ml/min.

**Side effects:** overall good tolerability, rarely gastrointestinal complaints and elevated transaminases. Reversible alopecia in approximately 10% of cases with more than 400 mg daily.

**Interactions, warnings:** long-term treatment may lead to development of *candida*-resistant strains. Fluconazole is not effective against *C. krusei* or aspergillus. In cases of *C. glabrata* infection higher doses are required (sensitivity is dose-dependent). Fluconazole levels are reduced with concurrent administration of rifabutin/rifampin. Fluconazole increases the serum levels of rifabutin, atovaquone, clarithromycin, theophylline, opiates, coumarin derivatives, benzodiazepines, cyclosporine, tacrolimus, phenytoin and anti-convulsive drugs as well as AZT.

**Comments:** Fluconazole is the first choice for HIV-associated candidiasis and for the secondary prophylaxis of cryptococcosis (also as component of acute therapy). The tablets have good absorption. Infusions (more expensive) are only required in cases of non-adherence, severe mucositis, and/or problems with absorption.

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**Fosamprenavir**

**Manufacturer:** ViiV Healthcare.

**Indications and trade name:** HIV infection, for both treatment-naïve and experienced patients (for limitations, see details below). US trade name: Lexiva®.

- Telzir® film-coated tablets, 700 mg.
- Telzir® suspension, 50 mg/ml (225 ml bottle).

**Dosage in treatment-naïve patients:**

- 700 mg BID + 100 mg ritonavir BID (2 x 2 pills, normal dose).
- 1400 mg BID (without ritonavir, not approved in Europe).
- 1400 mg QD + 200 mg ritonavir QD (1 x 4 pills; not approved in Europe).

**Dosage in PI-experienced patients:**

- 700 mg BID + 100 mg ritonavir BID (2 x 2 pills)

**Side effects:** most frequently diarrhea, may be severe in some cases. Also nausea, vomiting, rash (up to 20%). Rarely Stevens-Johnson syndrome (<1%).

**Interactions, warnings:** Fosamprenavir can be taken on an empty stomach or with a meal. Contraindicated: cisapride, pimozide, midazolam, triazolam, ergotamines. Flecainide and propafenone are also contraindicated when fosamprenavir is boosted with ritonavir. There may be life-threatening interactions upon concurrent administration of amiodarone, lidocaine (systemic), tricyclic anti-depressants and quinidine. Do not use together with rifampin (this reduces amprenavir plasma levels by 90%), delavirdine or St. John’s wort; use cautiously with simvastatin, lovastatin, sildenafil, vardenafil. Carbamazepine, phenobarbital, phenytoin and dexamethasone can lower plasma levels of amprenavir.

**Rifabutin:** dose reduction of rifabutin by at least 50%. If fosamprenavir is boosted with ritonavir, a 75% reduction of the rifabutin dose is required (instead of 300 mg daily, only 150 mg every other day, or 150 mg three times per week). An increased methadone dose may be required.
Efavirenz seems to lower plasma levels significantly (probably clinically relevant). However, this is not the case if fosamprenavir is boosted with ritonavir. If fosamprenavir + ritonavir are administered once daily, then the ritonavir dose should be increased to 300 mg. Caution in combination with lopinavir – plasma levels of both drugs are reduced. If dosed >400 mg daily, possibly dose reduction of ketoconazole/itraconazole. If fosamprenavir is boosted with ritonavir, ketoconazole and itraconazole maximum dose 200 mg daily. Caution in patients with sulfonamide allergy or with reduced liver function.

Comments: Except for diarrhea, this PI is well-tolerated. However, fosamprenavir currently does not play an important role in HIV medicine. One advantage of the drug is that there are no restrictions with respect to food intake.

For detailed information see page: 89

Fortovase®, see Saquinavir.

Foscarnet

Manufacturer: AstraZeneca.

Indications and trade name: reserve drug for induction and maintenance therapy of CMV retinitis. Severe acyclovir-resistant herpes or varicella zoster infections.

• Foscavir®, 250 ml with 24 mg/ml.

Dose: 90 mg/kg IV over at least 2 hours BID for induction therapy (2–3 weeks) of CMV retinitis. 90–120 mg/kg over 2 hours QD for maintenance therapy.

HSV and HZV infections: 60 mg/kg IV BID for 2 weeks.

Side effects: nephrotoxicity, usually reversible after discontinuation. Electrolyte changes (hypocalcemia, hypokalemia) are also common. More rarely, anemia, neutropenia, fever, rash, headache, nausea, vomiting, diarrhea. Often painful penile ulcerations (washing recommended after every urination).

Interactions, warnings: good hydration. At least 2.5 l fluids daily. To prevent hypocalcemia give one ampule of 10% calcium solution in 100 ml 5% glucose immediately prior to infusion of foscarnet. Give 500–1000 ml 5% glucose before or after foscarnet dose. Do not mix infusions.

Initial monitoring of Na, K, Ca, creatinine, blood count at least 3 x week.

No concurrent treatment with other nephrotoxic drugs.

Adjust dose in renal insufficiency. See prescribing information.

Comment: Since the approval of valgancyclovir, foscarnet is only used rarely. However, it can be useful in some resistance situations (herpes viruses).

Foscavir®, see Foscarnet.

Fuzeon®, see T-20.
Gancyclovir

**Manufacturer:** Hoffmann-La Roche.

**Indications and trade name:** CMV retinitis.
- Cymeven® IV, 500 mg.

**Dose:**
- Initial treatment with normal renal function: 5 mg/kg BID as an IV infusion for one hour. Treatment duration, 14 to 21 days.
- Maintenance therapy: 6 mg/kg IV QD, 5 x week.

**Side effects:** Leukopenia, anemia and thrombocytopenia are dose limiting. Nausea, vomiting or CNS symptoms such as confusion or headache are rare.

**Interactions, warnings:**
- Monitor blood count every other day. Discontinue drug when below 500/µl (G-CSF if necessary).
- Contraindicated in neutropenia <500/µl, thrombocytopenia <25,000/µl and concurrent chemotherapy (KS, NHL).
- Do not combine with AZT and ddI (increased toxicity).

**Comment:** Gancyclovir is a potential teratogen. Dose adjustment is necessary in renal insufficiency.

G-CSF

**Manufacturer:** Amgen, Chugai Pharma. Recently other companies (generics, biosimilars).

**Indications and trade name:** Neutropenia, especially drug-induced (AZT, gancyclovir, interferon, myelosuppressive chemotherapy), rarely HIV-related.
- Neupogen® prefilled syringe, 300/480 µg filgrastim (30/48 Mio I.U.) in 0.5 ml.
- Neulasta® prefilled syringe, 6 mg pegfilgrastim in 0.6 ml.
- Granocyte® injection vial, 13.4 and 33.6 MIU lenograstim.

**Dose:**
- According to protocol for chemotherapy, usually approximately 5 µg/kg Neupogen® daily on fixed days. Outside of chemotherapy protocols, 1–5 µg/kg Neupogen® 1–3 x week. The goal is usually at least 1000 neutrophil granulocytes/µl. For Granocyte® doses see product information.

**Side effects:**
- Bone, back or muscle pain in 10 to 20% of patients, sometimes severe (requiring generous analgesia). Irritation at the injection site.

**Comments:** G-CSF is expensive. Long-term treatment should be avoided (change the drug causing neutropenia if possible). Remainders of individual ampules should be kept refrigerated in a syringe. Monitor blood count twice weekly. The recently approved biosimilars are less expensive!

Hivid®, see ddC.

Incivek®, see telaprevir.
Indinavir

**Manufacturer:** Merck.

**Indications and trade name:** HIV infection.

- **Crixivan®** hard capsules, 200 mg and 400 mg.

**Dose:** Two established dosages in combination with ritonavir:

- 800 mg BID plus 100 mg ritonavir BID.
- 400 mg BID plus 400 mg ritonavir BID.

Dose reduction is often possible with TDM. Dose without ritonavir (uncommon):

- 800 mg TID (two 400 mg capsules TID) one hour before or two hours after meals.

**Side effects:** nephrolithiasis (in up to 25%). Less frequently, nephrotoxicity with elevated serum creatinine. Diarrhea, nausea, vomiting. Hyperbilirubinemia. A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Lipodystrophy (originally called Crixbelly), dyslipidemia, disorders of glucose metabolism.

**Interactions, warnings:** At least 2 l of fluid should be consumed daily to prevent nephrolithiasis. The occurrence of nephrolithiasis and probably skin problems too, correlates with plasma levels. No concurrent administration with ddI.

In combination with ritonavir, indinavir can be taken twice daily with meals. The concurrent use of rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John’s wort is contraindicated.

The following dose adjustments are necessary: When using IDV/r, 150 mg rifabutin every 2 days or three times a week. Ketoconazole and itraconazole: 600 mg indinavir TID. Sildenafil: maximum 25 mg sildenafil/48h.

**Comments:** Was one of the first PIs on the market in 1996. Due to toxicity and ease of use, indinavir does not play a role any longer in HIV medicine.

For detailed information see page: 89

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Interferon alfa-2a/2b

**Manufacturer:** Essex (interferon α-2b as Intron A®, pegylated as PegIntron®) and Roche (interferon α-2a as Roferon®, pegylated as Pegasys®).

**Indications and trade name:** chronic hepatitis C (IFN α-2b and IFN α-2a), possibly also for chronic hepatitis B (α-2a). Kaposi’s sarcoma with good immune status (>250 CD4 cells/µl); pegylated interferons are not licensed for KS in Europe.

