Roche

Diagnostics

Diagnosis and Management of HIV Infection

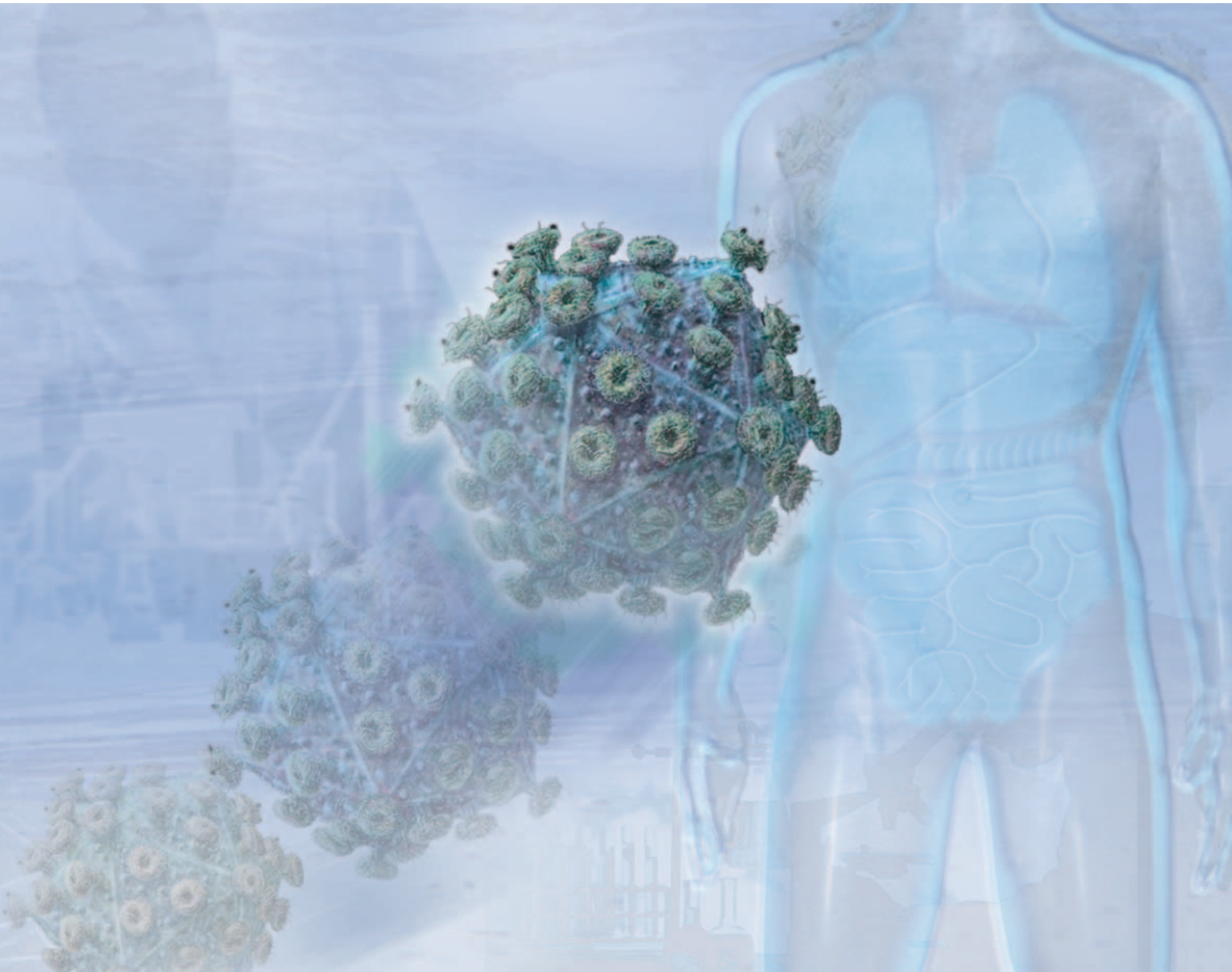

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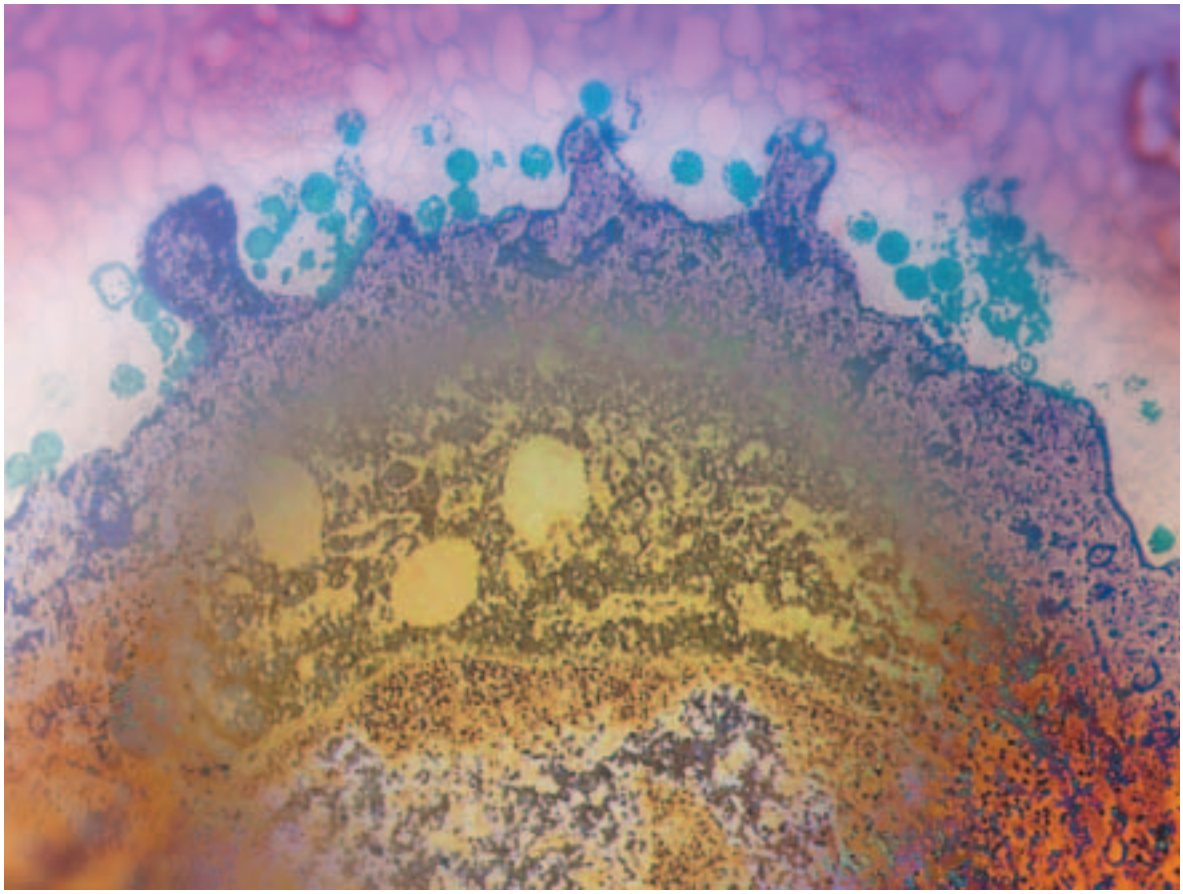
Table of Contents

Introduction

AIDS was first recognised in 1981 when cases of pneumocystis carinii pneumonia and Kaposi's sarcoma were reported in previously healthy homosexual men. Due to the fact that most affected individuals had received blood or blood products or had been exposed to high risk behaviour an infectious agent was considered to be the likely cause of this novel disease. In 1983, the human immunodeficiency virus (HIV) was first isolated from a patient presenting with lymphadenopathy. In 1984, it could be shown that this novel agent was the causative agent of AIDS and in 1985 the first immunoassay to detect this agent in blood was developed. Since then, much has been learned about the virology, the immunopathology, the transmission and the prevalence of that agent worldwide. On the other hand, antiviral therapies have been developed and established with a significant effect on survival and vaccines are currently under investigation with the aim of protecting against infection or supplementing the treatment of HIV-infected individuals. This brochure summarises key points of our knowledge on HIV and its related conditions and focuses on diagnostic procedures related to HIV infection.

HIV budding from a leukocyte



II The Human Retroviruses

The etiologic agent of AIDS is HIV and belongs to the family of human retroviruses and to the subfamily of lentiviruses. Nononcogenic lentiviruses are known to cause disease in other animal species including sheep, horses, goats, cattle, cats and monkeys. The four so far recognized human retroviruses belong to two distinct groups: the human T lymphotropic viruses (HTLV) such as HTLV- I and II and the transforming retroviruses that are designated HIV-1 and HIV-2, which are cytopathic viruses.

HTLV-I has been recognized in Africa, parts of Japan and appears to be rare in North America and Europe. HTLV-I is associated with T cell leukaemia and other specific clinical conditions. HTLV-II appears to be rare and can occasionally be found in drug addicts.

Both HIV-1 and HIV-2 are considered to be zoonotic as those viruses are believed to originate from SIV and in case of HIV-1 from the Pan troglodytes troglodytes species of chimpanzees and in the case of HIV-2 from sooty mangabeys. This species is prevalent in West Africa where HIV-2 is believed to have originated.

The phylogenetic relationship of the primate immunodeficiency virus is depicted in figure 1.

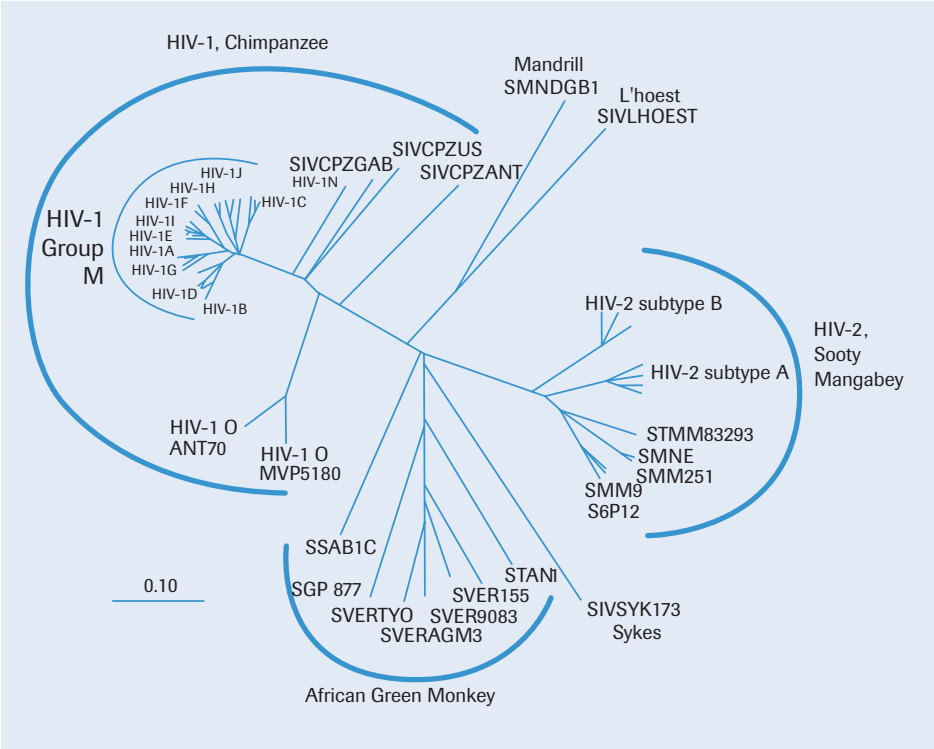


Figure 1: Phylogenetic relationship between primate lentiviruses

Adapted from "Harrison's Online Home, Principles of Internal Medicine" [25]

The morphology of HIV as demonstrated by electronmicroscopy is shown in figure 2 a. The virus has an icosahedral structure with numerous external spikes and contains two major envelope proteins, the external gp120 and the transmembrane gp41. When the virus buds from the infected cell (Figure 2 b) it incorporates a variety of host proteins which include the major histocompatibility complex (MHC) class I and class II antigens into its lipid bilayer. The morphology is shown by electronmicroscopy and is represented schematically in Figure 2a.

Infection of cells occurs via the CD4 receptor which represents a 55-kDa protein which is preferentially found on a subset of T lymphocytes, but is also expressed on monocytes, macrophages and dentritic/ Langerhans cells. In order to enter a cell a co-receptor is required, the major co-receptors for HIV-1 are CCR 5 and CXCR4. After entry into the cell and after uncoating the genomic RNA is transferred to a DNA via reverse transcriptase which is unique to HIV. The viral DNA is then integrated into the host genome. Integration occurs randomly and requires another virally encoded enzyme, the HIV integrase. This provirus remains transcriptionally inactive and thereby represents a latent state or it may manifest itself in varying levels of gene expression, up to active production of the virus. Figure 3 represents schematically the replication cycle of HIV including its entry.

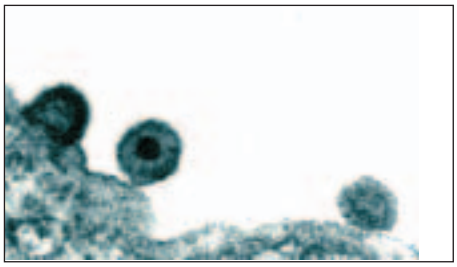


Figure 2 b: Budding of HIV from an infected cell

Adapted from "Harrison's Online Home, Principles of Internal Medicine" [25]

Cellular activation plays an important role in the life cycle of HIV and its pathogenesis. Activation of host cells is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or messenger RNA. Activation of HIV expression requires a number of cellular and viral factors,

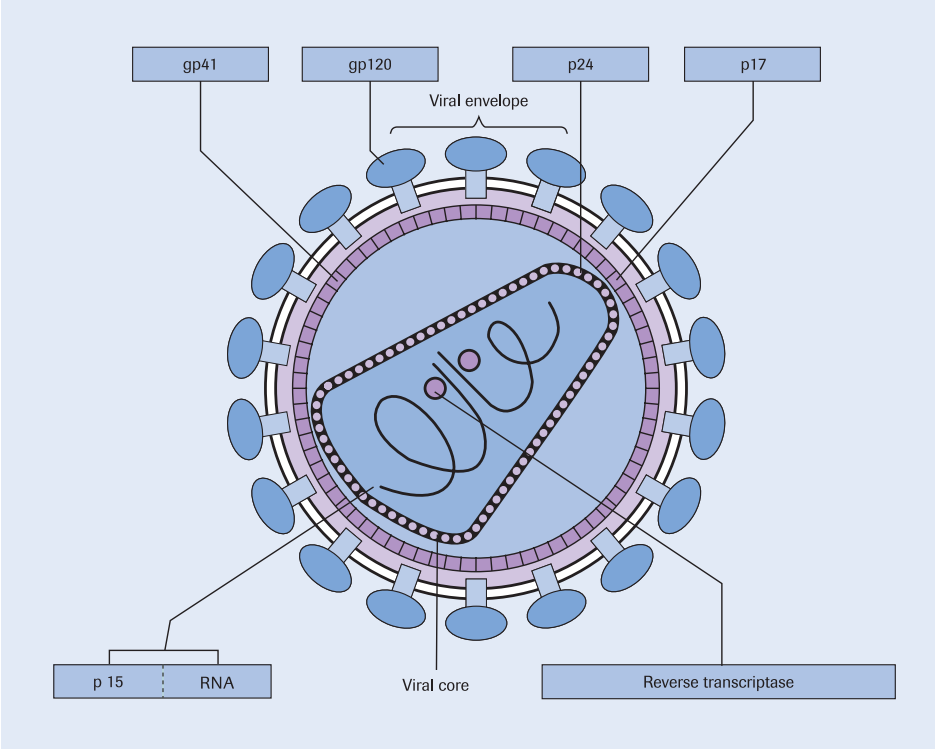


Figure 2 a: The structure of HIV

Adapted from Fields et al [17]

following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristylation, phosphorylation and cleavage. At the plasma membrane of the cells, a viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA. Budding occurs from the host cell membrane where the core acquires its external envelope (Figure 2 b). The virally encoded protease catalyzes the cleavage of the gag-pol precursor to develop to the mature virion. The life cycle of HIV is susceptible to therapeutic intervention especially on the reverse transcriptase and protease level (see below).

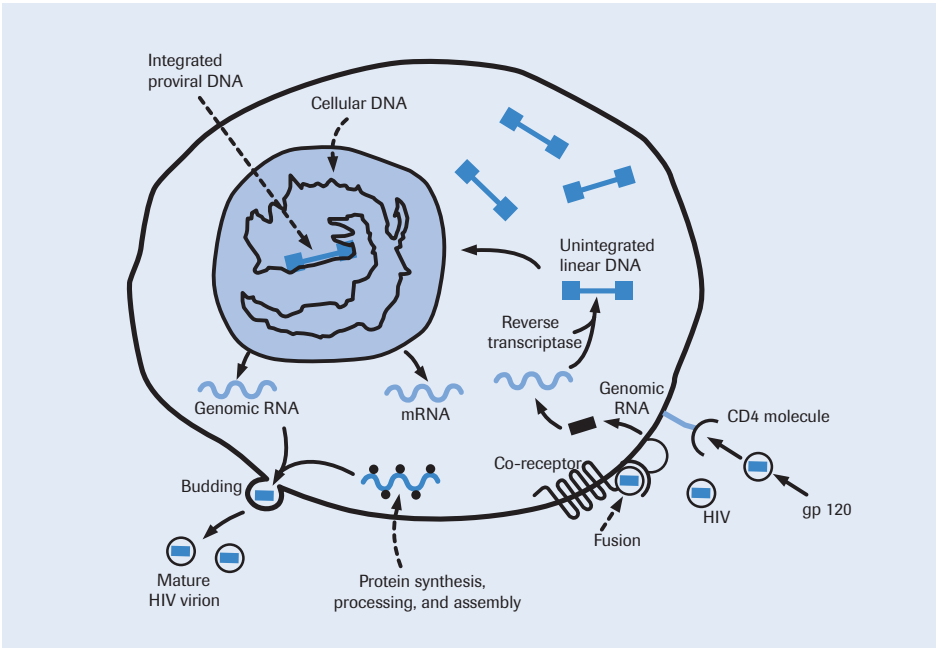
1. The HIV genome

The HIV genome is depicted in Figure 4. The genome contains genes that encode structural proteins, the gag gene encodes the proteins that form the core of the virion including p24 antigen, the pol gene encodes the enzymes responsible for reverse transcription and integration and the env gene encodes the envelope glycoproteins. In addition, there are at least six other genes (tat, rev, nef, vif, vpr and vpu) that represent regulatory proteins involved in the regulation of gene expression. They also play a role in the pathogenesis of HIV disease. Flanking these genes on the long terminal repeats (LTRs) which contain regulatory elements involved in gene expression such as the polyadenylation signal sequence, the TATA promoter sequence, the NFkB and Sp1 enhancer binding sites, the transactivating response (TAR) sequences where the Tat protein binds, and the negative regulatory element (NRE) whose deletion increases the level of gene expression.

There are differences between HIV-1 and HIV-2 in terms of the structure of the genome especially in that HIV-2 lacks the vpu gene and has a vpx gene which is not contained in the HIV-1. In addition, the two viruses are different in the composition of their structural proteins. HIV infection gives rise to antibodies to structural proteins in HIV-infected individuals. These proteins are used for diagnostic purposes. Adequate selection of HIV proteins in immunoassays has impact on sensitivity and specificity of immunoassay to detect HIV infection.

Figure 3: Replication cycle of HIV

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[25]



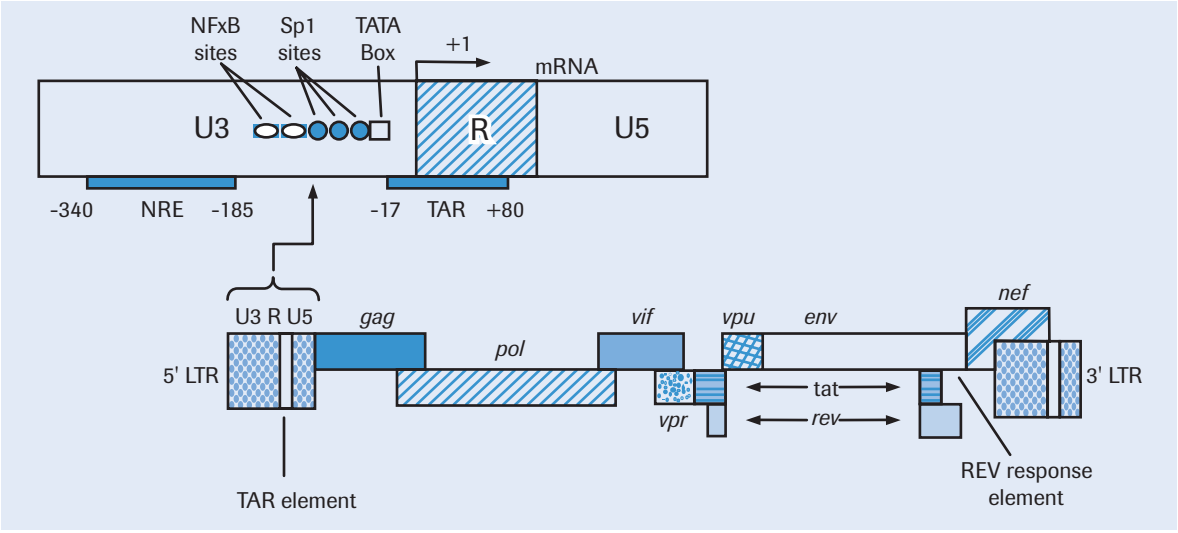


Figure 4
Structure of the HIV genome

Adapted from "Harrison's Online Home, Principles of Internal Medicine" [25]

2. Molecular heterogeneity of HIV-1

In contrast to HTLV-1 and 2 there is a significant molecular heterogeneity of HIV-1, the degree of differences might be up to 50% in the viral envelope region. Hypervariable regions such as V3 are the target for neutralizing antibodies and the recognition sites for T cell responses; they have an extremely high degree of genetic heterogeneity, most likely due to the pressure of the immune system.

Two groups of HIV-1 have been identified and designated group M (major) and group O (outlier). The group O of HIV-1 strains cluster in areas like Cameroon, Gabon and countries to which people from this region have been migrated to such as France. Group M comprises eight subtypes designated A, B, C, D, F, G, H and J, and four major groups of recombinant forms. These are AE which is prevalent in Asia, AG in West and Central Africa, AGI in Cyprus and Greece and AB in Russia. In addition, a third group (group N) has been found in Cameroon. Figure 5 demonstrates the phylogenetic tree constructed for HIV-1 group M, O and N.

The distribution of HIV-1 subtypes has been changed over time. While initially subtype B was the only subtype found in Europe, North America and Australia, migration of other subtypes has changed

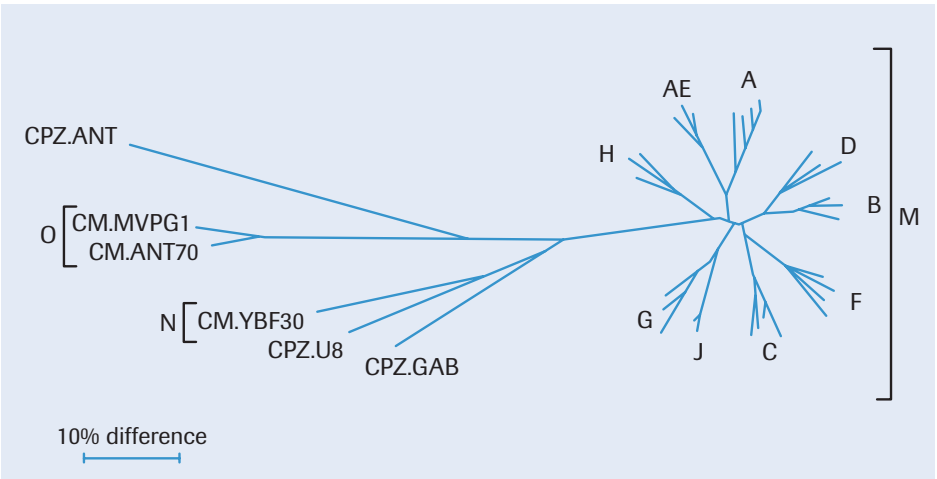


Figure 5:
Phylogenetic relationship between HIV subtypes

Adapted from "Harrison's Online Home, Principles of Internal Medicine" [25]

this pattern significantly (Figure 6 a + b). Knowledge on the molecular heterogeneity of HIV-1 has impact on the reliable recognition of HIV using nucleic acid technology. For this reason, selection of conserved regions of HIV is required to reliably detect all subtypes of HIV-1, including quantitatively.

3. Transmission of HIV

HIV is transmitted via different routes:
a) sexually
b) by blood and blood products
c) from mother to child
d) by other body fluids

Sexual transmission is the most frequent method of transmitting HIV either by heterosexual or by homosexual contacts. Inflammatory conditions such as urethritis, epididymitis, or STDs favour transmission of HIV. This is caused either by increased concentrations of HIV in the fluid or by lesions due to infections. In addition, transmission is increased when the mucosa is more vulnerable such as in the case of anal intercourse.

Transmission of HIV by blood and blood products has significantly decreased in the developed world since the introduction of HIV screening and recently by the introduction of HIV RNA testing of blood and blood units. In developing countries, blood or blood products may not be screened regularly for anti-HIV and more sensitive tests like HIV RNA to reduce the residual risk have not been implemented.

Another mode of transmission is by blood or its components, however sharing needles, syringes or unsafe practices in case of acupuncture, tattooing and piercing can lead to HIV transmission. Such unsafe practices are also more common in developing countries.

Figure 6 a: Prevalence of HIV-1 subtypes (1994)

Medical interventions with re-used needles and syringes might also contribute to the spread of HIV, particularly in developing countries.

Occupational exposure to blood components when health care workers are stuck by needles or other sharp medical instruments may result in the transmission of HIV. Normally a larger quantity of blood is required to result in transmission of HIV after parenteral exposure in the health care setting.

HIV positive mothers might transmit HIV to their newborn. HIV might be transmitted during pregnancy as early as the first and second trimester or during delivery. Factors influencing the transmission of HIV from mother to infant are concomitant STD infection, the presence of chorioamnionitis at the time point of delivery, cigarette smoking, drug abuse, preterm labour, obstetric procedures and finally, the level of viremia in the mother.

For example, the likelihood of transmission from mother to infant was 0 % in women with <1000 copies of HIV RNA/ ml of blood, 16.6 % between 1000 to 10000 copies /ml, 21.3 % among women with copies between 10000 and 50000/ml, 30.9 % with copy numbers between 50000 and 100000/ml and 40.6 % if the number of copies exceeded 100000/ml.

Breast feeding has also been shown to contribute to the transmission of HIV from mother to child and may account for 5 to 15% of infants becoming HIV positive after delivery.

To what extent other body fluids are responsible for the transmission of HIV is uncertain. There is no evidence that saliva which is not contaminated with blood is involved in the transmission of HIV. There is also no evidence that tears or sweat might be involved in the transmission of HIV.

Figure 6 b: Geographic spread of subtypes and recombinant HIV-1 (2001)

4. Epidemiology of HIV

Since its discovery in 1984, HIV has continued to spread worldwide. As can be seen from figures 7a, 7b and 7c, cases of HIV and AIDS are steadily increasing. In some countries in sub-Saharan Africa, the prevalence of HIV infection may exceed 20% of the population. Contributors to the spread include poverty in association with commercial sex, high level of promiscuity in the heterosexual population, intravenous drug abuse without the use of disposable syringes and needles, revival of unsafe sex in the homosexual population and other factors.

5. Epidemic types of HIV

In addition, long distance travel has also contributed to the spread of HIV. The opening of borders, an increase in intravenous drug abuse and prostitution has led to a significant increase in HIV in previously unaffected countries such as Russia and China. Overall, HIV is still on the rise although the increase in HIV has decelerated in certain areas like North America and Europe. In these countries however HAART (highly active antiretroviral therapy) has resulted in an increasing use of unsafe sex practises mainly in the high risk population (homosexual/bisexual men).

Figure 7a: Spread of HIV over time in Asia, 1982 – 1997

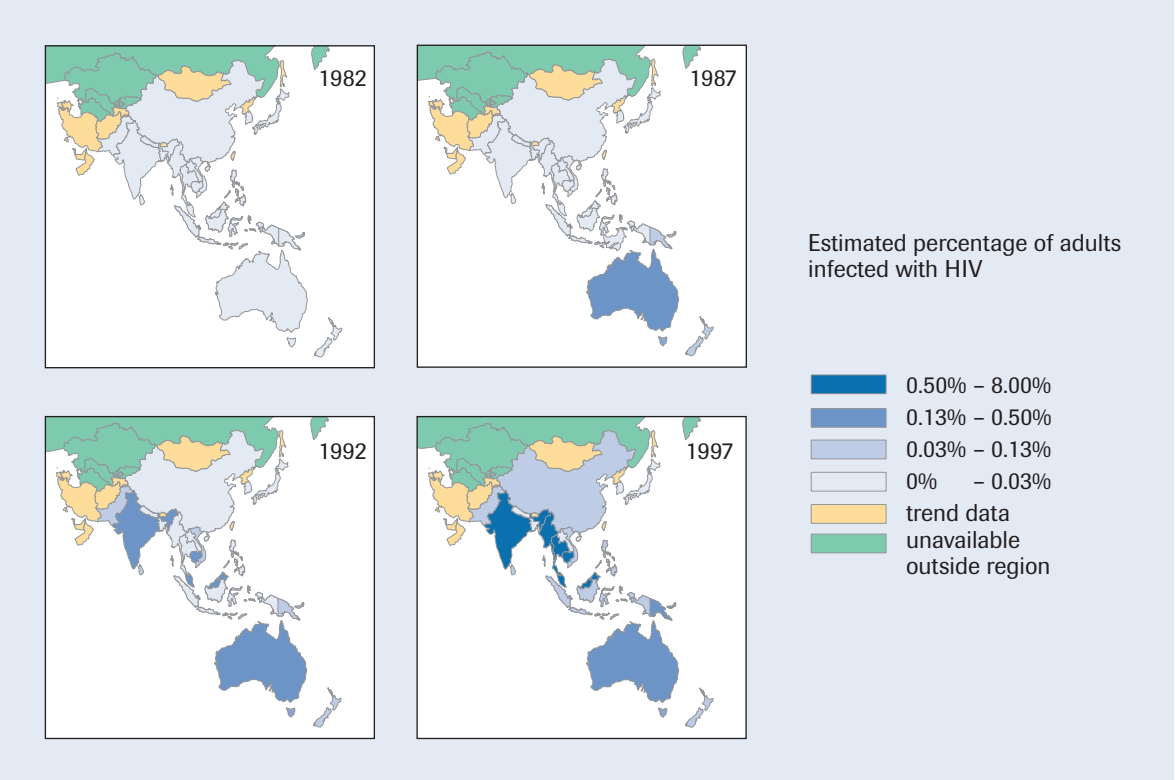


Figure 7b: Spread of HIV over time in Latin America and the Caribbean, 1982 – 1997

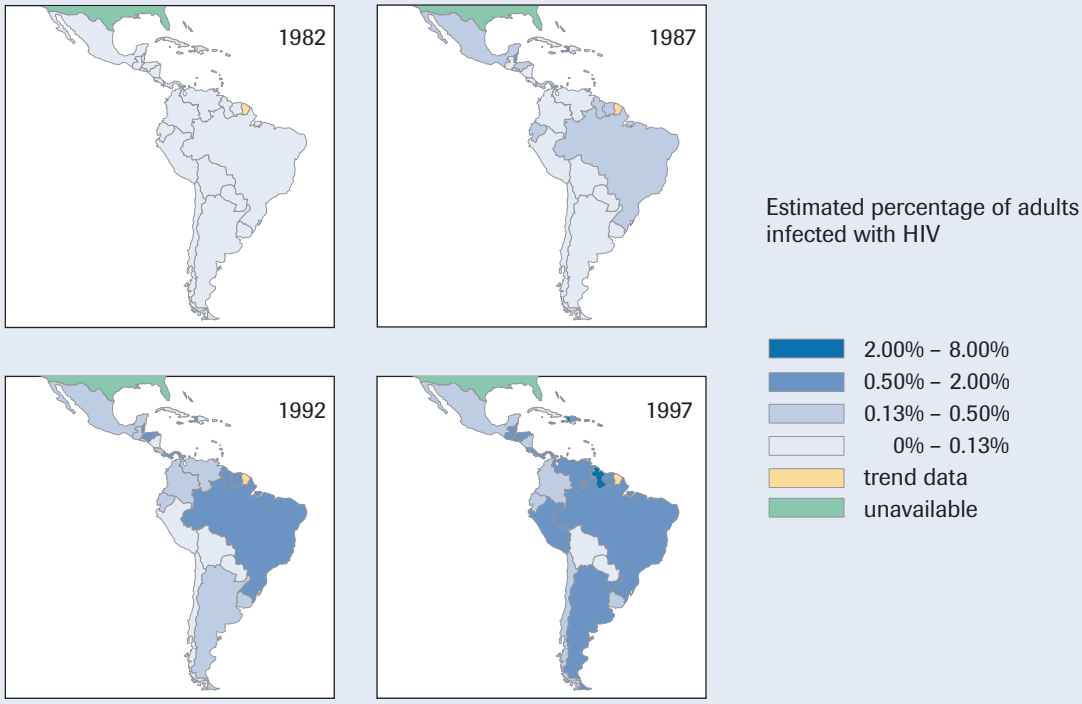
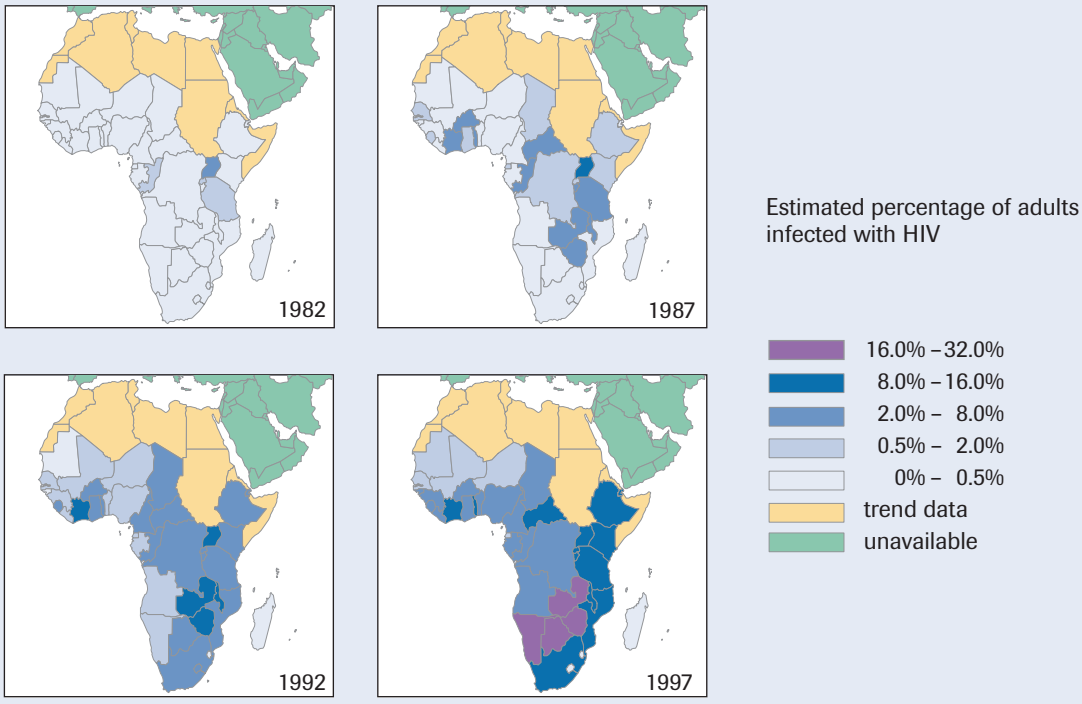