- PegIntron® injector, 50, 80, 100, 120, 150 µg in 0.5 ml.
- Pegasys® prefilled syringe, 135, 180 µg.
- Roferon-A® prefilled syringe, 3, 4.5, 9, 18 MIU.
- Intron A® pens, 18, 30, 60 MIU.

**Dose:** PEG-Intron®, 1.5 µg/kg body weight 1 x/week. Pegasys®, 180 µg 1 x/week

Standard interferons: 6 MIU 3 x/week.

Duration is dependent on success of treatment of KS, on HCV genotype and success of treatment. Interferon is injected subcutaneously.

**Side effects:** frequent side effects. Influenza-like symptoms such as fever and myalgia. Depression, even suicidal tendencies, fatigue, sleeping disorders, personality changes. Anemia, thrombocytopenia and leukopenia. Autoimmune thyroiditis. Reversible hair loss. Possibly impaired vision.
**Interactions, warnings:** influenza-like symptoms usually occur a few hours after dosing and can be reduced with paracetamol (take 1000 mg in advance). All side effects are usually reversible. Contraindications are severe liver or renal dysfunction, severe heart disease, bone marrow disorders, CNS disorders (e.g., epilepsy, severe depression), uncompensated thyroid disorders. Monitor blood count every two weeks initially, and then later, monthly with standard laboratory tests. TSH every three months. Interferons must be kept refrigerated.

**Intelence®,** see Etravirine.

**Intron A®,** see Interferon.

**Invirase®,** see Saquinavir.

**Isentress®,** see Raltegravir.

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**Isoniazid (INH)**

**Manufacturer and trade name:** isoniazid is made by various manufacturers and has many trade names.

**Indications:** part of combination therapy for tuberculosis. Prophylactic treatment after tuberculin conversion.

- Isozid comp® film-coated tablets, 200, 300, 400 mg INH and 40, 60, 80 mg vitamin B6 (pyridoxin-HCl).
- Also in various combination preparations (see rifampicin).

**Dose:** 200 to 300 mg QD (4 to 5 mg/kg, maximum 300 mg) orally, IV only in severe cases during the first two weeks of therapy. For prophylaxis of neuropathy 100 mg pyridoxine orally QD. Pyridoxine is contained in the dosage of 20 mg per 100 mg of isoniazid in Isozid comp®.

Pediatric dose: 6 (to 10) mg/kg QD, maximum 300 mg.

**Side effects:** toxic hepatitis, more frequent in older patients, and patients with chronic liver disease and alcohol abuse. Peripheral neuropathy. Discontinue isoniazid in severe cases and treat for several weeks with pyridoxine and vitamin B-12. Psychosis, CNS symptoms. Fever, rash, nausea, vomiting, anemia, leukopenia, thrombocytopenia.

**Interactions, warnings:** INH should not be used in acute hepatitis and patients with a history of INH-associated hepatopathy or severe febrile reactions, peripheral neuropathy, macrohемaturia. Always combine with vitamin B6.

Diverse interactions with barbiturates, cycloserine, theophylline, phenytoin and rifampin; doses of these drugs should be reduced due to CNS disorders. Reduced absorption if taken concurrently with aluminum-based antacids. Do not combine with ddI or d4T due to risk of peripheral neuropathy. Caution with alcohol during treatment.

Initially, biweekly monitoring of blood count, transaminases, bilirubin, and renal function. Discontinue isoniazid with elevation of transaminases to more than 3-fold initial levels and symptoms; or with a 5-fold elevation in the absence of symptoms.
Itraconazole

**Manufacturer and trade name:** diverse, with several trade names.

**Indications:** histoplasmosis, aspergillosis, treatment-resistant Candida infections (second choice). Also at derma/onychomycoses.
- Sempera® capsules, 100 mg.
- Sempera 7® capsules, 100 mg.
- Sempera Liquid® juice, 10 mg/ml (150 ml).

**Dose:** Fluconazole-resistant *Candida* infections: 100 mg QD to 100 mg BID (up to 200 mg BID) ideally as itraconazole oral solution. Histoplasmosis, aspergillosis 200 mg BID.

**Side effects:** nausea, vomiting, rash, dizziness. Toxic hepatitis.

**Interactions, warnings:** To achieve maximum absorption, the capsules should be taken immediately after a full meal. Acidic drinks such as coke and orange juice may increase absorption.

No concurrent administration of itraconazole capsules with ddl, H2 blockers, omeprazole, antacids. No concurrent administration (of capsules or oral solution) with rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, simvastatin, lovastatin and isoniazid (these lower the bioavailability of itraconazole).

Itraconazole increases serum levels of cyclosporine, calcium antagonists, digoxin, lovastatin, simvastatin and indinavir. Itraconazole has a negative inotropic effect and should not be given to patients with heart failure.

**Comments:** Due to numerous interactions and unreliable plasma levels, administration of itraconazole is problematic. However, in contrast to fluconazole, it is effective for many non-albicans strains, aspergillosis, and histoplasmosis.

Kaletra®, see Lopinavir/r.

Kivexa® (US: Epzicom)

**Manufacturer:** ViiV Healthcare

**Indications and trade name:** HIV infection.
- Kivexa® film-coated tablets, 600 mg abacavir and 300 mg 3TC.

**Dose:** 1 tablet QD. Replace Kivexa® with the individual drugs if kidney function is impaired (creatinine clearance below 50 ml/min), in order to adjust the 3TC dose.

**Side effects:** hypersensitivity reaction due to abacavir (see abacavir). Controversial data on a potentially enhanced risk of myocardial infarction in patients with an elevated risk of cardiovascular events. Otherwise well tolerated.

**Comments:** frequently-used fixed dose combination. The abacavir HSR has to be taken into account. However, HSR can be prevented by prior HLA-testing.

For detailed information see page: 72

Klacid®, see Clarithromycin.

Lamivudine, see 3TC (first page of this chapter).

Lexiva®, see Fosamprenavir.
Lopinavir/r

Manufacturer: Abbott.

Indications and trade name: HIV infection.

• Kaletra® film-coated capsules, 200 mg lopinavir + 50 mg ritonavir.
• Kaletra® film-coated capsules, 100 mg lopinavir + 25 mg ritonavir.
• Kaletra® solution, 80 mg lopinavir + 20 mg ritonavir per ml.

Dose: 2 capsules BID (400 mg lopinavir/100 mg ritonavir) or 5 ml solution BID. In the US, 4 capsules QD is approved. Tablets with a lower dose were developed for children (also known as Aluvia®).


Interactions, warnings: The solution should be kept in the refrigerator; this is not required for the tablets. No special food requirements. Drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, terfenadine, ergotamines, cisapride, midazolam, triazolam. In combination with efavirenz (perhaps also nevirapine) the dose should be increased to 3 capsules BID or 6.5 ml solution BID. Measure plasma levels. Rifampin and St. John’s wort reduce the blood levels of lopinavir. Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests or significantly elevated transaminases. If lopinavir is combined with ddi, then the latter must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no medication with disulfiram or metronidazole. Caution with contraception – not safe. Increasing the methadone dose may be necessary. When used with rifabutin, the rifabutin dose should be reduced by 75% (i.e., to 1 x 150 mg every two days).

Comments: Effective PI for both ART-naïve and pretreated patients and the only PI with a fixed dose of a ritonavir booster. Still one of the most prescribed drugs in HIV medicine. Disadvantages include gastrointestinal side effects (diarrhea) and the often significant dyslipidemia. As with all PIs, various drug interactions should be considered.

For detailed information see page: 90

Maraviroc

Manufacturer: ViiV Healthcare.

Indications and trade name: In Europe, maraviroc is approved only for pretreated adult HIV-infected patients with CCR5-tropic HIV strains (R5). In November 2009, FDA has expanded use of maraviroc to include treatment-naïve patients with R5 viruses.

• Celsentri® or Selzentry® tablets, 150 mg and 300 mg.

Dose: 300 mg BID with or without food. Depending on the co-medication, multiple dosage adjustments of maraviroc are recommended.
Combined Drugs

| Nevirapine, tenofovir, other NRTIs                  | none |
| Efavirenz + no protease inhibitors or other strong CYP3A4 inhibitors | 600 mg BID |
| Rifampicin + no concurrent CYP3A4 inhibitor     | 600 mg BID |
| Boosted PIs (exception: tipranavir/r and fosamprenavir/r → standard dosage) | 150 mg BID |
| Efavirenz + simultaneous PI therapy (exception: fosamprenavir/r) | 150 mg BID |
| Rifabutin + concurrent administration of PIs (exception: with tipranavir/r or fosamprenavir/r use standard dosage) | 150 mg BID |
| Itraconazole, ketoconazole, clarithromycin, telithromycin | 150 mg BID |

In combination, the dosage varies according to the PI; when both an inhibitor and an inducer are given, the inhibitor dominates.

The following adjustments are recommended to reduced creatinine clearance:

<table>
<thead>
<tr>
<th>Cr Cl (ml/min)</th>
<th>Without co-medication of a strong CYP3A4 inhibitor or together with tipranavir/r</th>
<th>Concurrent treatment with a strong CYP3A4 inhibitor, e.g., lopinavir/r, darunavir/r, atazanavir/r, ketoconazole</th>
<th>Concurrent treatment with saquinavir/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–80</td>
<td>no adjustment of dosage interval</td>
<td>every 24 hours</td>
<td>every 24 hours</td>
</tr>
<tr>
<td>30–49</td>
<td></td>
<td>every 48 hours</td>
<td>every 72 hours</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Side effects:** well tolerated, rare headaches, dizziness, fatigue, nausea. In high doses orthostatic hypotension. Occasional reports of CK increases, mycositis. Long-term data beyond 3–5 years is not yet available.

**Interactions, warnings:** the concurrent administration of maraviroc and rifampicin plus efavirenz is not recommended. St. John’s wort can lower maraviroc levels. The combination should be avoided.

It is required to have a valid tropism test indicating the presence of R5 viruses (genotyping generally suffices).

**Comments:** The first CCR5 antagonist and the first oral entry inhibitor that was licensed for HIV therapy. Since maraviroc inhibits only CCR5-tropic viruses, the co-receptor tropism has to be determined prior to treatment. Very well tolerated but complex dosage regulations.

For detailed information see page: 99

**Mavid®,** see Clarithromycin.

**Mycobutin®,** see Rifabutin.

**Nelfinavir**

Manufacturer: Hoffmann-La Roche (Europe), Pfizer (US).

**Indications and trade name:** HIV infection.

- **Viracept®** film-coated tablets, 250 mg.
- **Viracept®** film-coated tablets, 625 mg (not in Europe).
- **Viracept Powder®,** 50 mg/g.
**Dose:** 1250 mg BID (5 tablets) or 750 mg TID (3 tablets) with meals. Boosting with ritonavir is not useful.

**Side effects:** frequently reported diarrhea (>20%). Meteorism, nausea may also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

**Interactions, warnings:** contraindicated for co-medication with rifampin, the contraceptive pill, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John’s wort. With rifabutin, 150 mg rifabutin QD and increase nelfinavir to 1250 mg BID or 1000 mg TID.

If withdrawal symptoms occur while on methadone dose may be increased.

Sildenafil maximum dose 25 mg in 48 h.

Diarrhea can often be controlled with loperamide (maximum 16 mg/day).

**Comments:** Nelfinavir is less potent than boosted PIs or NNRTIs. May be useful in some pediatric patients (powder preparation) and during pregnancy. Roche is planning to discontinue the production when the marketing authorisation in the EU expires in early 2013. Clinicians are advised not to initiate nelfinavir in new patients and to discuss alternative treatment with patients currently on it.

For detailed information see page: 90

**Neupogen®,** see G-CSF.

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**Nevirapine**

**Manufacturer:** Boehringer Ingelheim.

**Indications and trade name:** HIV infection. ART-naïve patients with a good immune status (women >250, men >400 CD4 T cells/µl) should avoid nevirapine because of an elevated risk of hepatotoxicity (see below).

- Viramune® XR™ extended-release tablets, 400 mg.
- Viramune® tablets, 200 mg (for pediatric patients also 100 mg, 50 mg).
- Viramune Suspension®, 10 mg/ml.

**Dose:** 400 mg per day (1 XR tablet OD or 1 tablet BID). Always start with lead-in dosing (1 tablet 200 mg OD for 2 weeks) to reduce the frequency of rash. May be taken on an empty stomach or with meals.

**Side effects:** hepatotoxicity (elevation of transaminases 10–15%), rash. Caution is needed when both appear simultaneously (see below). Less frequently, fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash. GGT elevation on nevirapine is almost always the rule.

To detect hepatotoxicity (an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first three months of treatment. If hepatotoxicity does occur, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg QD. The dose may be increased to 200 mg BID only after a prolonged period of observation. If liver enzymes increase again, nevirapine should be permanently discontinued. The risk is greater with good immune status (women >250 CD4 T cells/µl, 12-fold; men >400 CD4 T cells/µl, 5-fold). This elevated risk applies probably only to ART-naïve patients.

A mild rash, usually occurring within the first weeks of treatment, can be treated with antihistamines (e.g., Fenistil retard® 1 x 1 tablet) if mucous membranes are not
involved and if transaminases are normal. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids are recommended (e.g., prednisolone 1 mg/kg for 3–5 days). Nevirapine should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, then the dose should not be increased until the rash has resolved completely. Prophylactic treatment (steroids, antihistamines) is not advised. Nevirapine has a favorable long-term profile. In particular, lipid levels are usually positively influenced. GGT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated.

Interactions, warnings: caution use in hepatic dysfunction (TDM). No concurrent treatment with rifampin, ketoconazole, and St. John’s wort. Dose adjustment in combination with methadone (methadone dose increase may be required) and lopinavir/rit (increase Kaletra® to 3 capsules BID). Nevirapine should not be given for post-exposure prophylaxis.

The inactive tablet matrix is eliminated in the feces (patients should be informed).

Comments: Nevirapine is a frequently prescribed NNRTI. As with all NNRTIs, a single point mutation is sufficient for high-level resistance. During the first weeks of treatment, nevirapine is saddled with allergies and hepatotoxicity (start with lead-in dosing). However, the long-term tolerance is excellent (favorable lipid profile). In 2011, extended-release tablets have been approved for OD use.

For detailed information see page: 78

Norvir®, see Ritonavir.

Pegasys®, see Interferon.

PegIntron®, see Interferon.

Pentacarinat®, see Pentamidine.

Pentamidine

Manufacturer: Sanofi-aventis/GlaxoSmithKline.

Indications and trade name: treatment and secondary prophylaxis of Pneumocystis pneumonia if cotrimoxazole is contraindicated (hypersensitivity, resistance to treatment). Also for visceral leishmaniasis.

• Pentacarinat® injection vials, 300 mg.

Dose: for treatment, 200–300 mg Pentacarinat® QD IV for five days (4 mg/kg), then halve the dose. In very mild cases, daily inhalations with 300 mg. In renal failure and creatinine clearance of 10 to 50 ml/min: 4 mg/kg q 24–36 h; below 10 ml/min: 4 mg/kg q 48 h. Prophylaxis: inhalation of 300 mg 1–2 x month.

Side effects: frequent with intravenous dosing. Nausea, vomiting, metallic taste; nephrotoxicity (increased creatinine in the second week of treatment) up to renal failure. Hypo- or hyperglycemia (possible even months after end of treatment), hypotension, arrhythmia, pancreatitis. Leukopenia and thrombocytopenia. Inhalation may induce cough, rarely asthma attacks.

Interactions, warnings: For inhalation, pentamidine as an aerosol is contraindicated in asthma. Inhalation is ineffective with several pulmonary diseases. Prior inhalation of a ß-mimetic (e.g., Berotec®) is desirable.
For infusions, caution with liver or renal failure, hyper- or hypotension, hyperglycemia, cytopenia. Always ensure sufficient intake of electrolytes and fluids. No concurrent administration of other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, foscarnet). Patient should remain in supine position before, during and after infusions of pentamidine (caution: hypotension). Pentamidine should be infused slowly over at least 2 hours. Daily monitoring of BUN, serum creatinine, blood count, fasting blood glucose, urinalysis and serum electrolytes, weekly monitoring of bilirubin, alkaline phosphatase, transaminases.

**Pyrimethamine**

**Manufacturer:** GlaxoSmithKline.

**Indications and trade name:** prophylaxis and treatment of cerebral toxoplasmosis. Prophylaxis of *Pneumocystis pneumonia*.

- Daraprim® tablets, 25 mg.

**Dose:** treatment of toxoplasmosis, Daraprim® 2 tablets (50 mg) BID (for 3 days, then 1 tablet BID) + Leucovorin® 3 x 1 tablets/week each 15 mg + either sulfadiazine, clindamycin or atovaquone (second choice). For PCP prophylaxis in combination with dapsone, Daraprim®2 tablets (50 mg) per week + Dapsone® 1 tablet (50 mg) QD + Leucovorin® 2 tablets (30 mg) per week.

**Side effects:** nausea, colic, vomiting, diarrhea, leukopenia, anemia or thrombocytopenia. Rarely seizures, tremor or ataxia.

**Interactions, warnings:** pyrimethamine is contraindicated in megaloblastic anemia resulting from folic acid deficiency. Caution in patients with seizures, renal failure, asthma or G6PD deficiency. All patients taking pyrimethamine should receive folinic acid to decrease risk of myelosuppression. Folic acid is pointless, since it cannot be metabolized with pyrimethamine present.

Initial monitoring of blood count at weekly intervals.

**Raltegravir**

**Manufacturer:** Merck.

**Indications and trade name:** pretreated HIV patients. Since September 2009, raltegravir is approved also for treatment-naïve patients.

- Isentress® film-coated tablets, 400 mg.

**Dose:** 1 tablet of 400 mg BID with or without food. In patients with renal or moderate hepatic impairment, no dose adjustment is required.

**Side effects:** Raltegravir is very well tolerated – in studies, there have generally been no more adverse events than seen with placebo. At a frequency of 1% to 10%, dizziness, stomach ache, flatulence, obstipation, hyperhidrosis, arthralgia, tiredness, weakness. Because of the dizziness, driving fitness may be (rarely) impaired. Rash (mild, very rarely requiring discontinuation). FDA warning on suicidal thoughts. Case reports on rhabdomyolysis, hepatitis, insomnia.

**Interactions, warnings:** Raltegravir is eliminated via UGT1A1-mediated glucuronidation, so that relevant interactions with other antiretroviral agents are not
expected. Strong inducers of UGT1A1 like rifampicin reduce plasma levels of raltegravir. If a combination is unavoidable, raltegravir dose should be doubled. Omeprazole or other gastric acid inhibitors may increase the plasma levels of raltegravir.

Comments: First-in-class integrase inhibitor. Well-tolerated and already an essential salvage agent, with impressive effectiveness in the setting of multiple resistance as well as in ART-naïve patients. Disadvantages: relatively low resistance barrier, BID dosing required.