Figure 7c: Spread of HIV over time in sub-Saharan Africa, 1982 – 1997



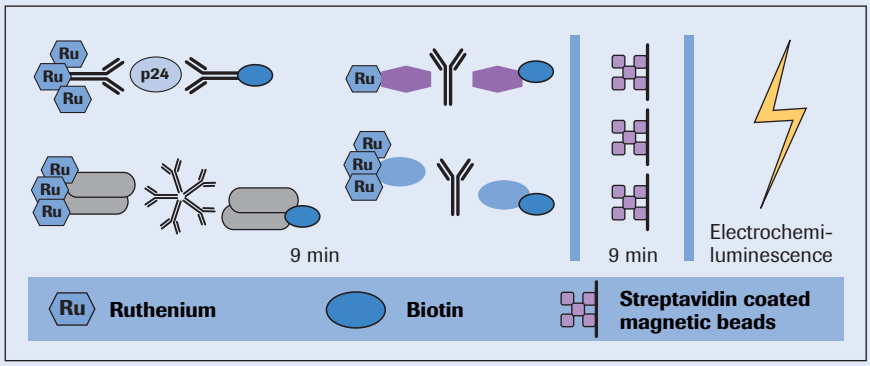
IV Diagnostic Methods of HIV Infection

The diagnostic methods in HIV infection serve different purposes

a) the identification and characterisation of HIV infection
b) analysis of the impact of HIV infection on the immune system
c) the assessment of infections that are transmitted via the same route as HIV
d) the assessment of complications of HIV infection or its treatment

1. Diagnosis of HIV infection

The cornerstone for the diagnosis of HIV infection is an immunoassay which recognises antibodies to HIV-1, HIV-2 and to the HIV-1 group O. The immunoassay may also contain a component which detects p24 antigen in addition to HIV antibodies (so-called HIV Ag/Ab combined assays or 4th generation HIV assay). The addition of p24 antigen detection into the immunoassay has the advantage of improved sensitivity in seroconversion samples (see below). The development of immunoassays to detect HIV infection has improved over time, e. g. by introducing components for the detection of HIV- 2 and HIV- 1 group 0 into the test. The initial immunoassay has a high level of sensitivity (over 99.5%) and is regularly scored as posi-



MODULAR *ANALYTICS* **<E>**

Elecsys 2010

Figure 8: Elecsys HIV combi test principle and automated immunochemistry analyzers Elecsys 2010 and MODULAR *ANALYTICS* **E. Total Assay Time: 20 min, throughput: 85 tests/h (Elecsys 2010) up to 170 tests/h (MODULAR** *ANALYTICS* **E).**

tive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). This highly sensitive immunoassay lacks however a very high level of specificity, especially in low risk individuals. The principle of an immunoassay to detect anti-HIV and p24 antigen (4th generation HIV assay) is shown in Figure 8.

Because of the limited specificity of HIV screening tests, a positive ELISA needs to be repeated and then confirmed by a more specific method which is the western blot. In the western blot, HIV proteins are separated by their molecular weight, and reactivity of the patient serum with the different proteins is assessed. Figure 9 shows different western blot results. Based on the criteria established by the FDA, positive western blot needs to have positive bands of at least two or three HIV proteins, p24, gp41 and gp120/160. If these criteria are fulfilled the individual needs to be considered HIV positive. Gp41 and gp120/160 reflect proteins related to structural envelope proteins, p24 represents the core protein, whereas p51 represents the reverse transcriptase.

If the western blot is not considered to be positive or negative it is categorized as indeterminate. There are basically two possible explanations for an indeterminate western blot result. The most likely explanation in a low risk individual is that the patient being tested has antibodies that cross-react with one of the proteins of HIV. The most common patterns of cross-reactivity are antibodies that react with p24 and/or p55. The least likely explanation in this setting is that the individual is infected with HIV and is in the process of mounting a classic antibody response. In either instance, the western blot should be repeated after one month to determine whether or not the indeterminate pattern is a pattern in evolution.

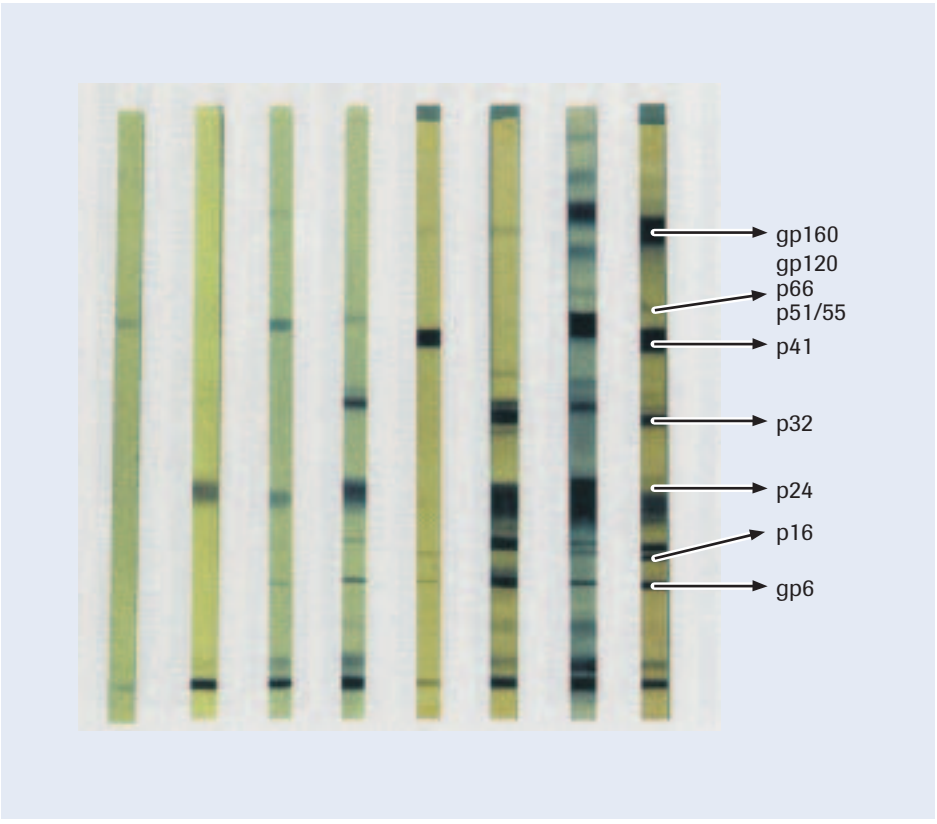


Figure 9:
HIV western blot

An alternative method to resolve indeterminate results is the performance of an HIV RNA test (see below).

P24 antigen (HIV Ag) is regularly detectable in the serum of individuals with established HIV infection and a high level of viral replication, and in early HIV infection. P24 antigen can be detected by an immunoassay and represents an indicator of HIV viremia. This test is increasingly replaced by the assessment of HIV RNA. Figure 10 describes an algorithm which may vary between countries – to confirm or exclude HIV infection.

HIV RNA can be found in the plasma of HIV-infected individuals in the early phase of infection and in chronic HIV infection (see below). The target amplification test works on the principle that conserved regions of HIV are amplified after reverse transcription, after amplification the amount of DNA is measured. Figure 11 shows the principle of an automated HIV RNA test. The sensitivity of current HIV RNA tests is approximately 50 copies/ml. Quantitation using HIV standards also allows in addition the estimation of the concentration of circulating HIV RNA in serum. HIV RNA concentration allows an estimate of infectivity (see above) and represents a biomarker for the efficacy of antiviral therapy (see below). Efficacy of amplification of the HIV RNA test is largely independent of the underlying HIV subtype. The current indications for HIV RNA tests are summarised in Table 1.

Figure 10: Example for an HIV testing algorithm

Adapted from Schüpbach J. , Human Immunodeficiency Viruses" [52]

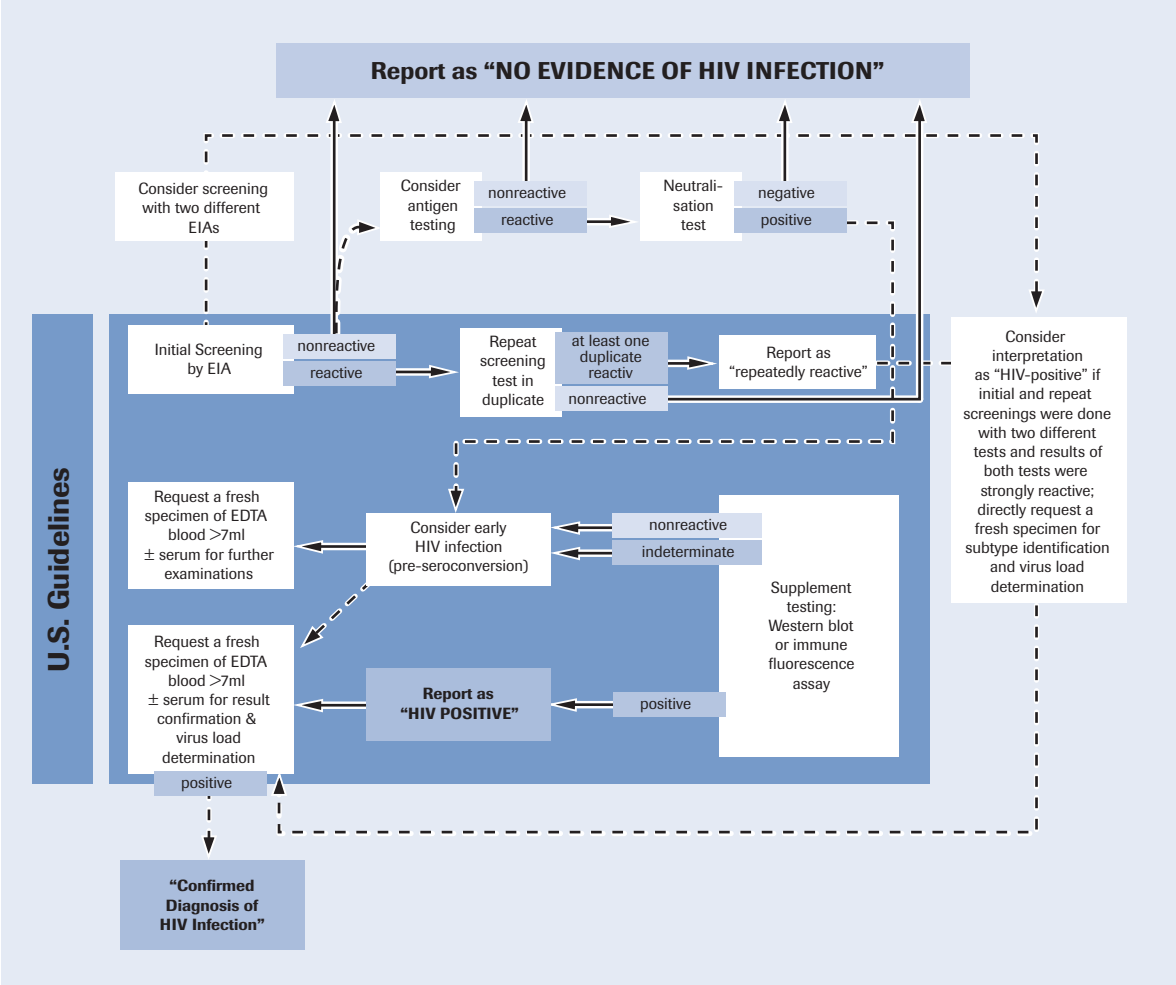
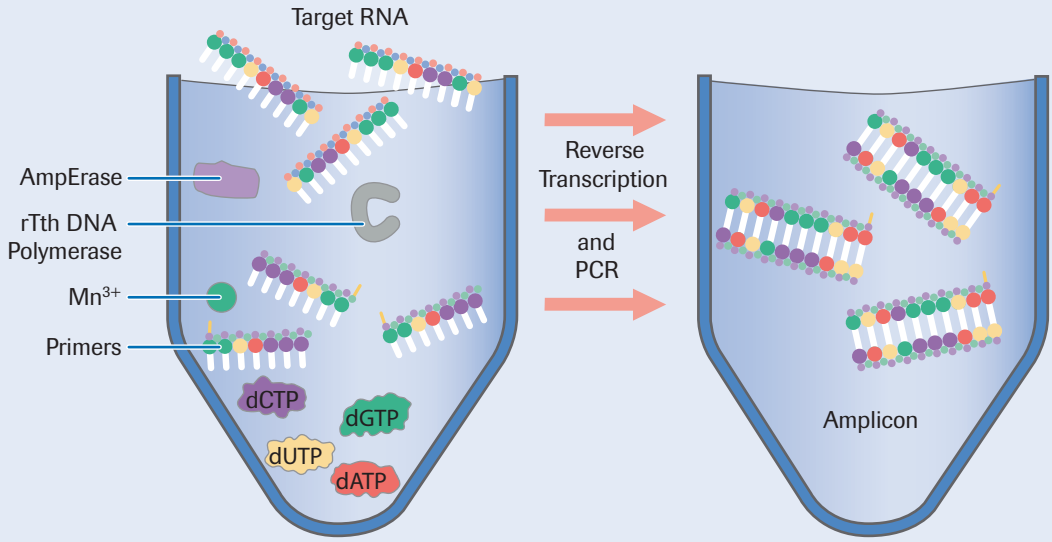


Figure 11: Principle of an HIV RNA test e.g. the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (in development). This test will be fully automated for both sample preparation (COBAS AmpliPrep Instrument) and amplification (COBAS TaqMan Analyzer). Included in the test is an internal control that is also a quantitation standard, and AmpErase to suppress carryover contamination. Total duration for the HIV-1 PCR result: 120 minutes for 24 sample preparations by the AmpliPrep + 230 minutes for TaqMan Analyzer amplification.



When using manual methods, HIV RNA is isolated from plasma or serum by lysis of virus particles with a chaotropic agent followed by precipitation of the RNA with alcohol. When using automated methods, the RNA is adsorbed onto magnetic glass particles, washed, and then eluted from the glass surface using a low salt buffer or water.

COBAS AmpliPrep Instrument

COBAS TaqMan Analyzer

Table 1

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnostics when HIV antibody test is negative or indeterminate	Diagnosis*
Initial evaluation of newly diagnosed HIV infection	Baseline viral load set point	Decision to start or defer therapy
Every 3 – 4 months in patients not on therapy	Changes in viral load	Decision to start therapy
2 – 8 weeks after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3 – 4 months after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3 – 4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or to change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable viral load	Decision to continue, initiate or change therapy

Acute illness (e. g. bacterial pneumonia, tuberculosis, herpes simplex virus, Pneumocystis carinii pneumonia), and vaccinations can cause an increase in plasma HIV RNA for 2 – 4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

*** Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods (e. g. Western blot serology performed 2 – 4 months after the initial indeterminate or negative test).**

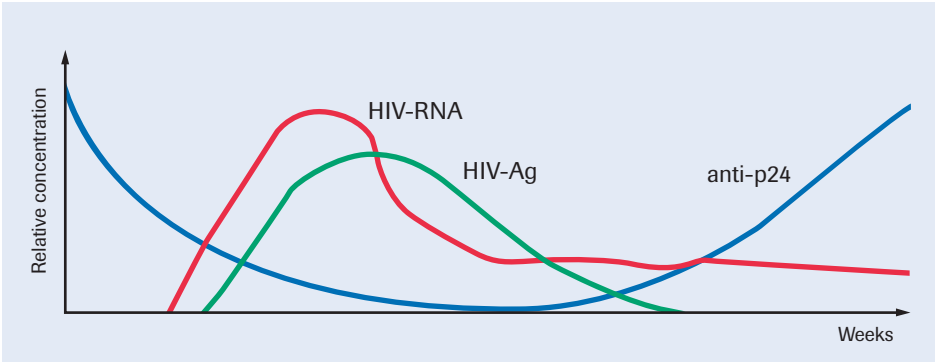
Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV- 1- Infected Adults and Adolescents"[62]

Proviral DNA can also be measured in peripheral blood mononuclear cells using a DNA PCR test. This is currently done for research use only and might be of use if serum HIV RNA becomes undetectable. The sensitivity of the proviral DNA test is extremely high and can measure 1 copy/10000 to 100000 cells.