For detailed information see page: 107

Rebetol®, see Ribavirin.

**Ribavirin**

**Manufacturer:** Roche and Essex.

**Indications and trade name:** chronic hepatitis C, only in combination with interferon. In Europe, the license for HIV/HCV-coinfected patients only applies to Copegus®.

- **Copegus®** film-coated tablets, 200 mg, 400 mg.
- **Rebetol®** hard capsules, 200 mg.
- **Rebetol®** solution, 40 mg/ml.

**Dose:** daily dose 800 mg for body weight <65 kg, 1000 mg for 65–85 kg, 1200 mg for >85 kg. Capsules are divided into two daily doses and taken with meals. Treatment duration depends on the genotype and success of treatment.

**Side effects:** the most frequent side effect is hemolytic anemia (Hb decrease by at least 2 g/dl obligatory), gastrointestinal complaints, headache and fatigue may also occur. Rarely lactic acidosis, pancreatitis in combination with NRTIs.

**Interactions, warnings:** ribavirin is contraindicated in severe coronary disease, renal failure, decompensated liver cirrhosis, and hemoglobinopathy. It is also contraindicated in pregnancy (teratogenicity).

Dose reduction for hemoglobin <10 g/dl. Reduce dose to 600–800 mg/day. Discontinue ribavirin at hemoglobin values <8.5 g/dl. Before reducing or discontinuing ribavirin, however, consider erythropoietin and transfusions. Avoid concurrent treatment with other myelosuppressive drugs (AZT).

Ribavirin can lead to lactic acidosis in combination with other NRTIs. Most importantly, ddl should be avoided while care should be taken with all other NRTIs like d4T. Possible antagonism with abacavir (mechanism unclear). Efavirenz-induced depression may worsen on ribavirin.

Monitoring of lab values (blood count, ALT, amylase, lipase) initially at biweekly intervals and then monthly. Measure lactate if unspecific symptoms occur.

**Recriptor®,** see Delavirdine.

**Retrovir®,** see AZT.

**Reyataz®,** see Atazanavir.
Rifabutin

Manufacturer: Pfizer.

Indications and trade name: infections with *Mycobacterium avium* complex (MAC) in combination with other drugs (usually ethambutol and azithromycin). Also for patients with tuberculosis, when rifampicin is contraindicated.

- Mycobutin® (previously, Alfacid®) capsules, 150 mg.

Dose: 300 mg rifabutin daily (+ azithromycin + ethambutol).

Renal failure, dose reduction by 50% for creatinine clearance <30 ml/min.

Dose adjustments for concurrent dosing with antiretroviral drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r*, darunavir/r, fosamprenavir/r, indinavir/r, lopinavir/r, saquinavir/r, tipranavir/r</td>
<td>Rifabutin: 150 mg every other day or three times per week (see product information)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Nelfinavir 1250 mg BID + rifabutin 150 mg/day</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Rifabutin contraindicated</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Increase rifabutin to 450 mg/day or 600 mg twice or three times weekly</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Standard dose</td>
</tr>
</tbody>
</table>

* /r = boosted with ritonavir

Side effects: Nausea, vomiting, elevation of liver enzymes, jaundice. Uveitis usually only with a daily dose >300 mg and concurrent treatment with clarithromycin or fluconazole. Red discoloration of urine, skin and body secretions (inform patients about this).

Interactions, warnings: Rifabutin should not be used in thrombocytopenia and severe hepatic dysfunction. Monitor blood count and liver enzymes initially biweekly and then monthly.

Rifabutin can decrease the efficacy of the following drugs: analgesics, anticoagulants, corticosteroids, cyclosporine, digitalis (except digoxin), dapsone, oral antidiabetics, oral contraceptives, narcotic analgesics, phenytoin and quinidine. Erythromycin, ketoconazole,itraconazole, fluconazole and clarithromycin can increase plasma levels of rifabutin. Antacids should be taken at least three hours after rifabutin.

Rifampin

Manufacturer and trade name: manufactured by several companies, therefore many trade names, also part of several fixed dose combinations (see below).

Indications: tuberculosis. Use only in combination.

- Rifa® tablets, 150, 300, 450, 600 mg Rifampicin.
- Eremfat® syrup, 20 mg rifampicin per ml.
- Eremfat® IV, 300 mg and 600 mg.
- Rifinah® or Tebesium duo® film-coated tablets, 300 mg rifampicin +150 mg INH.
- Rifater® or Tebesium trio® sugar-coated film-coated tablets, 120 mg rifampicin + 50 mg isoniazid + 300 mg pyrazinamide.

Dose: 600 mg daily (body weight >50 kg) or 450 mg (body weight <50 kg). Ideally taken in the morning on an empty stomach.
Side effects: toxic hepatitis (up to 20%), cholestatic changes. Red discoloration of urine and other body fluids (inform patients of this). Soft contact lenses may permanently stain red. Allergies are frequent. Gastrointestinal complaints such as nausea, vomiting, diarrhea.

Interactions, warnings: caution in patients with chronic liver disease. Discontinue rifampin if ALT >100 U/l or with elevated bilirubin (careful on re-exposure, gradually increasing doses is possible after normalization of values), and with patients who experience severe and persistent diarrhea (pseudomembranous colitis).

Rifampin should be avoided if concurrent NNRTIs or PIs are necessary. Rifampin increases metabolism of numerous drugs, reducing their efficacy if administered concurrently. These drugs include atovaquone, warfarin, barbiturates, benzodiazepines, beta-blockers, clarithromycin, contraceptives, steroids, oral antidiabetics, cyclosporine, dapsone, digitalis, doxycycline, erythromycin, haloperidol, ketoconazole, methadone, phenytoin, theophylline, trimethoprim, verapamil. Combination with ketoconazole or voriconazole is contraindicated.

Antacids, opiates and anticholinergics reduce the bioavailability of orally administered rifampin, if given simultaneously. To avoid this interaction, rifampin should be given several hours before these drugs.

Not for use in pregnancy.

Blood count and liver values should be monitored every two weeks.

Rilpivirine

Manufacturer: Janssen-Cilag.

Indications and trade name: ART naïve patients with a plasma viremia of less than 100,000 copies/ml

- Edurant® film-coated tablets, 25 mg rilpivirine (RPV).
- Complera® film-coated tablets, 25 mg RPV + 200 mg FTC + 300 mg tenofovir.

Dose: 25 mg OD. Should be taken with a meal.

Side effects: Headache, insomnia. CNS symptoms occur less frequently than with efavirenz. A generally mild rash may occur in the first weeks (continued treatment is usually possible). Prolongation of the cardiac QTc interval was observed in studies of HIV-uninfected subjects given supratherapeutic doses of rilpivirine.

Interactions, warnings: An acidic gastric environment is necessary for absorption – PPIs should not be given to persons taking rilpivirine. Rilpivirine is a substrate of hepatic cytochrome P450 3A, so drugs that induce or inhibit the action of this isoenzyme may alter serum rilpivirine levels. Rifamycins (eg, rifampin and rifabutin), certain anticonvulsants (eg, carbamazepine and phenytoin), and St. John’s wort may substantially decrease rilpivirine concentrations and should be avoided. Macrolides, azole antifungals and PIs may increase rilpivirine levels.

Comments: Rilpivirine is a new NNRTI which was approved in 2011. Mostly used in the single tablet regimen Complera®. Approval of rilpivirine is restricted to naïve patients with low viremia. As with the other members of this drug class, drug interactions, a low resistance barrier and cross-resistance have to be considered. Food intake is important!

For detailed information see page: 81
Ritonavir

Manufacturer: Abbott.

Indications and trade names: HIV infection. Also a component of Kaletra®.

- Norvir® soft gel capsules, 100 mg.
- Norvir® tablets, 100 mg.
- Norvir® oral solution, 80 mg per ml (7.5 ml = 600 mg).

Dose: in rare cases, when ritonavir is used as a single PI, the dose is 600 mg BID (increase dose over two weeks: 300 mg BID on day 1–2, 400 mg BID on day 3–5, 500 mg BID on day 6–13). However, ritonavir should ideally be used only for boosting of other PIs. Daily doses in combination with:

- Atazanavir (Reyataz®, 300 mg QD), 100 mg ritonavir QD
- Darunavir (Prezista®, 600 mg BID), 100 mg ritonavir BID
- Darunavir (Prezista®, 800 mg QD), 100 mg ritonavir QD
- Fosamprenavir (Telzir®, 700 mg BID), 100 mg ritonavir BID, also 1400 mg fosamprenavir QD + 200 mg QD (US only, naive patients)
- Indinavir (Crixivan®, 800 mg BID), 100 mg ritonavir BID, also 400 mg ritonavir BID + 400 mg indinavir BID
- Lopinavir (Kaletra®) fixed combination, see Lopinavir/r.
- Saquinavir (Invirase®, 1000 mg BID), 100 mg ritonavir BID
- Tipranavir (Aptivus®), 200 mg ritonavir BID

Side effects: depending on dosage, frequent, nausea, vomiting, diarrhea, perioral paresthesia and electric sensations on arms and legs. Elevated transaminases and GGT, dyslipidemia, lipodystrophy and rarely diabetes mellitus.

Interactions: even the low boosting doses have multiple drug interactions. The following drugs are contraindicated: rifampin, amiodarone, astemizole, bepridil, terfenadine, encaïnide, flecaïnide, cisapride, triazolam, ergotamine, lovastatin, quinidine and St. John’s wort. Sildenafil should be avoided. Caution should be taken and plasma levels measured for both ritonavir and (if possible) the following co-medications: methadone, immunosuppressants (cyclosporine, tacrolimus), macrolide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants, neuroleptics (haloperidol, risperidone, thioridazine), antimalarial drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

Comments: One of the first PIs. The dosage required to inhibit HIV replication is too toxic. Today ritonavir should only be used as booster for other antiretroviral drugs (mainly PIs). Numerous interactions.

For detailed information see page: 91

Saquinavir

Manufacturer: Hoffmann-La Roche.

Indications and trade name: HIV infection.

- Invirase 500® film-coated tablets, 500 mg saquinavir.

Dose: 1,000 mg saquinavir BID + 100 mg ritonavir BID.

Side effects: mainly gastrointestinal, diarrhea, nausea, abdominal discomfort, meteorism. Otherwise well-tolerated. Rarely elevation of transaminases or GGT, headache.
As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

**Interactions, warnings:** contraindicated with rifampin, astemizole, terfenadine, cis-apride, triazolam, ergotamine, simvastatin, lovastatin, and St. John’s wort. If saquinavir is not combined with other PIs it should be taken with meals.

**Comments:** saquinavir was the first PI to be licensed for HIV therapy in 1995. It is well-tolerated, except for gastrointestinal problems, and typically not associated with any serious short-term problems. Still recommended in several guidelines. However, pill burden is high, compared to other PIs.

**For detailed information see page: 91**

**Sempera®,** see Itraconazole.

**Sobelin®,** see Clindamycin.

**Stavudine,** see d4T.

**Stocrin®,** see Efavirenz.

### **Stribild®**

**Manufacturer:** Gilead Sciences.

**Indications and trade name:** Adult HIV-infected patients naïve for therapy. It should be noted that in Europe, approval for Stribild® is expected for early 2013.

- Stribild® film-coated tablets with 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 300 mg TDF.

**Dose:** one tablet daily in the evening, unchewed, on an empty stomach.

**Side effects:** Usually well tolerated. Nausea (mild), diarrhea (slightly more frequently than with raltegravir), ALT elevation (less than with raltegravir). A modest elevation in serum creatinine (0.1–0.2 mg/dl) and decrease in estimated creatinine clearance (CrCl 10–15 ml/min) is to be expected in most patients due to a cobicistat-related inhibition of tubular creatinine secretion. Actual GFR is not affected.

**Interactions, warnings:** Data on interactions are limited. Do not use in patients with renal impairment (CrCl <70 ml/min). Other nephrotoxic agents should be avoided. Routine monitoring of estimated creatinine clearance, urine glucose, and urine protein should be performed in all patients.

**Comments:** Approved in August 2012 by the FDA. The third complete ART in one single tablet per day (STR = single tablet regimen), the first including an integrase inhibitor. In Europe, the approval is pending. For side effects, see also sections on tenofovir (caution with renal function), and FTC.

**For detailed information see page: 125**
Sulfadiazin®

Manufacturer: Heyl.

Indications and trade name: treatment and prophylaxis of cerebral toxoplasmosis, only in combination with pyrimethamine.

- Sulfadiazin-Heyl® tablets, 500 mg.

Dose: For treatment, 2–3 500 mg tablets QD (= daily dose 4–6 g). For prophylaxis, halve the dose (500 mg QD).

Renal insufficiency: creatinine clearance 10–50 ml/min: halve dose, <10 ml/min: one third of the dose.


Interactions, warnings: sulfadiazine is contraindicated in sulfonamide hypersensitivity in G6PD deficiency, renal failure, severe hepatic disease or dysfunction (e.g., acute hepatitis) and during pregnancy and breastfeeding.

Sulfadiazine can increase the effect of sulfonylurea urea (oral antidiabetics), anticoagulants, diphenylhydantoin. Concurrent use of antacids reduces absorption of sulfadiazine (separate administration by 1–2 hours). Ensure sufficient intake of fluids (at least 2 l daily). Initially, monitor blood count, ALT, creatinine, and BUN at least weekly. Monitor urine. In case of crystalluria, alkalize urine.

Sustiva®, see Efavirenz.

T-20 (enfuvirtide)

Manufacturer: Hoffmann-La Roche.

Indications and trade name: treatment of patients with evidence of HIV replication despite ongoing ART with at least one PI, any NRTI or NNRTI.

- Fuzeon® 90 mg/ml powder and solvent.

Dose: 90 mg subcutaneously BID.

Side effects: generally well-tolerated. However, almost all patients have local injection site reactions: erythema, inflammation, induration, rash. In the licensing studies, approximately 10% of patients required intermittent use of analgesics or were temporarily affected in their daily activities.

Patients on T-20 may have an increased risk of bacterial pneumonia. It is important to be particularly vigilant in patients with risk factors for pneumonia (low baseline CD4 counts, high viral load, IV drug users, smokers, history of pulmonary disease). Hypersensitivity reactions with rash, fever, nausea, chills, hypotension or elevated transaminases are rare (< 1%).

Interactions, warnings: interactions are not known. Injection sites – upper arm, ventral hip, and abdomen. Change injection sites often. On the back, possibly fewer irritations. Do not inject at sites with inflammatory signs from previous injections. Do not inject at sites with birth marks, scars or disrupted skin integrity.

Comments: T-20 is an entry inhibitor used for heavily treatment-experienced patients. T-20 must be injected subcutaneously BID. Use is limited primarily by its administration and by the local skin side effects. Very expensive, may double the price of ART.

For detailed information see page: 103
Telaprevir

**Manufacturer:** Janssen-Cilag/Vertex.

**Indications and trade name:** as a component in a combination therapy with peginterferon alfa and ribavirin for patients with chronic hepatitis C, genotype 1. Incivek® must be administered with both peginterferon alfa and ribavirin (PEG+RIBA) for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of PEG-RIBA depending on viral response and prior response status.

- Incivek® film-coated tablets, 375 mg (Europe: Incivo®)

**Dose:** 750 mg taken 3 times a day (7–9 hours apart) with food (not low fat). Maximum of three months. To prevent treatment failure, the dose must not be reduced or interrupted. When combined with efavirenz, telaprevir dose should be increased to 1125 mg 3 times daily.

**Side effects:** Nausea (try haloperidol), vomiting, fatigue, diarrhea, pruritus, anemia. Mild skin rashes are common, leading to discontinuation of the drug in up to 7 %. However, serious skin reactions (DRESS, Stevens-Johnson Syndrome) were reported in less than 1%. Treatment of rash with oral antihistamines and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. Treatment of rash with systemic corticosteroids is not recommended.

**Interactions, warnings:** do not use in other HCV genotypes than genotype 1. No lead-in as with boceprevir. Telaprevir AUC decreased significantly when administered with lopinavir/r, darunavir/r or fosamprenavir/r but not with atazanavir. Darunavir and fosamprenavir levels fell by more than half when co-administered with telaprevir. Ritonavir alone did not significantly boost telaprevir levels. Incivek® is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance, such as rifampicin, ergot derivatives, atorvastatin, lovastatin, simvastatin, orally administered midazolam, or triazolam.

**Comments:** New HCV NS3/4A protease inhibitor which was approved in 2011. When combined with PEG+RIBA, SVR rates increase by 20–40 % in treatment naïve and experienced patients. Due to toxicities of the triple HCV therapy, the use of telaprevir is only recommended in experienced centers. Data on HIV-infected patients are encouraging but still limited.

For detailed information see page: 509

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Tenofovir

**Manufacturer:** Gilead Sciences.

**Indications and trade name:** HIV infection, chronic hepatitis B.

- Viread® film-coated (fc) tablets, 300 mg tenofovir disoproxil fumarate.
- Truvada® fc tablets, 300 mg tenofovir + 200 mg FTC.
- Atripla® fc tablets, 300 mg tenofovir + 200 mg FTC + 200 mg efavirenz.
- Complera® fc tablets, 300 mg tenofovir + 200 mg FTC + 25 mg rilpivirin.
- Stribild® fc tablets, 300 mg tenofovir + 200 mg FTC + 150 mg Elvitegravir + 150 mg cobicistat.

**Dose:** 300 mg QD, to be taken with a meal. Dose adjustments in patients with renal impairment are required. Double dosage interval (every 48 hours) at moderate kidney dysfunction (creatinine clearance 30–49 ml/min, below 30 ml/min it should be avoided). In hemodialysis patients, every 7 days following completion of hemodialysis.
**Side effects:** generally well-tolerated. Rarely, renal side effects (renal failure, tubulopathies including Fanconi’s syndrome, nephrogenic diabetes insipidus). Bone loss, osteomalacia. Rarely, elevation of liver enzymes. CK rises observed in up to 48% (macro CK, relevance is unclear).

**Interactions, warnings:** Patients with existing renal disease should either not receive tenofovir or, with no alternatives, reduce the dose. Controls (creatinine clearance and serum phosphate) before starting therapy, during the first year of treatment every four weeks and thereafter every three months.

When serum phosphate is <1.5 mg/dl (0.48 mmol/l) or creatinine clearance <50 ml/min check renal function again within one week. Simultaneous determination of blood glucose and potassium, as well as glucose in the urine. Interruption of therapy may be necessary, if creatinine clearance is <50 ml/min or serum phosphate is <1.0 mg/dl (0.32 mmol/l).