The screening methodology described using an anti-HIV 1/2 ELISA is not suitable in case of detection of HIV infection in newborns. Due to the passive transfer of anti-HIV from mother to child only the detection of p24 or HIV RNA is of diagnostic significance. Tests might become positive after weeks to months after delivery. If positive these tests indicate HIV-infection in the newborn (Fig. 12 a) Figure 12 b shows the sequence of events in seroconversion after HIV infection in adults. As can be seen from the figure, HIV RNA is the first test to become positive followed by p24 and anti-HIV. Thus in case of suspected early infection, HIV RNA remains the method of choice to identify early HIV infection with the possibility of early intervention (see below).

Laboratory tests in established HIV infection

Once HIV infection is established, clinical information and laboratory information need to be integrated to optimise patient management. The natural course of HIV infection is shown in Figure 12 c.



Figur 12 a: Markers of HIV infection in a newborn

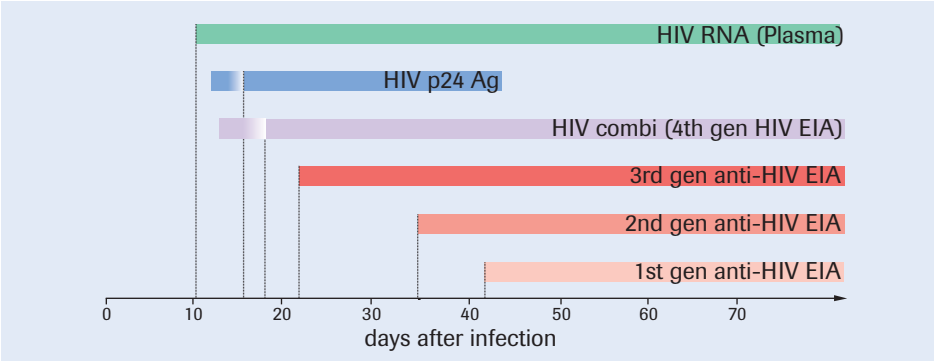


Figure 12 b: Early detection of HIV detection by diagnostic assays

Adapted from Weber et al, 2001 [71]

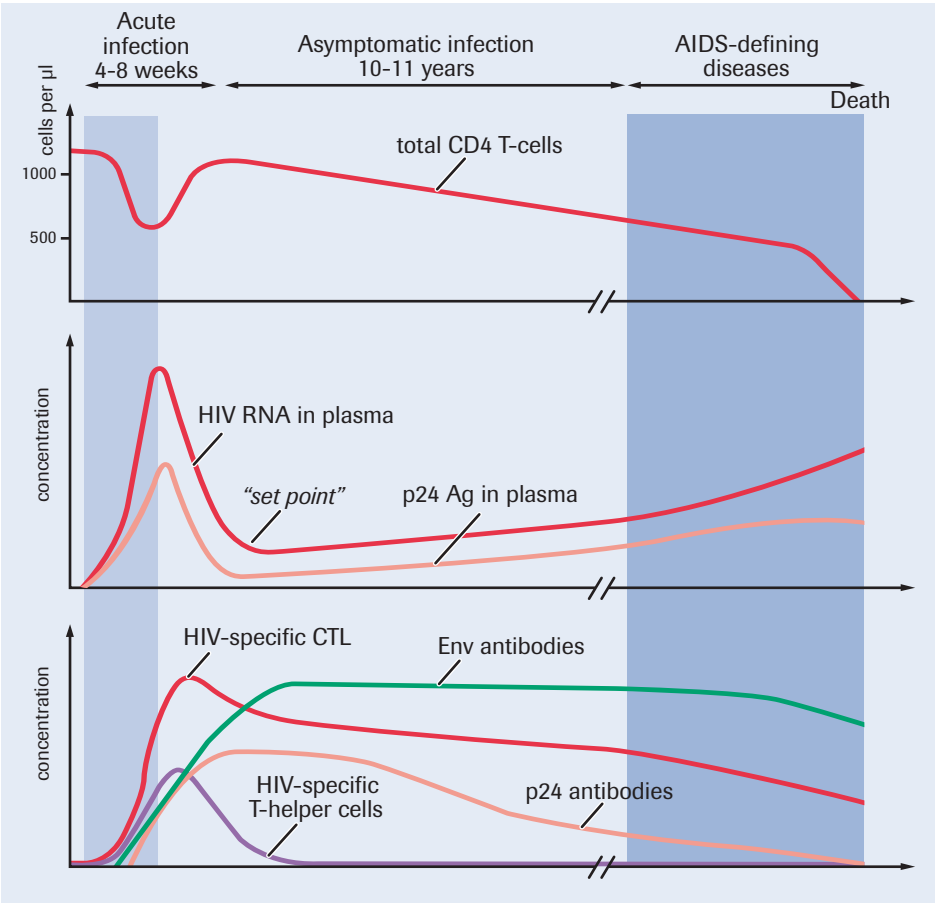


Figure 12 c: Natural course of HIV infection

Adapted from Schüpbach et al. [52]

2. CD4 and T cell counts

CD4 positive cells are the major target for HIV and are reduced over time to present a marker for the state of the immune system. CD4 positive cells are measured by flow cytometry in a quantitative fashion. CD4 positive cells are used for the staging of HIV disease and are also used to trigger intervention. CD4 positive cells should be measured at initial diagnosis and at three to six months intervals. CD4 positive cells do also indicate the likelihood of opportunistic infections to occur (Figure 13).

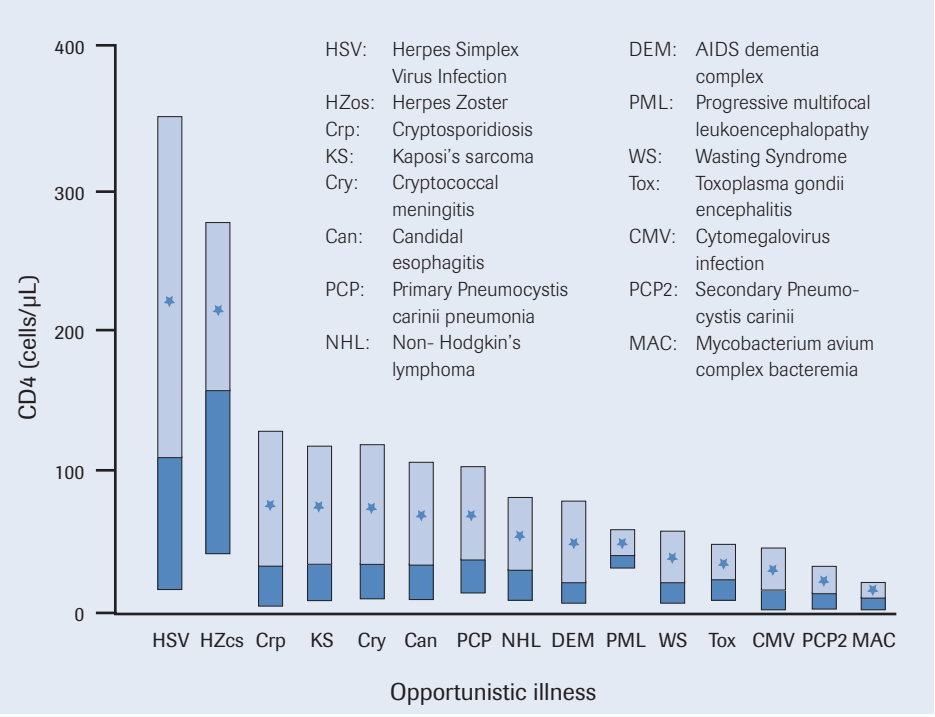
HIV RNA determination represents a second cornerstone in the monitoring of HIV-infected individuals. As discussed current HIV RNA tests have a sensitivity of approximately 50 copies/ml. Using appropriate standards HIV RNA can be quantitated quite precisely; however, different states such as concomitant infections or states of immune activation might affect viral replication. Therefore single determination and changes in HIV RNA should not be used for decision making, a second HIV RNA test is required to confirm the initial finding. HIV RNA determination is recommended at the time of HIV diagnosis and at three to four month intervals. Once the treatment is initiated HIV RNA should be monitored every four weeks until steady state levels of HIV RNA are reached. Effective therapy is considered to result in undetectable HIV RNA levels (Figure 14 a – c).

3. HIV resistance testing

In the era of HAART (highly active antiretroviral therapy) the occurrence of mutations indicating resistance to certain drugs is frequent both in primary HIV infection as well as in individuals with established HIV infection. In principle, two methods for HIV drug resistance testing are available, the genotypic and the phenotypic measurements. In genotypic assays, sequence analysis of the HIV genome obtained from patients is compared to sequences of viruses with known antiretroviral resistance profiles (Figure 15 a).

Figure 13: Likelihood of opportunistic infection, related to CD 4 counts

Adapted from Harrison's Online Home, Principles of Internal Medicine [25]



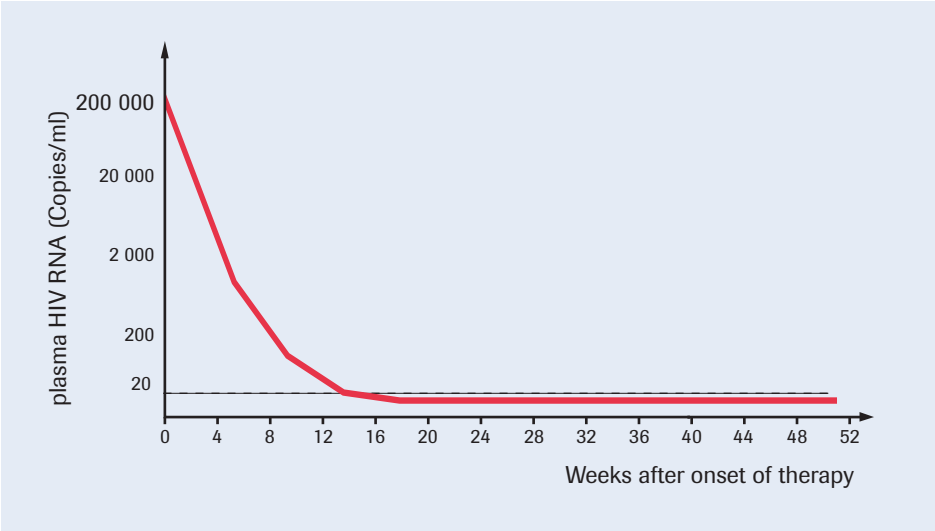


Figure 14 a: Response to antiretroviral therapy

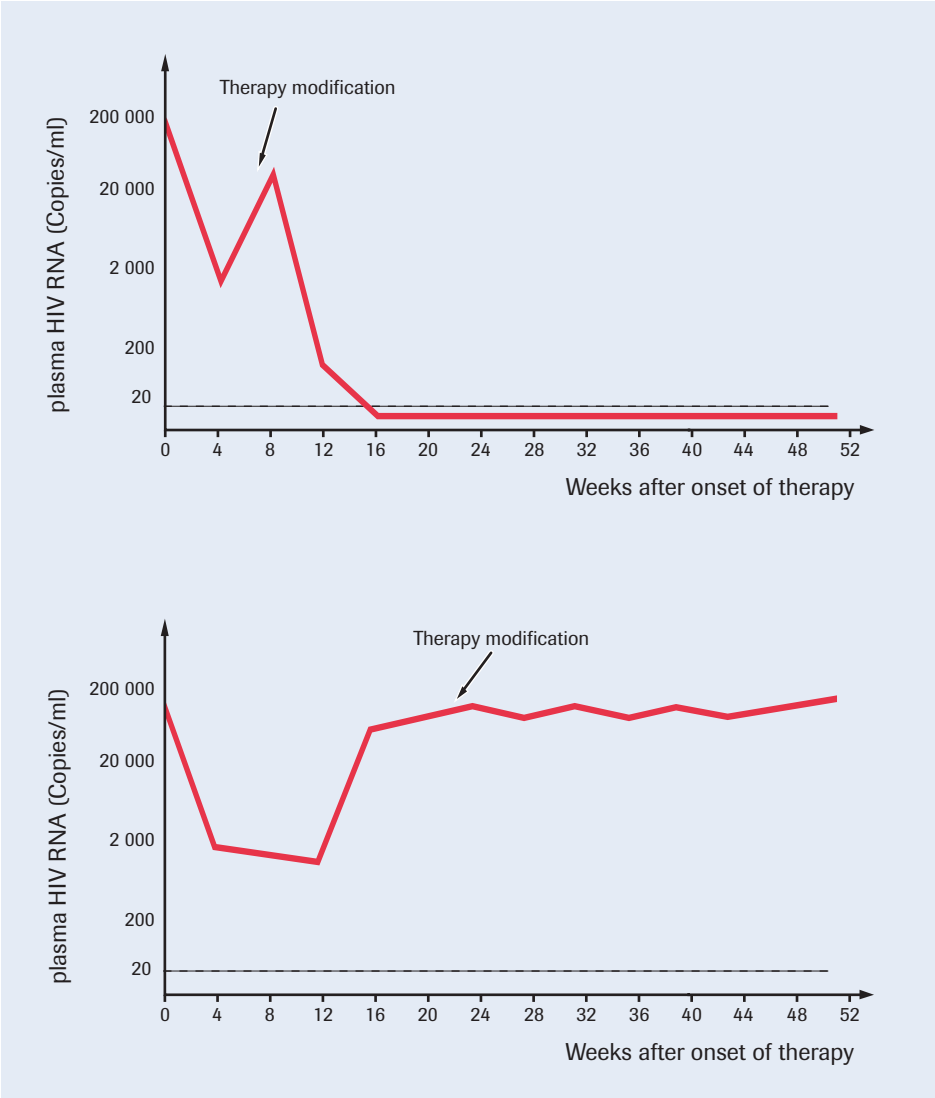
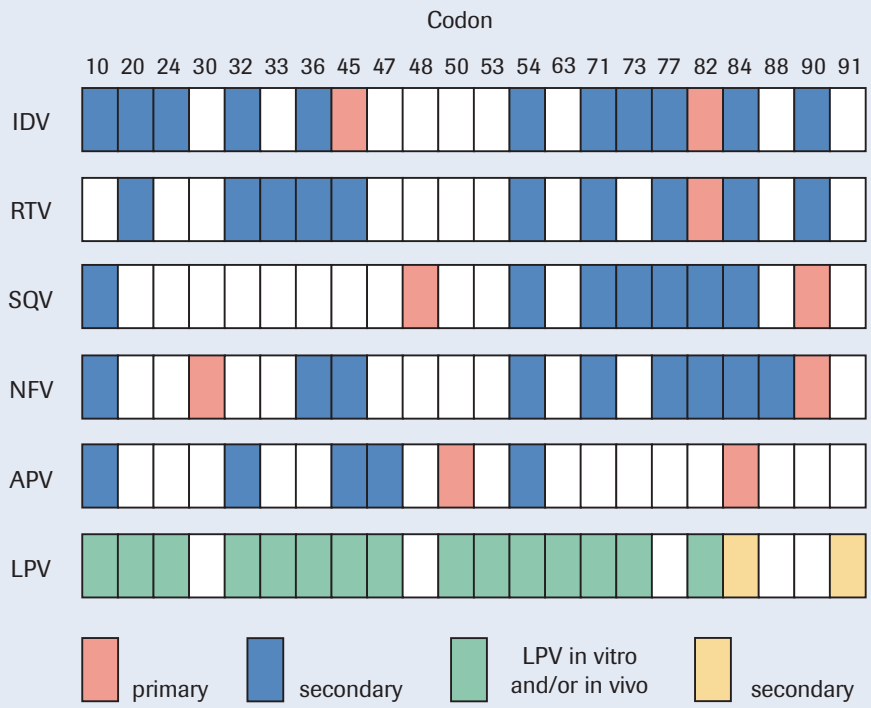


Figure 14 b + 14 c: Non-Response to antiretroviral therapy

Figure 15 a
Protease gene mutations selected by protease inhibitors (PI)

Adapted from website
http://www.Roche-HIV.com

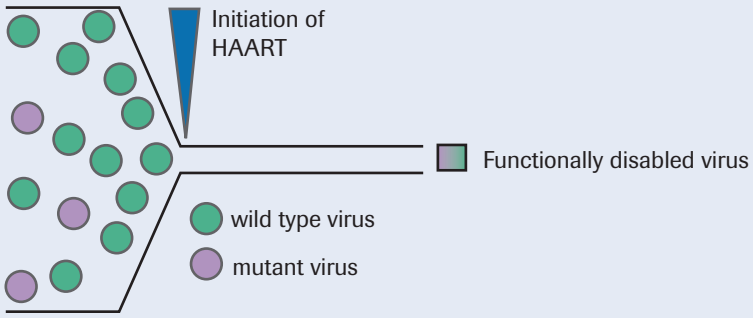


IDV = Indinavir, RTV = Ritonavir, SQV = Saquinavir, NFV = Nelfinavir,
APV = Amprenavir, LPV = Lopinavir

Source:
1. Hirsch JAMA 2000;283:2417-26
2. Carillo et al. J Virol 1998;72:7532-41
3. Molla et al. Antivir Ther 2001; 6 (suppl 1)49
4. Mo et al. 6th CROI 1999, Abs 117

Figure 15 b
Effective HAART reduces the probability of functional, fully resistant virus emerging

Adapted from website
http://www.Roche-HIV.com



In genotypic analysis only the sequence of the predominant strains becomes apparent and minor strains might not become visible (15 b).