Creatinine clearance in ml/min is calculated as follows:

- **Women:** \( \frac{1.04 \times (140 - \text{age}) \times \text{kg}}{\text{creatinine (µmol/l)}} \)
- **Men:** \( \frac{1.23 \times (140 - \text{age}) \times \text{kg}}{\text{creatinine (µmol/l)}} \)

Concurrent administration of tenofovir and drugs that are also eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, acyclovir, valacyclovir, gancyclovir, valgancyclovir.

Do not combine with ddI, co-medication with tenofovir increases the AUC of ddI by 44%. Atazanavir and lopinavir increase tenofovir levels. Tenofovir lowers the plasma levels of atazanavir (always boost with 100 mg of ritonavir).

**Comments:** One of the most frequently used drugs in HIV medicine. Part of several fixed dose regimens. Good tolerability profile and only low mitochondrial toxicity. However, potential nephrotoxicity has to be taken into account as well as some interactions. Tenofovir is also effective against hepatitis B virus; in April 2008, it was officially licensed for hepatitis B therapy.

**For detailed information see page:** 70, 194, 269

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**Tipranavir**

**Manufacturer:** Boehringer Ingelheim.

**Indications and trade name:** HIV-infected adults who are either highly treatment-experienced or who have multiple PI resistance.
- Aptivus® capsules, 250 mg.

**Dose:** 500 mg BID + 200 mg BID ritonavir with meals.

**Side effects:** The most frequent side effects are gastrointestinal, diarrhea and nausea. Elevated transaminases have been observed in at least 6% of patients, with clinical hepatitis and liver failure in rare cases. More frequent than with other PIs dyslipidemia (20%). Rare rash (urticarial or maculopapular). Occasional reports (and FDA warning) of intracranial bleedings (causality unclear).

**Interactions, warnings:** Tipranavir is a substrate, activator and inhibitor of cytochrome CYP3A and both a substrate and inhibitor of the P-glycoprotein. Consequently, various interactions have to be taken into account (see table). Tipranavir reduces the serum level of other PIs, so a double PI regime is not applicable. Fluconazole and clarithromycin increase the serum level of tipranavir. Antacids reduce the tipranavir levels by 30% (administer separately).
Drugs contraindicated on tipranavir therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone, bepridil, flecaïnide, propafenone, quinidine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Astemizole, terfenadine</td>
</tr>
<tr>
<td>Ergotamine derivatives</td>
<td>(Dihydro)-ergotamine, (methyl)-ergonovine</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Pimozide</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Midazolam, triazolam</td>
</tr>
</tbody>
</table>

Rifampicin reduces tipranavir levels by 80% (avoid). Tipranavir/r increases the serum levels of atorvastatin by 8–10 fold (use another statin like pravastatin or fluvastatin). Dose reduction by at least 75% for rifabutin: 150 mg every other day or three times per week. Tipranavir reduces the plasma levels of abacavir and AZT by 35–40% (relevance unclear).

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B and C). Use cautiously in patients with HBV or HCV coinfection. Determine liver function parameters (monthly during the first 6 months), transaminases, cholesterol and triglycerides before and during treatment. Women who take an estrogen-based contraceptive appear to have a higher incidence of rash.

Comments: Tipranavir is the first non-peptidic PI. In two large studies on intensively PI-experienced patients, it was superior to optimized background regimen. Helpful salvage agent. Tipranavir has to be boosted with elevated ritonavir doses. Numerous interactions have to be taken into account.

For detailed information see page: 91

**Trizivir®**

Manufacturer: ViiV Healthcare.

**Indications and trade name:** HIV infection.

- Trizivir® film-coated tablets, 150 mg 3TC + 300 mg AZT + 300 mg ABC.

**Dose:** 1 tablet BID. In cases of impaired renal function (creatinine clearance less than 50 ml/min), the individual drugs should be given separately to allow for dose adjustment of 3TC.

**Side effects:** mostly gastrointestinal, see individual drugs. Abacavir HSR (see abacavir). There are possibly additive effects with regard to mitochondrial toxicity. Possibly an increased risk for cardiovascular events (see abacavir).

Comments: Less effective than multi-class combinations. No longer recommended without a PI/r or NNRTI. Further disadvantages include mitochondrial toxicity, abacavir HSR, QD is not possible. Thus, Trizivir® is only indicated in patients with compliance problems or with interactive co-medication (for tuberculosis; coumarin derivatives, etc).

For detailed information see page: 180, 202
Truvada®

Manufacturer: Gilead (Truvada®)

Indications and trade name: HIV infection.

- Truvada® film-coated tablets, 300 mg tenofovir + 200 mg FTC.

Dose: 1 tablet QD. Caution in patients with renal dysfunction. If there are no alternatives, with a reduced creatinine clearance of 30–49 ml/min, then it is recommended to reduce the dose to 1 tablet every two days (<30: avoid Truvada®). Absorption of Truvada® not affected by food intake.

Side effects: monitoring of renal parameters, see tenofovir.

Interactions, warnings: see tenofovir. In patients coinfected with chronic hepatitis B, Truvada® is preferred. Exacerbation of hepatitis may occur after discontinuing Truvada®.

Comments: Combination pill consisting of tenofovir and FTC. To date, one of the most frequently prescribed HIV drugs. Well-tolerated. However, renal dysfunction and bone loss may occur (see tenofovir).

For detailed information see page: 71

Valcyte®, see Valgancyclovir.

Valgancyclovir

Manufacturer: Hoffmann-La Roche.

Indications and trade name: induction and maintenance therapy of CMV retinitis.

- Valcyte® tablets, 450 mg.

Dose: for induction therapy 900 mg BID for 3 weeks (or until scar formation of CMV lesions), then suppressive therapy with 900 mg QD. Should be taken with a meal. The following doses should be used for renal failure:

<table>
<thead>
<tr>
<th>Cr Cl (ml/min)</th>
<th>Induction therapy</th>
<th>Suppressive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>900 mg BID</td>
<td>900 mg QD</td>
</tr>
<tr>
<td>40–59</td>
<td>450 mg BID</td>
<td>450 mg QD</td>
</tr>
<tr>
<td>25–39</td>
<td>450 mg QD</td>
<td>450 mg q 48 h</td>
</tr>
<tr>
<td>10–24</td>
<td>450 mg q 48 h</td>
<td>450 mg 2x/ week</td>
</tr>
</tbody>
</table>

Side effects: frequent leukopenia, also thrombocytopenia, anemia. Gastrointestinal complaints such as nausea, vomiting and diarrhea are more frequent than with intravenously-administered gancyclovir.

Interactions, warnings: monitoring of blood count at least 2–3 x week during induction. Discontinuation if neutrophils below 500/µl (G-CSF if needed). Contraindicated in neutropenia <500/µl, thrombocytopenia <25,000/µl and concurrent chemotherapy.

Caution when concurrent dosing with ddl, as valgancyclovir can double levels of ddl (increased toxicity). Valgancyclovir is potentially teratogenic and carcinogenic; reliable contraception is required.
The drug is extremely expensive. It should be discontinued when sufficient immune reconstitution has been reached (see chapter on OIs).

Comment: Valgancyclovir was the first effective anti-CMV drug to be administered orally. Valgancyclovir is a prodrug of gancyclovir and therefore has a similar toxicity profile, neutropenia, anemia and thrombocytopenia.

**Victrelis®**, see Boceprevir.

**Videx®**, see ddI.

**Viracept®**, see Nelfinavir.

**Viramune®**, see Nevirapine.

**Viread®**, see Tenofovir.

**Vistide®**, see Cidofovir.

**Zerit®**, see d4T.

**Ziagen®**, see Abacavir.

**Zidovudine**, see AZT.

**Zovirax®**, see Acyclovir.
36. Drug-drug interactions

JAN THODEN

With an increasing number of antiretroviral drugs there is a growing risk of adverse drug-drug interactions. These might interfere with therapeutic success. Moreover, antiretroviral drugs are used by an aging patient population with a variety of co-morbidities requiring additional medications. Drug combinations as well as dosages need to be carefully chosen to avoid toxicity.

By inducing or inhibiting enzyme production, the elimination of a drug and hence its plasma levels are influenced. Especially metabolism by cytochrome-P450 plays a crucial role. As many other drugs, PIs and NNRTIs are mainly metabolized by CYP3A4 in liver and the gastrointestinal tract. Another pathway is the glucuronidation by glucuronosyltransferases, though this usually does not cause clinically relevant interactions. Moreover, there are major inter-individual differences in enzyme activity and drug metabolism rates. Other factors that need to be considered include genetic polymorphisms, ethnicity, age, sex, and co-morbidities.

The tables provide a brief overview of drug combinations deemed safe (+) as well as those that should be avoided (⃕). However, for many combinations the interactions are uncertain, unknown or can only be assumed based on theoretical calculations (☀). In these cases, use might still be safe and should be controlled by TDM.

The first part focuses on ART/ART interactions, the second part deals on those between ART and concomitant medications. Clinically irrelevant drugs, such as delavirdine, as well as drugs which are not yet approved are not included. Except for nelfinavir, all PIs are assumed to be given boosted with ritonavir. T-20 is only mentioned in the first part as there are no known relevant interactions with concomitant medications. Ritonavir is only mentioned in the first part, too, yet interactions between it, used as a booster, and concomitant medications need to be considered.

This chapter is intended as a tool to support rapid decision making in the daily practice, but - when in doubt - should not replace a literature search. On rare occasions, drug combinations with known adverse effects might be unavoidable due to a lack of alternatives. In these cases, close monitoring of the patients and the drug levels is necessary, as well as regular TDM.

Abbreviations:

+ Combination of these drugs possible

☀ Potential interactions or unknown, combination of these drugs is often possible, therapeutic drug monitoring suggested

⃕ Combination of these drugs should be avoided or is contraindicated

↑ up to 50% increased drug levels, ↑↑ up to 100%, ↑↑↑ > 100%

↓ up to 50% decreased drug levels, ↓↓ up to 100%, ↓↓↓ > 100%

BID Twice daily (TID = Three times daily)

QD Once daily

TDM Therapeutic drug monitoring
**Part 1: ART + ART**

### NRTIs + NRTIs

<table>
<thead>
<tr>
<th></th>
<th>3TC</th>
<th>ABC</th>
<th>DDI</th>
<th>D4T</th>
<th>FTC</th>
<th>TDF</th>
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<td>+</td>
<td>⊔</td>
<td>+</td>
<td>⫸3</td>
<td>+</td>
</tr>
</tbody>
</table>

1 Antagonism  
2 Increased mitochondrial toxicity (lactic acidosis, pancreatitis, polyneuropathy)  
3 DDI ↑↑ (reduce daily dose to 250 mg), increased toxicity, reduced efficacy

### NRTIs + NNRTIs

<table>
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<th>3TC</th>
<th>ABC</th>
<th>DDI</th>
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</table>

1 Take DDI fasting, ETV with food – if taken apart, no dose adjustment necessary

### NRTIs + PIs

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<th>ABC</th>
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1 ATV ↓↓, ATV to be taken > 2 hrs before DDI  
2 ATV ↓, TDF ↑, ATV always boosted  
3 TDF ↑, caveat: combination with nephrotoxic drugs, increased nephrotoxicity possible  
4 NRTI ↓ (unknown relevance)

### NRTIs + Entry-/Integrase Inhibitors

<table>
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<th>3TC</th>
<th>ABC</th>
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### NNRTIs + Entry-/Integrase-Inhibitors, Entry-/Integrase-Inhibitors + Entry-/Integrase-Inhibitors

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1. MVC ↓↓, increase MVC to 2 x 600 mg/d, if not combined with PI or potent CYP3A4 inhibitor
2. RAL ↓, relevance unclear
3. RAL ↓, MVC ↓, probably without clinical relevance

### NNRTIs + PIs, Entry-/Integrase-Inhibitors + PIs

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1. ATV ↓↓, ATV always boosted
2. MVC ↑↑↑, reduce MVC to 2 x 150 mg/d
3. FPV ↑↑, relevance unclear, monitor FPV levels
4. LPV ↓, increase LPV to 2 x 3 tablets (controversial in combination with NVP, use TDM)
5. SQV ↓↓, always boosted
6. ETV ↓↓, TPV ↑, combination therefore not recommended
7. T-20 can be increased by PIs, PIs by T-20, too, no clinical relevance; TDM if problems

### PIs + PIs

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1. ATV ↑, SQV ↑, combination well tolerated
2. FPV with 200 mg RTV, combination possible

Comment: The combination of two PIs is probably not more effective compared to second generation PIs (DRV and TPV), is therefore only recommended for special indications.
Part 2: ART + concomitant medications

Gastrointestinal agents

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1 NNRTIs are strong enzyme inductors, ondansetron levels can be decreased
2 RPV should not be coadministered with H2-blocking agents, alternatively H2-blocker > 12h before or 4h after RPV
3 No combination of RPV and PPIs, RPV-levels strongly decreased
MCP = metoclopramide, PPIs = proton pump inhibitors

PIs/Entry-/Integrase inhibitors

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1 PIs ↓, take antacids at least 2 hours apart 2 Cimetidine ↑, SQV ↑↑↑
3 ATV boosted, TDM recommended, avoid this combination. 4 Potential interactions with esomeprazole, other PPIs probably without relevant interactions.
5 RAL ↑↑, relevance unclear
Antiarrhythmic drugs

Most PIs increase the drug levels of antiarrhythmic drugs. While in combination with NNRTIs the levels might be fluctuating. If antiarrhythmic drugs are necessary, they need to be introduced with the lowest possible dosage. There are no known relevant interactions between antiarrhythmic drugs and NRTIs. Calcium channel inhibitors will be discussed separately.

Maraviroc: TDM in combination with amiodarone. No interactions with Raltegravir expected.

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Antibiotics

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1 AZT ↓, take 1–2 h apart  2 active metabolite  ↑, consider alternatives e.g. azithromycin.
3 Caveat: renal function  4 Caveat: hematotoxicity  5 Caveat: neuropathy, avoid; dapsone ↓
6 Theoretical data on interactions with NRTIs  7 NNRTI ↑, consider alternatives (azithromycin)
8 Rifabutin ↓, increase dosage to 450-600 mg/d  9 ETV ↓, rifabutin ↓, avoid this combination
10 EFV ↓, increase EFV to 800 mg/d  11 ETV approved in combination with P/r – rifampin contraindicated

Comment: No relevant interactions with azithromycin, ciprofloxacin and tetracyclines.
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1 NFV ↓, azithromycin ↑↑ 2 QT-prolongation possible, clarithromycin ↑ – 50%, reduce dose 3 TPV ↑↑ 4 MVC ↑↑, reduce MVC to 2x150 mg/d 5 PIs ↑, erythromycin ↑, consider azithromycin 6 Little data, probably no relevant interactions 7 rifabutin ↑↑, reduce to 150 mg every other day 8 Increase MVC to 2 x 600 mg/d, if not combined with PI or potent CYP3A4 inhibitor

Comment: (Probably) no relevant interactions with ciprofloxacin, clindamycin and streptomycin.
# Antidepressants

## NRTIs/NNRTIs

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1 CNS-effects of EFV can be increased

Comment: No data exists for most antidepressants and their interactions with NRTIs

## PIs/Entry-/Integrase inhibitors

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1 Tricyclic antidepressants and boosted PIs: PI ↑ antidepressant ↑
2 Paroxetine ↓, adjust if applicable
3 Sertaline ↓, adjust if applicable
4 Antidepressant ↑, titrate dose!
5 Boosted PIs ↑ and venlafaxine ↑, TDM of PIs, careful titration!
6 Tricyclic antidepressants and boosted PI: PI ↑, antidepressants ↑
Antidiabetics (oral)

NRTIs/NNRTIs

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1 TDM of NNRTIs recommended

PIs/Entry-/Integrase inhibitors

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Antihistamines

No relevant interactions with NRTIs, MVC and RAL to be expected.

PIs/NNRTIs

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1 Caveat: Arrhythmia    2 CNS-effects of EFV can be increased

Comment: No relevant interactions with NRTIs

Antihypertensive therapy

Calcium-channel blockers (CCB) can be increased (separate chapter), especially in combination with PIs. They should be introduced carefully. In combination with NNRTIs variations in drug levels are possible. In general, alternatives should be considered. The combination of beta blockers and atazanavir can lead to QT-prolongation.
## Anticonvulsants

### NRTIs/NNRTIs

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1. EFV ↓, NVP ↓, avoid combination or monitor closely (TDM)  
2. CNS-effects of EFV can be increased  
3. AZT ↑↑, monitor for side effects

### PIs/Entry-/Integrase inhibitors

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1. Pls ↓, Carbamazepine ↑, avoid if possible or monitor closely (TDM)  
2. Lamotrigine ↓, increase if necessary

### Antimycotic agents

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1. Caveat: additive nephrotoxicity possible  
2. Increased hematotoxicity  
3. AZT ↑↑, Fluconazole ↓  
4. NVP ↑↑, monitor liver function tests; in combination with azoles Fluconazole still preferred  
5. azoles increase ETR levels, relevance unclear  
6. NNRTIs ↑, azoles ↓  
7. Itraconazole ↓ (take 2 h apart)  
8. NVP ↑, Ketoconazole ↓↓  
9. Caspofungin ↓, dose 70mg/d recommended.  
10. Efavirenz ↑↑ (reduce or TDM), Voriconazole ↓↓, dose 400mg BID recommended.  
11. Posaconazole ↓↓.
**PIs/Entry-/Integrase inhibitors**

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1 Fluconazole ↑↑, do not exceed 200 mg/d  
2 PIs ↑, Itra-/Ketoconazole ↑, avoid doses >200 mg/d  
3 LPV ↑, Itraconazole ↑; avoid doses > 200 mg Itrac./d  
4 Keto-/Itraconazole: MVC 150 mg BID  
5 Voriconazole ↓ by RTV, avoid boosted PIs if possible  
6 MVC to 150 mg BID  
7 ATV-Clearance ↓, TDM!

**Calcium channel antagonists (CCB)**

The serum levels of CCB can be increased, especially if combined with PIs. In combination with NNRTIs serum levels might be fluctuating. Start CCB at low dose and titrate to full effect, monitor BP or discuss alternatives.

**NRTIs/NNRTIs**

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### Immunosuppressants/Chemotherapeutic agents

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1 Neuropathy! Avoid combination if possible  
2 AZT: Hematotoxicity, avoid if possible  
3 Additive nephrotoxicity possible  
4 Immunosuppressants ↑ - ↓, always TDM and dose adjustments!  
5 Paclitaxel ↓

### PIs/Entry-/Integrase inhibitors

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1 Cyclosporine, Sirolimus and Tacrolimus ↑ - ↑↑↑ in combination with PIs, always TDM, dose adjustments if necessary!  
2 Irinotecan toxicity may be increased  
3 PIs-drug levels variable in this combinations, TDM!  
4 Irinotecan ↓  
5 Paclitaxel ↓
Contraception

The serum levels of both ethinylestradiol and norethindrone can be very fluctuation especially in combination with (boosted) PIs. Therefore the use of oral contraceptives containing these hormones might be unsafe. Furthermore their levels can be fluctuating if combined with EFV and NVP. Combination with ETV is usually safe. For these reasons as well as for STD and HIV transmission prophylaxis oral contraceptives should always be combined with an additional method of contraception, preferably a condom.