In phenotypic assays, in vivo growth of viral isolates obtained from the patients are compared to the growth of reference strains of the virus in the presence or absence of different antiretroviral drugs. A modification of this phenotypic approach utilises a comparison of the enzymatic activities of the reverse transcriptase or protease genes obtained by molecular cloning of patients' isolates to the enzymatic activities of genes obtained from reference strains of HIV in the presence or absence of different drugs targeted to these genes.

Both methods in general present good evidence of the presence or absence of resistance, especially in conjunction with changes in HIV RNA concentrations over time. Recommendations for the use of drug resistance testing are summarised in Table 2.

Clinical setting/ recommendations	Rationale
Drug- resistance assay recommended	
Virologic failure during combination antiretroviral therapy (AI)	Determine the role of resistance in drug failure and maximise the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after antiretroviral therapy initiation (BIII)	Determine the role of resistance and maximise the number of active drugs in the new regimen, if indicated.
Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy (AIII)	Determine if drug- resistant virus was transmitted and change regimen accordingly.
Drug- resistance assay should be considered	
Chronic HIV infection of drugs (DIII)	Available assays might not detect minor drug- resistant species. However, should consider if significant probability that patient was infected with drug- resistant virus (i. e., if the patient is thought to have been infected by a person receiving antiretroviral drugs).
Drug- resistance assay not usually recommended	
After discontinuation of drugs (DIII)	Drug- resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug- resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug- resistant species.
Plasma viral load < 1,000 HIV RNA copies/ ml (DIII)	Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/ providers may incur charges and not receive results

Table 2
Recommendations for the use of drug resistance testing

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" [62]

4. Other tests

There are a number of other tests that have been done mostly on the research level that might change in the context of HIV infection. Such markers include quantitative culture of replication-competent HIV from plasma, peripheral blood mononuclear cells, or resting CD4+ T cells, circulating levels of β_2-microglobulin, soluble IL-2 receptor, IgA, acid-labile endogenous interferon, or TNF-α; and the presence or absence of activation markers such as CD38 or HLA-DR on CD8+ T cells.

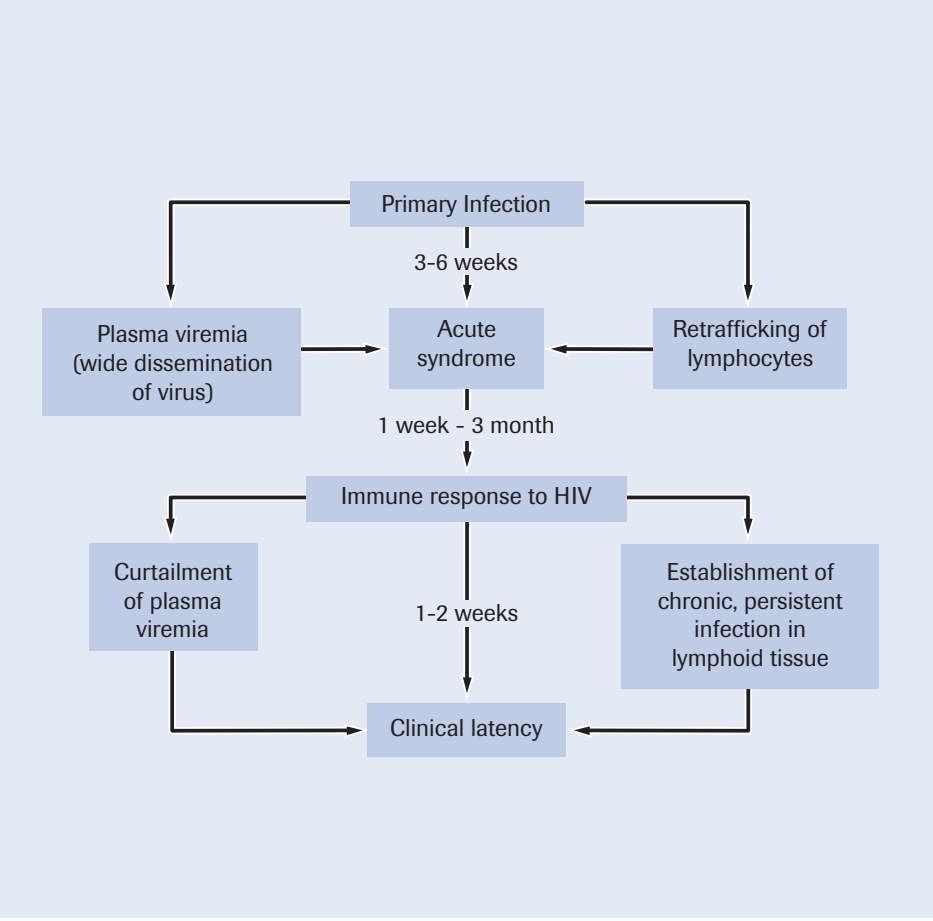
Other laboratory tests that reflect co-infections with other agents that are transmitted in a similar way to HIV or complications from HIV infection will be discussed below in association with those agents and/or complications.

5. Clinical presentation of HIV

The acute HIV syndrome occurs in approximately 50 to 70 % of individuals with HIV infection which occurs approximately 3 to 6 weeks after primary infection (Figure 16) The typical findings associated with this syndrome are listed in Table 3. During acute HIV syndrome, generally CD4 cells temporarily decrease whereas CD8 cells temporarily increase. After resolution of the acute HIV syndrome, the asymptomatic clinical latency stage develops. Clinical latency is followed by the lymphadenopathy syndrome which in turn proceeds to symptomatic disease. According to the classification system of HIV infection and expanded AIDS survey case definition for adolescents and adults, HIV is classified by clinical findings and the number of CD4 cells. This is listed in Tables 4 and 5.

Figure 16
Acute HIV infection

Adapted from Harrison's Online Home, Principles of Internal Medicine [25]



Life threatening complications are expected if CD4+ cells drop below 200 cells/µl. As approximately 80 % of deaths among AIDS patients are the result of an additional infection and not of HIV, it is recommended to prevent opportunistic infections. Current guidelines are listed in Table 6. In addition, immunization is recommended against hepatitis A, hepatitis B, influenza virus and Streptococcus pneumoniae and prevention strategies are recommended for recurrent infections such as herpes simplex and candida infections.

General	Fever
	Pharyngitis
	Lymphadenopathy
	Headache/ retroorbital pain
	Arthralgias/ Myalgias
	Lethargy/ Malaise
	Anorexia/ weight loss
	Nausea/ Vomiting/ Diarrhea
Neurologic	Meningitis
	Encephalitis
	Peripheral Neuropathy
	Myelopathy
Dermatologic	Erythematous Maculopapular Rash
	Mucocutaneous Ulceration

Table 3: Symptoms in acute HIV infection

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[23]

CD4 + T Cell Categories	A Asymptomatic, Acute (Primary) HIV or PGL	B Symptomatic, Not A or C Conditions	C AIDS- Indicator Conditions
> 500/ L	A1	B1	C1
200 - 499/ L	A2	B2	C2
< 200/ L	A3	B3	C3

Table 4: Clinical Categories of HIV infection

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[25]

Category A: Consists of one or more of the conditions listed below in an adolescent or adult (> 13 years) with documented HIV infection. Conditions listed in categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B: Consists of symptomatic conditions in an HIV- infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples include, but are not limited to, the following:

- Bacillary Angiomatosis
- Candidiasis, Oropharyngeal (thrush)
- Candidiasis, Vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe) / cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5) or diarrhea lasting > 1 month
- Hairy Leukoplakia, oral
- Herpes Zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic Thrombocytopenic Purpura
- Listeriosis
- Pelvic Inflammatory Disease, particularly if complicated by tuboovarian abscess
- Peripheral Neuropathy

Table 5 Conditions of clinical categories of HIV infection

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[25]

Table 5 continued

Category C: Conditions listed in the AIDS surveillance case definition

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extra pulmonary
- Cryptococcosis, extra pulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcer(s) (> 1 month's duration); or bronchitis, pneumonia, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronical intestinal (1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extra pulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extra pulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extra pulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Table 6: Guidelines for the prevention of opportunistic infections in persons infected with HIV

Adapted from "Harrison's Online Home, Principles of Internal Medicine" [25]

Pathogen	Indications	First Choice(s)	Alternatives
Strongly recommended as standard of care for primary and secondary prophylaxis			
Pneumocystis carinii	CD4 count < 200 µl or Oropharyngeal candidiasis or unexplained fever > 2 weeks prior bout of PCP	Trimethoprim/ sulfamethoxazole (TMP/ SMZ), 1 DS tablet qd	Dapsone 50 mg bid PO or 100 mg/d PO Dapsone 50 mg/d PO+ Pyrimethamine 50 Mg/ wk PO+ Leucovorin 25 mg /wk PO TMP/ SMZ, 1 SS tablet Qd Dapsone 200 mg PO+ Pyrimethamine 50 mg + Leucovorin 25 mg PO Weekly Aerosolized Pentamidine, 300 mg Qm via Respirgard II Nebulizer Atovoquone 1500 Mg/ d PO TMP/SMZ 1 DS tablet PO 3X/ weekly

Table 6 continued

Pathogen	Indications	First Choice(s)	Alternatives
Mycobacterium tuberculosis			
Isoniazid sensitive	Skin test > 5 mm or prior positive test without treatment or contact with case of active TB	Isoniazid 300 mg PO+ Pyridoxine 50 mg/d PO X 9 mo	Rifabutin 300 mg PO+ Pyrazinamide 20 (mg / kg) / d PO X 2 mo
		Isoniazid 900 mg PO+ Pyridoxine 100 mg PO 2 X/ wk X 9 mo	Rifampin 600mg/ d PO X 4 mo
Isoniazid resistant	Same with high probability of exposure to isoniazid-resistant TB	Rifampin 600 mg PO+ Pyrazinamide 20 (mg/kg)/d PO q X 2 mo	Rifabutin 300 mg PO+ daily Pyrazinamide 20 (mg/kg)/d PO X 2 mo Rifampin 600 mg/ d PO X 4 mo Rifabutin 300 mg/ d PO X 4 mo
Multidrug resistant	Same with high probability of exposure to multidrug resistant TB	Consult local public health authorities	
Mycobacterium-avium complex	CD4 count < 50 / µl	Azithromycin 1200 mg weekly PO Clarithromycin 500 mg bid PO	Rifibutin 300 mg/ d PO Azithromycin 1200 mg weekly PO+ Rifabutin 300 mg/ d PO
	Prior documented disseminated disease	Clarithromycin 500 mg bid PO+ Ethambutol 15 (mg/kg) / d PO+/ - Rifabutin 300 mg/d PO	Azithromycin 500 mg/d PO+ Ethambutol 15 (mg/kg)/d PO+/- Rifabutin 300 mg/d PO
Toxoplasma gondii	IgG antibody and CD4 count > 100 / µl	TMP/ SMZ 1 DS tablet qd	TMP/ SMZ 1 SS tablet qd Dapsone 50 mg/ d PO+ Pyrimethamine 50 mg weekly PO+ Leucovorin 25 mg weekly PO Atovoquone 1500 mg/d PO
	Prior toxoplasmic encephalitis	Sulfadiazine 500 – 1000 mg qid PO+ Pyrimethamine 25 – 75 mg/ d PO+ Leucovorin 10 mg/d PO	Clindamycin 300 – 450 mg 16 – 8h PO+ Pyrimethamine 25 – 75 mg/ d PO+ Leucovorin 10 – 25 mg/d PO
Varicella zoster virus	Significant exposure to chickenpox or shingles in a patient with no history of immunization or prior exposure to either	Varicella zoster immune globulin 6.25 mL within 96 h	
Cryptococcus neoformans	Prior documented disease	Fluconazole 200 mg/d PO	Amphotericin B 0.6 – 1.0 mg/kg 3 X /wk IV
Histoplasma capsulatum	Prior documented disease	Itraconazole 200 mg bid PO	Amphotericin B 1.0 (mg/ kg)/ wk IV
Coccidioides immitis	Prior documented disease	Fluconazole 400 mg/d PO	Amphotericin B 1.0 (mg/ kg)/ wk IV Itraconazole 200
Salmonella Species	Prior bacteremia	Ciprofloxacin 500 mg bid PO for several months	

Table 6 continued

Pathogen	Indications	First Choice(s)	Alternatives
Cytomegalovirus	Prior eng-organ disease (any)	Ganciclovir, 5 – 6 mg/ kg, 5 – 7 days/ wk IV Ganciclovir 1000 mg tid PO Foscarnet 90 - 120 (mg/ kg)/ d IV	Cidofovir 5 mg/ kg every other week IV
	Prior retinitis	Ganciclovir sustained-release implant q6 – 9 mo + ganciclovir 1 – 1.5 g tid PO	Fomivirsen, 1 vial injected into the vitreous q2 – 4 wk
Immunizations generally recommended			
Hepatitis B virus	All susceptible (anti- HBc and anti HBs negative) patients	Hepatitis B vaccine: 3 doses	
Hepatitis A virus	All susceptible (anti- HAV negative) patients with chronic hepatitis C	Hepatitis A vaccine: 2 doses	
Influenza virus	All patients annually	Whole or split virus 1 dose yearly	
Streptococcus pneumoniae	All patients	Pneumoccal vaccine 0.5 mL IM X 1 if CD4 count then increases to > 200 µl	
Recommended for prevention of severe or frequent recurrences			
Herpes simplex	Frequent / severe recurrences	Acyclovir 200 mg tid PO Acyclovir 40 mg bid PO Famiciclovir 500 mg bid PO	
Candida	Frequent / severe recurrences	Fluconazole 100 – 200 mg/d PO Itraconazole solution 200 mg/d PO Ketoconazole 200 mg/ d PO	

NOTE: DS, double strength; SS, single strength; PCP, Pneumocystis carinii pneumonia; TB, tuberculosis

1. Diseases of the respiratory system

Sinusitis and acute bronchitis are frequent disorders in HIV infection, most frequently associated with Haemophylus influenzae and Streptococcus pneumoniae. Pneumonia represents a disease in late stage HIV disease frequently caused by Streptococcus pneumoniae and Haemophilus influenzae. Pneumocystis carinii infection has decreased in number, however, if present, represents a severe life threatening disease. Mycobacterium tuberculosis is also highly associated with HIV infection and contributes worldwide to approximately one-third of all deaths from AIDS. In addition atypical mycobacteria also occur in AIDS patients such as Mycobacterium avium complex. In addition to bacterial and mycobacterial infections, fungal infections might occur in AIDS patients, especially in late stages. The most common pulmonary manifestation of fungal infections is histoplasmosis. In addition, idiopathic interstitial pneumonia has been identified; histologically defined as lymphoid interstitial pneumonitis (LIP) or non-specific interstitial pneumonitis (NIP).

Diagnosis of respiratory complications is regularly done by imaging (chest x-ray, CT scan, NMR), by culture (bacterial infections) and by microscopy (pneumocystis carinii infection) or by histology.

2. Diseases of the vascular system

Clinically cardiovascular disease is infrequent; however, it is a common finding post mortem in approximately 25 to 75 % of autopsy cases. The most severe HIV related disease is cardiomyopathy which histologically resembles myocarditis. Congestive heart failure might also be the result of side effects of interferon α, nucleoside analogues, Kaposi's sarcoma, cryptococcosis, Chagas disease and toxoplasmosis.

Pericarditis and pericardial effusions have been shown to be associated with advanced HIV infection. Predisposing factors include TB, other mycobacterial infections, cryptococcosis, pulmonary infections, lymphoma and Kaposi's sarcoma.

Diagnostic methods include imaging, specifically echocardiogram, if needed CT scan and MRI and more recently, as a novel marker for myocardial dysfunction natriuretic peptides (NT-proBNP).
Cardiovascular disease has been shown to evolve as patients with HIV infection have increase life expectancy and as interventions might add to the acceleration of cardiovascular disorders (see below).

3. Diseases of the Oropharynx and the gastrointestinal system

Oral lesions comprise hairy leuloplakia and aphthous ulcers as the most common lesions as well as thrushes caused by candida infections. Candida infections might extend to the esophagus, however, reactivation of CMV and herpes viruses may also cause esophagitis that might be associated with multiple small ulcers. Kaposi's sarcoma and lymphomas might occur in the stomach.

The gastrointestinal tract is also affected by bacteria and fungi including Salmonella typhimurium, Shigella, Campylobacter, M. avium intracellularae, coccidiomycosis, histoplasmosis, Isospora belli and cytomegalovirus infection. The majority of these disorders are characterised by diarrhea and abdominal discomfort at different levels. Also, AIDS enteropathy or HIV enteropathy has also been described as a direct result of HIV infection.

Diagnostic methods include culture for bacterial and fungal infections as well as imaging to detect lesions. An algorithm to evaluate diarrhoea in HIV disease management is shown in Figure 17.

4. Hepatobiliary disorders

Hepatitis B and hepatitis C virus infections are frequent in HIV-infected individuals as they share modes of transmission. Hepatitis A, E and D infections might also occur, but less frequently. Hepatitis A and E are orally transmitted. Co-infection of HBV with HIV is in general associated with a decreased evidence of inflammatory liver disease and HBV responds less well to treatment. Hepatitis C virus infection has been shown to be more severe in HIV-infected individuals, to be associated with significantly higher HCV RNA levels than in non HIV-infected individuals.

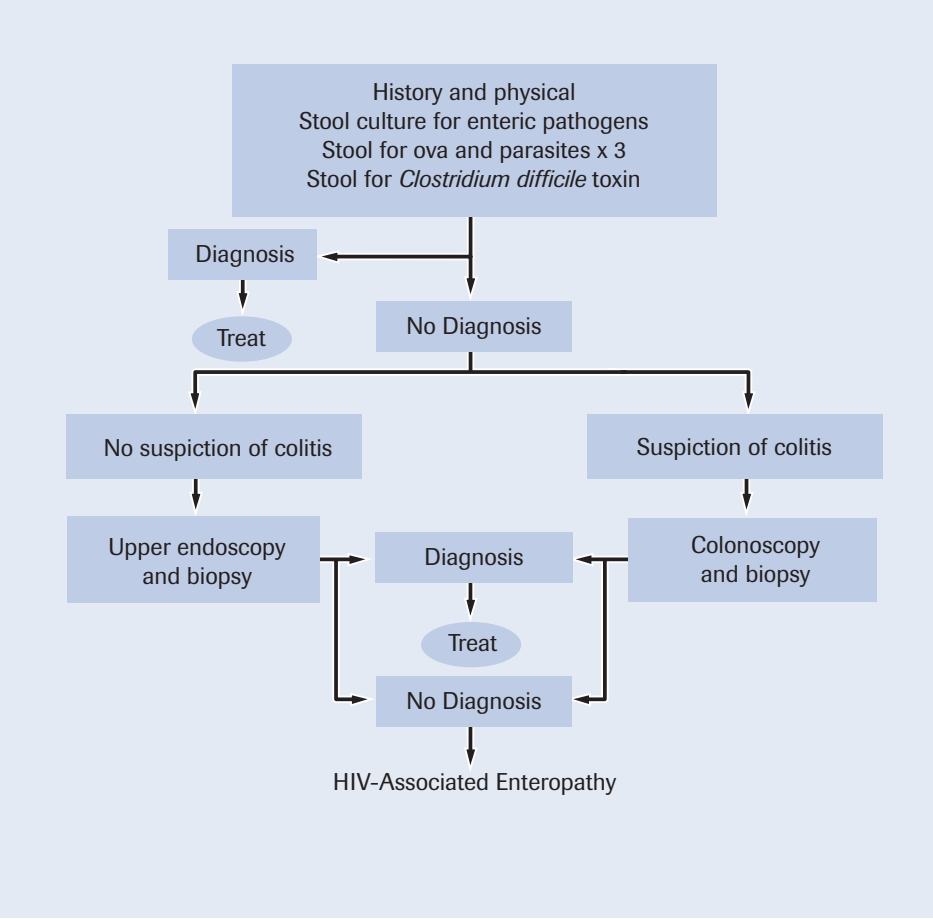
HGV/GBV-C has recently been discovered, but has not been confirmed to be a hepatitis virus. Recent data suggest that HGV/GBV-C infection prolongs life of HIV-infected individuals only when active co-infection of HGV/GBV-C occurs (Figure 18). Individuals who have recovered from HGV/GBV-C infection have no clinical benefit after recovery from this infection.

In addition to these predominant hepatitis infections, fungal infection, mycobacterium avium intracellulare infection, tuberculosis, cryptosporidiosis, CMV and Kaposi's sarcoma have been described. Cryptosporidiosis, CMV infection and Kaposi's sarcoma most frequently present as papillary stenosis or sclerosing cholangitis.

In addition, liver disorders might occur as a result of liver injury due to drugs, especially nucleoside analogues, because these drugs are frequently metabolised in the liver. Diagnostic methods: imaging, liver

Figure 17
Evaluation of diarrhoea in HIV infection

Adapted from Harrison's Online Home, Principles of Internal Medicine [25]

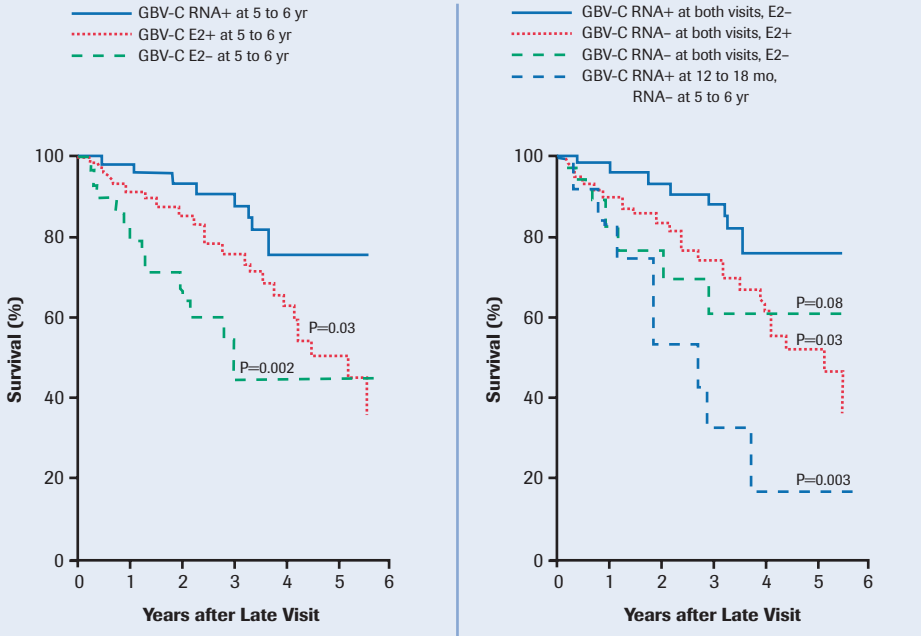


enzymes recognise liver function abnormalities, tests for hepatitis viruses including HBV DNA and HCV RNA and HGV RNA.

5. Diseases of the kidney and genitourinary tract

Disease of the kidney or genitourinary tract may be a direct consequence of HIV infection or of opportunistic infections or neoplasm or drug toxicity. HIV-associated nephropathy is characterised by microalbuminuria and may be found in as many as 20% of untreated HIV infected patients.

Among the drugs that may cause renal damage are pentamidine, amphotericin, adefovir, cidofovir, and foscarnet. In addition, TMP/SMZ might cause an increase in creatinine levels. The HIV protease inhibitor indinavir might also cause complications associated with renal calculi, this might occur in up to 10% of patients treated with this drug.



	Total No.	No. of Deaths	Relative Hazard (95% CI)
GBV-C RNA+ at 5 to 6 yr	50	9	1.00
GBV-C E2+ at 5 to 6 yr	59	23	2.83 (1.10–5.15)
GBV-C E2– at 5 to 6 yr	29	14	3.85 (1.66–8.95)

	Total No.	No. of Deaths	Relative Hazard (95% CI)
GBV-C RNA+ at both visits, E2–	49	9	1.00
GBV-C RNA– at both visits, E2+	59	23	2.40 (1.11–5.20)
GBV-C RNA– at both visits, E2–	17	6	2.57 (0.91–7.24)
GBV-C RNA+ at 12 to 18 mo, RNA– at 5 to 6 yr	12	8	5.87 (2.24–15.38)

Kaplan–Meier Estimates of Survival among 137 Men According to the GB Virus C (GBV-C) RNA and E2 Antibody Status Measured Five to Six Years after Human Immunodeficiency Virus (HIV) Seroconversion (the Late Visit) (Panel A) and Longitudinal GBV-C RNA and E2 Antibody Status Measured at Both Visits (Panel B).

In Panel B, the group that was deemed negative for GBV-C RNA and positive for E2 at both visits had E2 antibody detected at either visit. Among the 12 who were positive for GBV-C RNA 12 to 18 months after HIV seroconversion but who were negative for GBV-C RNA by the late visit, 3 had E2 antibody at the late visit. The one man who was negative for GBV-C RNA at the early visit and positive for RNA at the late visit was excluded from this analysis.

P values are for the comparison with the group that was persistently positive for GBV-C RNA, which served as the reference group in the calculations of the relative hazard of death. CI denotes confidence interval.

Figure 18
Infection with a GB Virus C virus and reduced mortality among HIV infected patients

Adapted from Williams et al [74]

Diagnostic methods include imaging, microalbumin urine determination and tests for kidney function.

Diseases of the genitourinary tract are frequently associated with sexually transmitted disorders such as Treponema pallidum, the etiologic agent of syphilis, papilloma virus infection as presented by condylomata lata, herpes virus infections, candidiasis, trichomonas infections and other infections.
Sexually transmitted infections co-occurring with HIV are listed in Table 7.

Table 7: Sexually transmitted disorders associated with HIV

Adapted from Donovan et al, 2004 [15]

Pathogen	Global prevalence (WHO estimate) and epidemiology	Diagnostic advances	Management trends
Neisseria gonorrhoeae	62 4 million (> two-thirds population in sub-Saharan Africa and South/ South East Asia). Mainly developing nations and disadvantaged groups in developed nations. Re-emerging among homosexually active men in developed nations.	Commercially available NAATs now permit easier sample collection e.g., urine or self-collected vaginal swabs. NAATs need further assessment for non-genital sites and low-prevalence populations, but have exposed insensitivity of culture in some settings. Culture remains standard (just).	Quinolone resistance becoming widespread, especially in Asia and Pacific, forcing change to third-generation cephalosporins.
Chlamydia trachomatis (serovars A- K)	92 million. Common in most countries, particularly among young people, with growing awareness of asymptomatic infection of men. Incidence probably increasing.	Commercially available NAATs permit easier sample collection and provide higher sensitivity, particularly for asymptomatically infected.	Single-dose treatment with oral azithromycin provides similar efficacy to 1-week doxycycline treatment
Mycobacterium genitalium	Epidemiology largely unknown, but possibly as widespread and as common as C trachomatis.	NAATs provide only practical diagnostic method, but are not commercially available	Preliminary evidence suggests azithromycin offers better efficacy than tetracyclines.
Ureaplasma urealyticum	Ubiquitous organism in female genital tract. Generally commensal, but can cause urethritis in men.	NAATs provide only practical diagnostic method, but not commercially available.	Thought to be responsive to tetracyclines and macrolides.
Treponema vaginalis	174 million. Endemic everywhere: prevalence higher in underserved populations and increases with age	NAATs, which are gradually becoming commercially available, have highlighted poor sensitivity of microscopy and culture.	Unchanged

Table 7 continued

Pathogen	Global prevalence (WHO 1999 estimate) and epidemiology	Diagnostic advances	Management trends
Treponema pallidum	12 million. Distribution shadows N gonorrhoeae, including resurgence among homosexually men	NAATs for direct indentification might have limited application, but not commercially available. Newer EIA serological tests offer improved sensitivity and specificity.	Unchanged: parental penicillin G (with oral doxycycline as alternative if intolerant). Azithromycin shows some promise but no controlled trials.
HSV-2	10 – 30% of adults globally, risk cumulative with age. Prevalence higher in women and high- risk populations: most remain undiagnosed.	Commercially available NAATs for direct indentification offer higher sensitivity than cell culture. Type- specific serological tests now commercially available. Cell culture and direct immunofluourescence still most common methods of diagnosis	Individualised antiviral treatment. 3-day course of valaciclovir effective as 5 days for recurrent lesions. 2-day trials underway.
HSV- 1	25 – 90% adults globally, mostly acquired (non-sexually) as children. Increasing role in primary genital herpes in more developed countries.	As for HSV-2	Distinguishing HSV-1 from HSV-2 aids education of patients and counselling.
Haemophilus ducreyi	Developing nations and southern USA, linked to HIV. Incidence of chancroid declining in countries offering services to sex workers.	NAATs for direct identification offer highest sensitivity but not commercially available. Serological tests useful only for epidemiological studies. Still mainly diagnosed clinically.	Single-dose azithromycin or ceftriaxone offer high efficacy. Poorer response in HIV infected individuals.
Calymmatobacterium (or Klebsiella) granulomatis	Endemic with sporadic cases in southern Africa, India, Papua New Guinea, remote northern Australia, and Carribean.	Diagnosis of LGV still mainly clinical but can be supported by high-titre sereology or identification of organism in ulcers or bubo fluid.	Tetracyclines or erythromycin remain most common, with long-term courses sometimes needed.
Human papillomavirus infection (> 30 types affecting genital area)	Probably most adults become infected, with only few developing disease (warts or anogenital cancer)	Clinical appearance mainstay for genital warts. Commercially available NAATs can be used to diagnose or type subclinical infections, but role in screening or clinical management remains uncertain	Increasing role of self-treatment of genital warts (podophyllotoxin, imiquimod). Crude podophyllin treatment should be abandoned.

Table 7 continued

Pathogen	Global prevalence (WHO 1999 estimate) and epidemiology	Diagnostic advances	Management trends
Molluscum contagiosum virus	Poorly understood. Different subtypes might preferentially affect children (type 1) and adults (type 2).	Normally diagnosed clinically	Curettage or ablation of lesions most common. Self- applied podophyllotoxin 0.5% or imiquimod 1% provide alternatives.
Hepatitis B virus	> 350 million chronic carriers globally, most acquired perinatally or in infancy, particularly in developing nations. Continuing risk of sexual transmission in all settings.	NAATs developing role in monitoring treatment, but diagnosis still hinges on serology.	Increasing antiviral treatment options available. Need for better targeting of active vaccination for young people at risk through sex or drug injecting.
Hepatitis A virus	Re-emergence of outbreaks among homosexually active men.	Serological diagnosis is still mainstay.	Homosexually active men need to be included in active vaccination programmes.
Cytomegalovirus	Most adults eventually become infected (generally as children in developing countries), but disease largely confined to immunocompromised and fetuses exposed to mothers' primary infection.	Histology, antigen detection, cell culture and sereology all have roles. NAATs for circulating virus might have role in monitoring immunocompromised patients.	Increasing antiviral options
Human herpes virus type 8	Highly variable, <10% prevalence in US, Europe, and Asia but >40% in Africa. Disease (Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease) largely confined to immunocompromised and elderly.	Histology of lesions remains the mainstay. Serology only useful for epidemiological studies, while NAATs are too insensitive for clinical use.	Managing underlying HIV infection offers best prognosis.

6. Diseases of the endocrine system and metabolic disorders

A variety of endocrine and metabolic disorders are seen in the context of HIV infection. One-third to two-thirds of patients with HIV infection receiving HAART develop lipodystrophy consisting of elevations in plasma triglycerides, total cholesterol, apolipoprotein B, and high-density lipoprotein cholesterol as well as hyperinsulinemia. This is associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting. Truncal obesity is related to increasing mesenteric fat, a dorsocervical fat pad ("buffalo hump") and enlargement of the breasts. This symptom has been described as occuring primarily in association with protease inhibitors, but might occur also with other antiviral drug regiments. Adrenal insufficiency is

shown to be associated with low serum sodium level and can be the result of mycobacterial infections, CMV disease, cryptococcal disease, histoplasmosis, or ketoconazole toxicity.

Thyroid function is normally not altered in HIV infection, but it might be in cases of P. carinii, CMV, mycobacteria, Toxoplasma gondii and Cryptococcus neoformans infections. Hypogonadism might occur in up to 50% of HIV-infected men and might be the result of ganciclovir treatment.
The diagnostic methods are laboratory tests for serum lipids, adrenalin function and thyroid in association with imaging technologies and biopsy if needed.

7. Rheumatologic disorders

Reactive arthritis and disorders associated with immune reactivation syndromes, the latter associated with the initiation of HAART, have been described and are frequently associated with infections. In addition, HIV or AIDS-related arthropathy has been found that may last as long as 1 to 6 weeks or even longer and affects normally one joint and presents subacute. Also, a symptom called painful articular syndrome has been identified which occurs in up to 10 % of AIDS patients, the cause is unclear and the symptom lasts for 2 to 24 hours. In addition, fibromyalgia has been identified in HIV-infected individuals and might result as a direct effect of HIV infection. The diagnostic methods are imaging, laboratory tests for immune reactivation syndromes including electrophoresis, biopsy and culture.