Antimalarials/Antiprotozoals

Little data exist on combination with entry inhibitors or integrase inhibitors. The data presented here is based on theoretical interactions.

NRTIs/NNRTIs

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1 AZT ↑, monitor for toxicity  2 Caveat: Nephrotoxicity  3 Caveat: Hematotoxicity

Pls/Entry-/Integrase inhibitors

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Phosphodiesterase type 5 inhibitors

Combinations of most PDE5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) with PIs can cause severe increase in PDE5 serum levels. Thus they should be started carefully with a reduced (usually half) dose every 48 to 72 hours. In combination with NNRTIs the levels of PDE5 inhibitors are fluctuating strongly, TDM and individual dosing are recommended (ETV and Sildenafil can be combined, sometimes Sildenafil needs to be increased). There are no known relevant interactions of PDE5 inhibitors with NRTIs, T-20, MVC and RAL. If PDE5 inhibitors are prescribed for pulmonary arterial hypertension alternatives such as endothelin receptors inhibitors should be evaluated.

Due to an FDA warning Sildenafil is now contraindicated for treatment of PAH in combination with a PI. Tadalafil and bosentan need to be adjusted if prescribed as treatment for PAH in combination with a PI. Coadministration of bosentan and ATV (without Ritonavir booster) is not recommended.

Statins/Lipid lowering drugs

The combination of NRTIs, Entry- and Integrase inhibitors with statins is generally possible, but the combination with PIs can cause problems.

Pis/NNRTIs

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1 Atorvastatin ↑ if combined with PIs, low dosing! Consider alternatives: e.g. Pravastatin
2 Atorvastatin ↓, increase dose if applicable or chose alternatives: e.g. Fluvastatin / Pravastatin
3 Statin levels severely increased, avoid these combinations!

Comment: All statins should be started low-dose if combined with Pis!

Anti-addictive drugs

NRTIs/NNRTIs

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1 Buprenorphine ↓, increase dose if necessary
2 Methadone ↓, increase dose if necessary
3 DDI ↓, relevance unclear
4 AZT ↑, relevance unclear
**PIs/Entry-/Integrase inhibitors**

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1 Buprenorphine ↑ · ↑ ↑, reduce dose if necessary  
2 Methadone (↓), adjust dose if necessary  
3 Buprenorphine ↓, adjust dose if necessary

**Antiviral drugs**

There are no known relevant interactions between PIs/NNRTIs and antiviral drugs. No data exists on interactions with CCR5- and integrase inhibitors.

**NRTIs/ NNRTIs**

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1 Caveat: Nephrotoxicity, increased levels through tubular secretion  
2 Hematotoxicity increased  
3 Caveat: Mitochondrial toxicity, Lactic acidosis  
4 Possible antagonism (controversial)  
5 Caveat: Possible resistance (M184V), sparse data on combination with HIV-NRTIs  
6 Caveat: TDF-levels may increase, caveat: Nephrotoxicity  
7 Telaprevir-levels decreased, increase dose to 1,125 mg every 8h  
8 Avoid: Boceprevir-levels decreased.
PIs/ Entry-/Integrase inhibitors

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1 Increased hyperbilirubinemia / jaundice  
2 Strong interactions between Boceprevir, Telaprevir and most boosted PIs, avoid (see Drugs)!  
3 RAL-level increased, probably clinically irrelevant

Others

In the following additional drugs are listed in alphabetical order, which are of interest for HIV clinicians. This group does not represent single categories of drugs.

NRTIs/NNRTIs

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¹ Because of an FDA warning Bosentan needs to be dose adjusted if combined with a PI
² Bosentan is contraindicated in combination with unboosted ATV

### References


Drug information: Aptivus®, Atripla®, Celsentri®, Combivir®, Crixivan®, Emtriva®, Edurant®, Eplivir®, Eplivera®
Fuzeon®, Intelenca®, Inverase®, Isentress®, Kaletra®, Kivexa®, Norvir®, Prezista®, Retrovir®, Reyataz®, Sustiva®, Telzir®,
Trizivir®, Truvada®, Videx®, Viracept®, Viramune®, Viread®, Zerit®, Ziagen®.

Pocket guide to pharmacokinetic interaction profiles of ritonavir boosted PIs; October 2008, Boehringer Ingelheim
Pocket guide to pharmacokinetic interaction profiles of ritonavir boosted PIs; October 2008, Boehringer Ingelheim
www.dosing-gmbH.de Wechselwirkungs-Check (Dosing-GmbH)

www.fda.gov (FDA 04/2010)
www.hiv-druginteractions.org
www.hivinsite.org
www.ifi-interaktions-hotline.de
1. Pneumocystis pneumonia (PCP)
2. CT scan of the lungs with typical PCP findings.
3. Chest x-ray of a PCP patient before and three weeks after treatment with co-trimoxazole.
2. Cerebral toxoplasmosis (TE)
1. and 2. MRI scan of the same patient, multiple, small TE lesions.
3. Solitary TE lesion with typical ring enhancement (CT scan).
4. Cerebral CT scan with a large, solitary lesion and extensive edema.
5. MRI with a solitary lesion.
3. Herpes simplex and Herpes zoster
1. and 2. Refractory herpes simplex-infection in a patient with massive immune deficiency (1), lesions completely resolved after weeks of foscarnet treatment (2).
3. Herpes Zoster at the right arm, hemorrhagic.
4. and 5. Herpes Zoster, prior and three weeks after therapy
4. Tuberculosis, different manifestations
1. Tuberculosis pleuritis with right sided effusion. Left sided “Tree-in-bud” phenomenon as seen in bronchial spread of tuberculosis.
2. Tuberculosis cavities in the left upper lobe. Right sided fine miliar nodules.
3. Tuberculosis, involvement of the spleen.
4. Lymph node tuberculosis, cervical abscess in the setting of an IRIS.
5. Rare AIDS-defining diseases
1. CT scan of the abdomen with multiple lymph nodes, infection with M. avium complex.
2. Fundoscopy, CMV retinitis.
3. Wasting syndrome.
4. and 5. Cutaneous infection with *Penicillium marneffii* (non-AIDS-defining, however frequent in South East Asia)
6. Candida esophagitis
7. CT scan of the lungs with pulmonal cryptococcosis
6. PML and HIV-associated neurological deficit (HAND)
1. and 2. MRI with relatively discrete PML lesions. In the occipital lesion (2) the cortical grey matter is spared which is characteristic for PML.
3. MRI with extensive PML lesions.
4. Axial T2-weighted MRI scan of a 60-year-old patient with HAND. Moderate atrophy, hyperintense lesions at the rostral and caudal ends of the cella media of lateral ventricles. This is typical but not specific for HAND.
7. Candidiasis, OHL
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2. Oral hairy leukoplakia (OHL) with typical plaques on the sides of the tongue which cannot be scraped off.
3. Solitary oral wart on tongue
4. Solitary wart on oral mucosa and corners of mouth.
8. Other oral manifestations in HIV infected patients
1. Necrotizing ulcerative parodontosis on teeth 33 and 35.
2. Linear gingival erythema on vestibular gingiva.
4. Disseminated oral warts on vestibular gingiva.
5. Mouth ulcer vestibular on tooth 37.
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2. Cutaneous, solitary KS lesion.
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4. Primary CNS lymphoma, large solitary lesion with contrast enhancement.
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11. Hodgkin’s disease (HD), Multicentric Castleman’s Disease (MCD)
1. and 2. HD with cervical manifestation, before and after chemotherapy (complete remission).
3. MCD with hepatosplenomegaly (CT scan of the abdomen).
4. MCD, large swollen spleen (autopsy finding).
5. MCD, histological findings, germinal center with a typical “onion-skin” pattern.
12. Dermatological findings
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2. Seborrheic dermatitis (indicator disease!) with flaky, white to yellowish scales to form on oily areas.
3. Severe rash during allergic reaction to nevirapine.
4. Rash, 12 days after initiation of nevirapine
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1. and 2. Lipodystrophy with dorsocervical fat pads (“buffalo hump”).
3. Blood sample of a patient with a hypertriglyceridemia of > 3000 mg/dl which was caused by PI therapy.
4. Lipoatrophy with loss of subcutaneous fat, after years of NRTI treatment
5. and 6. Lipodystrophy, accumulation of the visceral fat.
7. Lipoatrophy, loss of buccal fat.
8. Avascular necrosis of the humeral head
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1. Maculo-papular eruptions, palmoplantar.
2. Polymorphic picture.
3. Primary syphilis with ulcus durum.
4. Ulcus durum, perianal.
5. Exanthema, secondary syphilis.
15. HPV infections
1. Anal condylomata acuminata.
2. Genital condylomata acuminata.
5. Invasive anal carcinoma.
7. Anal carcinoma/AIN III.
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3: 1+2 CH, 3 JR, 4+5 CH
4: 1+2 CL, 3 JR, 4 CH
5: 1-3 JR, 4+5 GH, 6 JR, 7 CH
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7: 1+2 HJS, 3+4 RJ
8: 1-5 RJ
9: 1 JT, 2 CH, 3 JT, 4–6 HJS
10: 1–6 CH
11: 1+2+5 CH, 3+4 CG
12: 1 JR, 2 HJS, 3+4 CH
13: 1–7 CH
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