8. Diseases of the haematopoietic system

Disorders of the hematopoietic system are very common in HIV infection and include lymphadenopathy, anaemia, leukopenia and/or thrombocytopenia. They might be the result of HIV infection directly, manifestations of secondary infections and neoplasms or side effects of therapy.
Table 8 summarises the major causes of bone marrow suppression in HIV-infected individuals.
Persistent lymphadenopathy represents an early clinical manifestation of HIV infection. Lymphadenopathy might also occur in HIV associated infections or in certain tumours. Anaemia is the most common hematologic abnormality in HIV-infected patients. Anaemia might be quite severe and require repeated blood transfusions. The causes include drug toxicities, systemic fungal and mycobacterial infections, nutritional deficiencies and parvovirus B19 infections. Haemolytic anaemia might be caused by dapsone, autoimmune haemolytic anaemia affects approximately 20 % of patients with HIV and might be the consequence of polyclonal B cell activation. Erythropoietin can be used to increase haemoglobulin levels. Neutropenia is also frequent in HIV-infected individuals and found in advanced HIV disease and in individuals with immunosuppressive therapies, G-CSF and GM-CSF are found to increase the level of neutrophils. Thrombocytopenia is also frequently found in HIV infection. It responds frequently well to antiretroviral therapy and resembles clinically idiopathic thrombocytopenic purpura.

HIV infection	
Mycobacterial infections	
Fungal infections	
B19 parvovirus infection	
Lymphoma	
	Medications:
	Zidovudine
	Dapsone
	Trimethopim/ Sulfamethoxazole
	Pyrimethamine
	5- Flucytosine
	Ganciclovir
	Interferon
	Trimetrexatre
	Foscarnet

Table 8: Causes of bone marrow suppression in patients with HIV infection and medication

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[25]

Table 9: Neurologic diseases in patients with HIV infection

Adapted from "Harrison's Online Home, Principles of Internal Medicine"[25]

Opportunistic Infections
Toxoplasmosis
Cryptococcosis
Progressive multifocal leukoencephalopathy
Cytomegalovirus
Syphilis
Mycobacterium tuberculosis
HTLV- I Infection
Neoplasms
Primary CNS lymphoma
Kaposi's sarcoma
Result of HIV infection
Aseptic meningitis
HIV encephalopathy (AIDS dementia complex)
Myelopathy
Vacuolar myelopathy
Pure sensory ataxia
Paresthesia/ Dysesthesia
Peripheral neuropathy
Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Mononeuritis multiplex
Distal symmetric polyneuropathy
Myopathy

The diagnostic methods are: blood cell counts including assays to differentiate causes of bone marrow suppression, bone marrow biopsy including evaluation, culture for opportunistic infections.

9. Dermatologic disorders

Dermatologic disorders are frequent in HIV-infected individuals and include seborrheic dermatitis, eosinophilic pustular folliculitis, severe forms of Norwegian scabies, more severe psoriasis and ichtyosis, reactivation of varicella-zoster virus presented as herpes zoster, activation of herpes simplex virus infection, condyloma acuminata as a result of papilloma virus infection, Molluscum contagiosum, Stevens-Johnson syndrome as a result of drug therapy. Fungal infections and Kaposi's sarcoma are also seen. The diagnostic methods are clinical diagnosis, culture, biopsy and others.

10. Neurological Disorders

A significant proportion of disorders found in HIV-infected individuals do come from neurologic disorders and they are quite heterogeneous. They are summarised in Table 9. The causes of neurologic disorders include opportunistic infections such as Toxoplasmosis, Cryptococcosis, progressive multifocal leukoencephalopahty, mycobacteria, syphilis, CMV, HTLV-1 or Acanthamoeba. In addition, AIDS dementia complex or HIV encephalopathy might occur.

Aseptic meningitis may occur in all stages of HIV infection, may occur as early as acute HIV infection and is believed to be an immunomodulated disease. Cryptococcus neoformans is the leading cause of meningitis in patients with AIDS. Other fungi that cause meningitis include Cryptococcus immitis and Histoplasma capsulatum or Acanthamoeba or Naegleria.

HIV encephalopathy occurs quite frequently in AIDS patients at different levels, its cause is unknown and might include involvement of HIV infection in the brain.

Seizure may be a cause of opportunistic infections, but may also occur with HIV encephalopathy or neoplasm. Opportunistic infections that cause seizures include cerebral toxoplasmosis, primary CNS lymphoma, cryptococcal meningitis, CNS tuberculosis and others.

Toxoplasmosis is the most common cause of secondary CNS infections in patients with AIDS; however, its incidence is decreasing in the era of HAART.

Progressive multifocal leukoencephalopathy is caused by the JC virus, a human papilloma virus. Chagas' disease which

represents American trypanosomiasis may also present as acute meningoencephalitis in AIDS patients.

Spinal cord disease or myelopathy occurs in approximately 20 % of AIDS patients and in general is part of HIV encephalopathy. An important disease is also polyradiculopathy, a myelopathy of the peripheral nerves which is frequently associated with CMV infection. Peripheral neuropathies are also common in AIDS patients, they might be the consequence of direct HIV infection or of side effects of antiretroviral therapy, e.g. with dideoxynucleosides. Other causes of peripheral neuropathy include diabetes mellitus, vitamin B12 deficiency or side effects from metronidazole or dapsone.

The diagnostic methods include imaging including CT scan and MRI, specific neurological examination, serology and culture for opportunistic infections, special examination of CSF.

11. Myopathy

Myopathy can also occur in the context of AIDS, in general in context of the general wasting syndrome, caused by HIV itself or by drugs such as zidovudine.
Diagnostic methods: Histology from skeletal muscles.

12. Ophthalmologic Disorders

Ophthalmologic disorders occur in up to 50 % of HIV-infected individuals with advanced HIV infection. The most severe disease has been CMV Retinitis which has declined in number after the introduction of HAART. Acute retinal necrosis syndrome may also occur due to reactivation of herpes simplex virus or varicella zoster virus. Ocular involvement has also been described with Pneumocystis carinii infection and toxoplasmosis.
Diagnostic methods: eye examination, imaging, serology of opportunistic infections.

13. Additional disseminated infections and wasting syndrome

Bartonella represents a gram-negative rickettsia-like organism which occurs with increasing frequency in HIV-infected individuals. It might present as angiomatosis that might involve lymph nodes, liver (peliosis hepatitis), spleen, bone marrow, heart, CNS, the respiratory tract, and the gastrointestinal tract. Histoplasmosis is caused by Histoplasma capsulatum and primarily endemic in the US and rarely occurs in Europe. Penicillium marneffei was recognised as an AIDS related disorder in Asia, specifically in Thailand and represents a systemic disorder. Visceral leishmaniasis is also seen at increased frequency in AIDS patients, with clinical manifestations of the liver, the spleen, the hematologic systems and other organs. The generalized wasting syndrome occurs in approximately 10% of AIDS patients and represents an HIV related progressive disorder.
Diagnostic methods: imaging, culture.

14. Neoplastic Disorders

There are a number of neoplastic disorders found in HIV patients favoured by the state of immunosuppression. Kaposi's sarcoma has been related to herpes virus type 8 infection, it might occur in the skin, but also affects all other organs. Lymphomas such as cerebral lymphoma, but also other types of lymphoma, are also seen in an increased frequency in AIDS patients. Immunoplastic lymphomas represent approximately 60% of all lymphomas on AIDS patients, in some of those tumours relationship to herpes virus type 8 has been described. Small non-cleaved cell lymphoma

(Burkitt's lymphoma) is also found with increased frequency in AIDS patients; in the majority of cases EBV genome has been identified. Primary CNS lymphoma accounts for approximately 20 % of cases of lymphoma in patients with HIV infection. These lymphomas are usually positive for EBV sequences.

Intraepithelial dysplasia of the cervix or the anus is frequently caused by human papilloma virus and may cause invasive cervical cancer in women. In HIV patients this represents an isolated disorder. Diagnostic methods: imaging including CT scan and MRI.

Antiviral Treatment of Human Immunodeficiency Virus Infection

VI

HAART (Highly Active Antiviral Treatment) has been the basis for a longer survival of HIV infected individuals. The purpose of HAART is to suppress HIV replication and thereby to slow down the progression of HIV. With the development of new drugs, the emergence of new studies, guidelines for the use of antiretroviral agents are subject to change. The following section summarises recommendations updated in November 2003.

Antiviral therapy

Antiviral agents are used for different purposes.

1. For the treatment of HIV-infected adults and adolescents.
2. For the treatment of HIV-infected individuals in pediatric settings.
3. To prevent mother-child-transmission by the use of antiretroviral agents perinatally.
4. To prevent HIV infection after exposure in the healthcare worker or after non-occupational exposure.

The decision on whom to treat is dependent on clinical categories, the number of CD4 cells and HIV RNA levels. In some of the described instances recommendation for treatment is controversial.

Different drugs for treatment of HIV are currently available that can be classified into different types of mode of action.

1. nucleoside analogues as reverse transcriptase inhibitors
2. non nucleoside analogues as reverse transcriptase inhibitors
3. protease inhibitors
4. fusion inhibitors

A list of currently available antiviral drugs is shown in Table 10.

Table 10: Antiviral drugs for treatment of HIV infection

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1- Infected Adults and Adolescents"[62]

Generic Name/Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Abacavir (ABC) Ziagen®	300 mg tablets or 20 mg/mL oral solution	300 mg two times/day or with ZDV and 3TC as Trizivir, 1 dose two times/day	Take without regard to meals; Alcohol increases abacavir levels 41%; has no effect on alcohol	83%	1.5 hours	3.3 hours	Metabolised by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82%	Hypersensitivity reaction which can be fatal; symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath
Didanosine (ddI) Videx®, Videx EC®	25, 50, 100, 150, 200 mg* chewable/dispersible-buffered tablets; 100, 167, 250 mg buffered powder for oral solution; 125, 200, 250 or 400 mg enteric coated capsules	Body weight ≥ 60 kg: 400 mg once daily (buffered tablets or enteric coated capsule); or 200 mg two times/day (buffered tablets) Body weight < 60 kg: 250 mg daily (buffered tablets or enteric coated capsule); or 125 mg two times/day (buffered tablets)	Levels decrease 55 %; Take 1/2 hour before or 2 hours after meal	30 – 40%	1.6 hours	25 – 40 hours	Renal excretion 50 % Dosage adjustment in renal insufficiency	Pancreatitis; peripheral neuropathy; nausea; diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with using of NRTIs.
Emtricitabine (FTC) Emtriva™	200 mg hard gelatin capsules	200 mg once daily	Take without regard to meals	93%	10 hours	39 hours	Renal excretion Dosage adjustment in renal insufficiency	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs.)

Table 10
continued

Generic Name/Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Lamivudine (3TC) Epivir®	150 mg and 300 mg tablets or 10 mg/mL oral solution	150 mg two times/day; or 300 mg daily with ZDV as Combivir, or with ZDV and abacavir as Trizivir, 1 dose two times/day	Take without regard to meals	86%	3 – 6 hours	12 hours	Renal excretion Dosage adjustment in renal insufficiency	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs.)
Stavudine (d4T) Zerit®	Zerit® 15, 20, 30, 40 mg capsules or 1 mg/mL for oral solution **Zerit-XR®** 75 and 100 mg extended release capsule-FDA approved, not yet in market	**Zerit®:** Body weight ≥ 60 kg: 40mg two times/day; Body weight < 60 kg: 30 mg two times/day **Zerit-RX®:** Body weight ≥ 60 kg: 100 mg once daily Body weight < 60 kg: 75 mg once daily	Take without regard to meals	86%	1.0 hour	3.5 hours	Renal excretion 50% Dosage adjustment in renal insufficiency	• Peripheral neuropathy • Lipodystrophy • Rapidly progressive ascending neuromuscular weakness (rare) • Pancreatitis • Lactic acidosis with hepatic steatosis
Tenofovir Disoproxil Fumarate Viread®	300 mg tablet	300 mg daily for patients with creatinine clearance ≥ 60 mL/min	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	10 – 50 hours	Renal excretion Dosage adjustment in renal insufficiency	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs – not yet reported with renofovir use); rare reports of renal insufficiency.
Zalcitabine (ddc) Hivid®	0.375, 0.75 mg tablets	0.75 mg three times/day	Take without regard to meals	85%	1.2 hours	3 hours	Renal excretion 70% Dosage adjustment in renal insufficiency	• Peripheral neuropathy • Stomatitis • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs); pancreatitis
Zidovudine (AZT, ZDV) Retrovir®	100 mg capsules, 300 mg tablets, 10 mg/mL intravenous solution, 10 mg/mL oral solution	300 mg two times/day or 200 mg three times/day with lamivudine as Combivir, 1 dose two times/day or, with abacavir and lamivudine as Trizivir, 1 dose two times/day	Take without regard to meals	60%	1.1 hours	3 hours	Metabolised to AZT glucuronide (GAZT) Renal excretion of GAZT	• Bone marrow suppression: anaemia or neutropenia; • Subjective complaints: gastrointestinal intolerance, headache, insomnia, asthenia; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs).

Table 10
continued

Generic Name / Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavail-ability	Serum half-life	Elimination	Adverse Events
Delavirdine/ Rescriptor®	100 mg tablets or 200 mg tablets	400 mg by mouth 3 times/day; 4 100 mg tablets can be dispersed in ≥ 3 oz. of water to produce slurry; 200 mg tablets should be taken as intact tablets; separate buffered preparations dosing with didanosine or antacids by 1 hour	Take without regard to meals	85%	5.8 hours	Metabolised by cytochrome P450 (3A inhibitor); 51 % excreted in urine (< 5 % unchanged); 44% in faeces	• Rash; • Increased trans-aminase levels; • Headaches
Efavirenz/ Sustiva®	50, 100, 200 mg capsules or 600 mg tablets	600 mg by mouth daily on an empty stomach, preferably at bedtime	High-fat / high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%; take on an empty stomach	Data not available	40-55 hours	Metabolised by cytochrome P450 (3A mixed inducer/ inhibitor); 14 % – 34 % excreted in urine (glucuronidated metabolites, < 1 % unchanged); 16% – 61% in faeces.	• Rash; • Central nervous system symptoms; • Increased transaminase levels; • False-positive cannabinoid test; • Teratogenic in monkeys
Nevirapine/ Viramune®	200 mg tablets or 50 mg/5 mL oral suspension	200 mg by mouth daily for 14 days; thereafter, 200 mg by mouth two times/day	Take without regard to meals	> 90%	25 – 30 hours	Metabolised by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites; < 5% unchenged); 10% in faeces	• Rash; • Hepatitis, including hepatic necrosis, have been reported

Generic Name / Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavail-ability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Amprenavir/ Agenerase®	50 mg, 150 mg capsules 15 mg/mL oral solution (capsules and solution NOT interchangeable on mg per mg basis) **Note:** Oral solution contains propylene glycol, contraindicated in pregnant women and children < 4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole	Body weight > 50 kg: 1200 mg two times/day (capsules) or, 1400 mg two times/day (oral solution) Body weight < 50kg: 20 mg/kg two times/day (capsules) maximum 2400 mg daily total; 1.5 mL/kg two times/day (oral solution) maximum 2800 mg daily total;	High-fat meal decreases blood concentration curve 21%; can be taken with or without food, but high fat meal should be avoided.	Not determined in humans	7.1 – 10.6 hours	Cytochrome P450 (3A4 inhibitor (less than ritonavir; similar to indinavir, nelfinavir), inducer, and substrate	Room temperature	• GI intolerance, nausea, vomiting, diarrhea • Rash • Oral paresthesias • Transaminase elevation • Hyperglycemia • Fat redistribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia
Atazanavir/ Reyataz™	100, 150, 200 mg capsules	400 mg once daily If taken with efavirenz (or tenofovir) Ritonavir 100 mg + atazanavir 300 mg once daily	Administration with food increases bioavailability Take with food	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature	• Indirect hyperbilirubinemia • Prolong PR interval – some patients experienced asymptomatic 1st degree AV block • Use with caution in patients with underlying condition defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with haemophilia

Table 10
continued

Generic Name / Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavail-ability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Indinavir/ Crixivan®	200, 333, 400 mg capsules	800 mg every 8 hours;	Levels de-crease 77% Take 1 hour before or 2 hours after meals; may take with skimmed milk or low-fat meal	65%	1.5 – 2 hours	Cytochrome P450 3A4 inhibitor and substrate (less than ritonavir)	Room temperature	• Nephrolithasis • GI intolerance, nausea • Lab: Increased indirect bilirubinemia (inconse-quential) • Misc.: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, throm-bocytopenia, alopecia, and haemolytic anaemia • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia
Lopinavir + Ritonavir/ Kaletra®	Each capsule contains lopinavir 133.3 mg + ritonavir 33.3 mg Oral solution: Each mL contains lopinavir 80 mg + ritonavir 20 mg	400 mg lopinavir + 100 mg ritonavir (3 capsules) two times/day	Moderate fat meal increases AUC of cap-sules and solution by 48% and 80%, respectively. Take with food.	Not de-termined in humans	5 – 6 hours	Cytochrome P450 (3A4 inhibitor)	Refrigerated capsules are stable until date on label expires; if stored at room tem-peratures table for 2 months	• GI intolerance, nausea vomiting, diarrhea • Asthenia • Elevated serum transami-nases • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia • Oral solution contains 42% alcohol
Nelfinavir/ Viracept®	250 mg tablets 625 mg tablets – FDA approved, not yet in market 50 mg/g oral powder	750 mg three times/day or 1.250 mg two times/day	Levels in-crease 2 – 3 fold Take with meal or snack	20 – 80 %	3.5 – 5 hours	Cytochrome P450 (3A4 inhi-bitor; less than ritonavir)	Room temperature	• Diarrhea • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes among patients with haemophilia • Serum transaminase elevation
Ritonavir/ Norvir®	100 mg capsules 600 mg/7.5 mL solution	600 mg every 12 hours* (when ritonavir is used as sole PI)	Levels in-crease 15% Take with food if pos-sible; this may improve tolerability	Not de-termined	3 – 5 hours	Cytochrome P450 (3A4 > 2D6; Potent 3A4 inhibitor)	Refrigerate capsules Capsules can be left at room temperature for ≤ 30 days; Oral solution should NOT be refriger-ated	• GI intolerance, nausea vomiting, diarrhea • Paresthesias – circumoral and extremities • Hepatitis • Pancreatitis • Asthenia • Taste perversion • Lab.: Triglycerides increase > 200%, transaminase elevation, elevated CPK and uric acid • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia
Saquinavir hard gel capsule/ Invirase®	200 mg capsules	Invirase is not recom-mended to be used as sole PI With Ritonavir: ritonavir 400 mg + Invirase 400 mg two times/day	No food effect when taken with ritonavir	4 % erratic	1 – 2 hours	Cytochrome P450 (3A4 inhi-bitor; less than ritonavir)	Room tem-perature	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase en-zymes • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia

Table 10
continued

Generic Name / Trade Name	Form	Dosing Recommendations	Food Effect	Oral Bioavail-ability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Saquinavir soft gel capsule/ Fortovase®	200 mg capsules	1,200 mg three times/day	Levels increase 6- fold. Take with large meal	Not de-termined	1 – 2 hours	Cytochrome P450 (3A4 inhi-bitor; less than ritonavir)	Refrigerate or store at room tem-perature (up to 3 months)	• GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia • Headache • Elevated transaminase enzymes • Hyperglycemia • Fat restribution and lipid abnormalities • Possible increased bleeding episodes in patients with haemophilia

Generic Name / Trade Name	Form	Dosing Recommendations	Bioavailability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Enfuvirtide/ Fuzeon™	• Injectable – in lyophilized powder • Each single-use vial con-tains 108 mg of enfuvirtide to be reconstituted with 1.1 ml of sterile water for injection for delivery of ap-proximately 90 mg/l mL	90 mg (1 mL) subcutaneously (SC) two times/day	84.3% (SC compared to IV)	3.8 hours	Expected to undergo cata-bolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature Reconstituted solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and used within 24 hours	• Local injection site reactions (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased rate of bacterial pneumonia • Hypersensitivity reaction (<1%) – symptoms may in-clude rash, fever, nausea, vomiting, chills, rigors, hypo-tension, or elevated serum transaminases; may recur on rechallenge

According to the available data, antiretroviral regimens are recommended for the treatment of HIV infection in antiretrovirally naive patients. Current recommendations are listed in Table 11. After initiation of antiretroviral therapy HIV RNA levels and CD4 counts should be monitored as described. A decrease of HIV RNA levels by one log within one month indicates response to treatment. This is generally associated with an increase in CD4 positive cells. In a typical response HIV RNA falls to undetectable levels and remains there unless a treatment failure occurs (see above). In some instances, discrepant results are obtained with HIV RNA levels and CD4 cells. If this is the case, it is recommended to adhere to the information obtained from HIV RNA concentrations.

Table 11: Recommendation of the treatment of naive HIV infected patients

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV- 1- Infected Adults and Adolescents"[62]

NNRTI- Based Regimens		**# of pills per day**
Preferred Regimes	**Efavirenz + Lamivudine + (Zidovudine or Tenofovir DF or Stavudine*) - except for pregnant women or women with pregnancy potential**	**3 – 5**
	Efavirenz + Emtricitabine + (Zidovudine or Tenofovir DF or Stavudine*) - except for pregnant women or women with pregnancy potential**	3 – 4
Alternative Regimes	Efavirenz + (Lamivudine or Emtricitabine) + Didanosine - except for pregnant women or women with pregnancy potential**	3
	Nevirapine + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine* or Didanosine)	4 – 5
PI- Based Regimens		**# of pills per day**
Preferred Regimens	**Lopinavir/ Ritonavir (co- formulated as Kaletra®) + Lamivudine + (Zidovudine or Stavudine)**	**8 – 10**
Alternative Regimens	Amprenavir/ Rieonavir*** + (Lamivudine or Emrticitabine) + (Zidovudine or Stavudine)	12 - 14
	Atazanavir + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine*)	4 - 5
	Indinavir + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine*)	8 - 10
	Indinavir/ Ritonavir*** + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine*)	8 - 11
	Lopinavir/ Ritonavir (co-formulated as Kaletra®) + Emitricitabine + (Zidovudine or Stavudine*)	8 - 9
	Nelfinavir§ + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine*)	6 - 14
	Saquinavir (sgc or hgc)"/ Ritonavir*** + (Lamivudine or Emtricitabine) + (Zidovudine or Stavudine*)	14 - 16
Triple NRTI Regimen - Only when an NNRTI- or a PI- based regimen cannot or should not be used as first line therapy		**# of pills per day**
Only as alternative to NNRTI- or PI-based regimen	Abacavir + Lamivudine + Zidovudine (or Stavudine*)	2 - 6

* Higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities reported with stavudine than with other NRTIs

** Women with child bearing potential implies women who want to conceive or those who are not using effective contraception

*** Low-dose (100 - 400 mg) Ritonavir

§ Nelfinavir available in 250 mg or 625 mg tablet

" sgc = soft gel capsule; hgc = hard gel capsule

In case of a treatment failure, there are a number of different explanations

a) non adherence to the drug regimen
b) inadequate dosing of the drugs to be used
c) development of resistance to one or more drugs

In this case, guidelines should be followed when a change in antiretroviral regiment for suspected treatment regimen failure. This is summarised in Table 12.

Table 13 suggests the use of drugs after biological failure after initial recommended therapy regimen.

Patient Assessment (AIII)

- Review antiretroviral treatment history
- Perform physical exam to assess for signs of clinical progression
- Assess adherence, tolerability, and pharmacokinetic issues
- Distinguish between first or second, and multiple treatment regimen failures
- Perform resistance testing while patient is taking therapy
- Identify susceptible drugs and drug classes

Patient Management: Specific Clinical Scenarios

- **Limited prior treatment with low (but not suppressed) HIV RNA level (e.g. up to 5000 copies/mL):**
  The goal of treatment is to re-suppress viral replication. Consider intensifying with one drug (e.g., tenofovir) (BII) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) (BII), or most aggressively, change to a completely new regimen (CIII). If continuing the same treatment regimen, need to follow HIV RNA levels more closely, because ongoing viremia will lead to the accumulation of resistance mutations.

- **Limited prior treatment with single drug resistance:** Consider changing one drug (CIII), pharmacokinetic enhancement (few data available) (BII), or, most aggressively, change to a completely new regimen (BII).

- **Limited prior treatment with more than 1 drug resistance:** The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimising regimen by changing classes (e.g. PI-based to NNRTI-based and vice versa) and/or adding new active drugs (AII). **(See Table 13: Treatment options following virologic failure on initial recommended therapy regimens).**

- **Prior treatment with no resistance identified:** Consider the timing of obtaining the drug resistance test (e.g. was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g. 2 – 4 weeks) to see if a resistant strain has been selected (CIII).

- **Extensive prior treatment:** It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options (CIII). In general, avoid adding a single active drug because of the risk for the development of resistance to that drug. In advanced disease with a high likelihood of clinical progression, adding a single drug may reduce the risk of immediate clinical progression (CIII). In this complicated scenario, expert advice should be sought.

Table 12: Summary of guidelines for changing an antiretroviral regimen for suspected treatment regimen failure

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" [62]

Table 13: Treatment options following virologic failure on initial recommended therapy regimens

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" [62]

Regimen Class	Initial Regimen	Recommended Change
NNRTI	2 nucleosides + NNRTI	• 2 nucleosides (based on resistance testing) + PI (with or without low-dose ritonavir) (AII)
PI	2 nucleosides + PI (with or without low- dose ritonavir)	• 2 nucleosides (based on resistance testing) + NNRTI (AII)
Triple nucleosides	3 nucleosides	• 2 nucleosides (based on resistance testing) + NNRTI or PI (with or without low-dose ritonavir) (AIII) • NNRTI + PI (with or without low-dose ritonavir) (CIII) • Nucleoside(s) (based on resistance testing) + NNRTI + PI (with or without low-dose ritonavir) (CII)

There are multiple drug-drug interactions between HIV antiviral drugs as well as other drugs that are being used for opportunistic infections or for common disorders. These interactions need to be considered when choosing the appropriate treatment schedule.

The use of drug monitoring in the treatment of HIV-infected individuals remains controversial as it does not necessarily reflect the intracellular concentration. It has however been described that the addition of certain drugs increases the plasma concentration of antiretroviral drugs significantly. This might lead to dose sparing and thereby side effects sparing regimen. For a number of antiviral drugs the minimum target through concentration for persons with wild-type HIV infection has been determined and is summarised in Table 14.

2. Antiviral therapy in the paediatric setting

Guidelines for antiretroviral therapy have also been developed for pediatric HIV infection. The considerations are similar to those described for adults with the exception that less data is available in HIV infected children. Monitoring for treatment efficacy or failure of antiretroviral therapy is similar in paediatric patients and adult patients and will not be discussed here a second time.

Table 14: Suggested minimum target through concentrations for persons with wild-type HIV-1

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" [62]

Drug	Concentration (ng/mL)
Amprenavir (Agenerase)	400
Indinavir (Crixivan)	100
Lopinavir/ Ritonavir (Kaletra)	1000
Nelfinavir (Viracept)*	800
Ritonavir (Norvir)**	2100
Saquinavir (Fortovase, Invirase)	100 – 250
Efavirenz (Sustiva)	1000
Nevirapine (Viramune)	3400

* Measurable active (M8) metabolite

** Ritonavir given as a single PI

Time of ZDV Administration	Regimen
Antepartum	Oral administration of 100 mg ZDV five times daily*, initiated at 14 – 34 weeks gestation and continued throughout the pregnancy.
Intrapartum	During labour, intravenous administration of ZDV in a one-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight/hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every six hours) for the first six weeks of life, beginning at 8 – 12 hours after birth.**

* Oral ZDV administered as 200 mg three times daily or 300 mg twice daily is currently used in general clinical practice and is acceptable alternative regimen to 100 mg orally five times daily.

** Intravenous dosage for full-term infants who cannot tolerate oral intake is 1.5 mg/kg body weight intravenously every six hours [119] ZDV dosing for infants < 35 weeks gestation at birth is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if > 30 weeks gestation at birth or at 4 weeks of age if < 30 weeks gestation at birth.

Table 15: Paediatric AIDS clinical trials group (PACTG) 076 Zidovudine (ZDV) Regimen

Adapted from "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" [62]

3. Use of antiviral therapy for the prevention of transmission of HIV from mother to child

Recommendations have been implemented on how to use Zidovudine ante partum, intra partum and post partum. This is summarised in Table 15.

There are however many more possible scenarios that require specific discussion and need to stay in the hands of expert paediatricians. Such scenarios include the time of recognition of HIV infection during pregnancy, current or previous antiretroviral therapy, CD4 count and clinical presentation of the infected mother and more.

4. Occupational exposure and post exposure prophylaxis

Post exposure prophylaxis for HIV requires the consideration of a number of issues which include severity of exposure, status of the donor (HIV RNA level, possibility of drug resistant HIV), and other circumstances like pregnancy, breast feeding and the presence of renal or hepatic disorders. In general HIV prophylaxis should be initiated as soon as possible; the donor should also be evaluated also in due course if possible. In case of a less severe injury with a known HIV positive source, a two drug regimen should be initiated. In case of a more severe exposure, a three drug regimen is recommended. If the sources are unknown, no post exposure prophylaxis is warranted. Prophylaxis should preferentially be intracutaneous, injuries might also be considered after exposure to mucosal membranes or exposure to non intact skin.

Individuals who were exposed to HIV should be monitored for at least six months, e.g. at the time point of exposure, at six weeks, at twelve weeks and at six months. HIV testing includes HIV PCR as well as HIV antibody testing.

The test procedure of the exposed individuals should be carried out as outlined in Tables 16 and 17.

Table 16: Recommendations after HIV exposure I
Adapted from [5]

Infection status of source					
Exposure type	**HIV-Positive Class 1[1]**	**HIV-Positive Class 2[1]**	**Source of unknown HIV status[2]**	**Unknown source[3]**	**HIV-Negative**
Less severe[4]	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] for source with HIV risk factors[6]	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] in settings where exposure to HIV-infected persons is likely	No PEP warranted
More severe[5]	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP[6] for source with HIV risk factors[6]	Generally, no PEP warranted; however, consider basic 2-drug PEP[7] in settings where exposure to HIV-infected persons is likely	No PEP warranted

1 HIV-Positive, Class 1 – asymptomatic HIV infection or known low viral load (e.g. <1.500 RNA copies/mL). HIV-Positive, Class 2 – symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
2 Source of unknown HIV status (e.g. decreased source person with no samples available for HIV testing).
3 Unknown source (e.g. a needle from a sharps disposal container).
4 Less severe (e.g. solid needle and superficial injury).
5 The designation "consider PEP" indicates that PEP is optional and should be based on an individual decision between the exposed person and the treating clinician.
6 If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.
7 More severe (e.g. large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein).

Table 17: Recommendations after HIV exposure II
Adapted from [5]

Infection status of source					
Exposure type	**HIV-Positive Class 1[1]**	**HIV-Positive Class 2[1]**	**Source of unknown HIV status[2]**	**Unknown source[3]**	**HIV-Negative**
Small volume[4]	Consider basic 2-drug PEP[6]	Recommend basic 2-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] for source with HIV risk factors[6]	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] in settings where exposure to HIV-infected persons is likely	No PEP warranted
Large volume[7]	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] for source with HIV risk factors[6]	Generally, no PEP warranted; however, consider basic 2-drug PEP[5] in settings where exposure to HIV-infected persons is likely	No PEP warranted

1 HIV-Positive, Class 1 – asymptomatic HIV infection or known low viral load (e.g. <1.500 RNA copies/mL). HIV-Positive, Class 2 – symptomatic HIV infections, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
2 Source of unknown HIV status (e.g. deceased source person with no samples available for HIV testing).
3 Unknown source (e.g. splash from inappropriately disposed blood).
4 Small volume (i.e. a few drops).
5 The designation "consider PEP" indicates that PEP is optional and should be based on an individual decision between the exposed person and the treating clinician.
6 If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.
7 Large volume (i.e. major blood splash).

5. Vaccines against HIV

Vaccines against HIV have been generated comprising the gp120 protein. They have been tested in phase I and phase II trials for safety and immunogenicity. So far, phase III trials have not shown efficacy in humans in that they have either protected completely from HIV infection or in that they have reduced the number of HIV infections in comparison to controls. As work is ongoing the hope for a protective HIV vaccine remains. However, the hyper variable region of HIV indicates that the virus is prepared for an escape, thus conventional methods for protection from HIV remain the best tool to deal with the HIV epidemic.

VII Outlook

Since the discovery of HIV in the mid Eighties, HIV has become an endemic, although many efforts have been made to prevent the spread of this deadly disease. On the other hand, much progress has been made in the understanding of this disorder, on diagnostic procedures including nucleic acid testing and in antiviral treatment. The latter has resulted in a significant increase in life expectancy, in a change of frequency of opportunistic infections and in the occurrence of novel disorders not observed in the initial natural course of HIV infection. As the fight against HIV continues novel developments will require continuous adjustment to new developments which will change diagnostic and therapeutic recommendations over time.

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Useful Web Sites

http://www.ias.se/
International Aids Society, Sweden

http://www.unaids.org/
Joint United Nations Program on HIV/AIDS

http://www.cdc.gov
Centers for Disease Control, USA

http://www.aidsinfo.nih.gov/
U.S. Department of Health and Human Services (DHHS) issues guidance documents for the medical management of HIV infection and other issues surrounding HIV infection.

http://www.hiv.lanl.gov
HIV databases containing data on HIV genetic sequences, immunological epitopes, drug resistance-associated mutations, and vaccine trials, funded by the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH), USA.

http://www.roche-diagnostics.com
Roche Diagnostics

http://www.roche-hiv.com
Roche in HIV

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X Glossary

AIDS	Acquired Immunodeficiency Syndrome
CNS	Central Nervous System
CMV	Cytomegalovirus
CT	Computer Tomography
DNA	Desoxyribonucleic Acid
EBV	Epstein-Barr Virus
EIA	Enzyme Immunoassay
Gp	Glycoprotein
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGV	Hepatitis G Virus
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HTLV	Human T -Lymphotrophic Virus
MRI	Magnetic Resonance Imaging
NA(A)T	Nucleic Acid (Amplification) Techniques
NRTI	Nucleoside Reverese Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
mRNA	messenger Ribonucleic Acid
RNA	Ribonucleic Acid
STD	Sexually Transmitted Disease
TB	Tuberculosis

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