

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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Acquired immune deficiency syndrome (AIDS) has been recognized and described for the first time in homosexual patients in 1981. First cases of infection in children were described two years later. In 1983, Center for Disease Control (CDC) from Atlanta established the clinical definition of this syndrome. In the same year, the virus involved in producing the disease was identified and the first case of blood transmission was reported.

Presently, the following AIDS definition is accepted: an infection produced by the retroviruses HIV-1 or HIV-2, with a large spectrum of clinical manifestations, from asymptomatic carrier to severe alterations with lethal evolution, due to cellular immune deficits.¹

ETIOLOGY AND TRANSMISSION

The human immunodeficiency virus (HIV) is a retrovirus with RNA genome that possess a reverse-transcriptase. This enzyme is essential in viral replication and allows synthesis of the DNA copy after the viral RNA.

Two main serotypes are recognized, HIV-1 and HIV-2, that differ not only by their geographic distribution but also by their virulence. HIV-2 determines an infection with a longer clinical latency and a more reduced vertical transmission from mother to infant. The third serotype, HIV-0, equally shares the features of the other two.

The structure of HIV is depicted in Figure 1 and consists of:²

- the viral envelope is made by a lipid bilayer and

the glycoproteins gp 120 and gp 41, coded by env genes;

- the capsid consists of protein p 24, matrix protein p 17, and nucleocapsid proteins p 6 and p7, coded by gag genes;

- the genome is composed of two molecules of RNA associated with a reverse transcriptase, coded by pol genes.

HIV attachment receptors are important for cell infection and are represented by:

- main receptors, represented by CD4 molecule on helper T lymphocytes, monocytes/macrophages, microglial cells and on Langerhans cells;

- co-receptors: chemokine receptors (C_xCR4, CCR5) are described in situations when HIV infection does not take place after exposure (in cases resistant to infection) because CCR5 does not have a normal structure;

- accessory receptors, represented by Fc receptors, complement receptors, and some adhesion molecules.

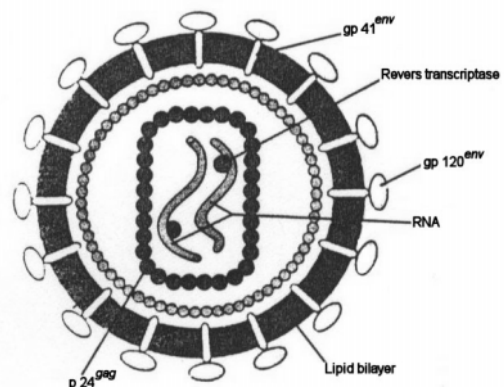


Figure 1. HIV structure

The cells that exhibit these receptors and therefore can become HIV-infected are: helper T lymphocytes, monocytes/macrophages, Langerhans cells, microglia and nervous endothelial cells, follicular dendritic cells, B lymphocytes, mucous intestinal cells, the retinal cells. The main reservoir of HIV is represented by the macrophages.³

For HIV transmission contact with a body fluid

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that contains infected cells or virus particles is mandatory; such fluids include blood, semen, vaginal secretions, cerebrospinal fluid, and breast milk. HIV also is present in tears, urine, and saliva, but in much lower concentrations.⁴

HIV is mainly transmitted through sexual relation with an infected person, blood and blood-contaminated objects and by vertical route. Modalities for HIV infection differ with the geographic area. In USA and Europe, the most frequent transmission routes are blood and blood-contaminated objects (needles sharing by injecting drug users, blood transfusion for hemophilia) as well as sexual contacts in homosexuals and heterosexuals.² In Africa, South America and Asia, the transmission is mainly heterosexual.⁵ In Romania most HIV infection cases are encountered in children born between 1986 and 1991, with an evident peak between 1988 and 1989 (probably an epidemiological accident).

1. Sexual transmission

In case of heterosexual intercourse, the infection takes place through infected cells from the genital fluids and less through free HIV in the genital secretions. The risk of infection is increased in case of inflammation of genital mucosa following Chlamydia, gonococcus, trichomonas and herpes simplex virus infections and in case of spirochetal infections (syphilis).^{6,7} The transmission from an infected man to a woman during sexual relation is 2 to 5 times more frequent than that from an infected woman to her male partner. The risk of infection is proportional with the plasmatic viral load.⁸

During primary infection, transmission can be 100 to 1000 greater than in the asymptomatic period (i.e., every 1 in 10 to 1 in 20 sexual contacts during primary infection are infectious, compared to 1 in 1000 to 1 in 10000 in case of sexual contacts during the asymptomatic period).⁹

During anal intercourse, the risk of infection is given by the presence of HIV in the intestinal mucosal cells. For oral sexual practices, the group at risk is represented by subjects with multiple partners and by homosexuals.¹⁰

Sexual practices that do not involve exposure to genital secretions are considered risk-free. The use of latex condoms (not of those made of natural rubber) decreases but not completely eliminates the risk of HIV transmission. Oil-based lubricants decrease the protection conferred by condoms.²

2. Blood and blood contaminated objects

This route is dose-dependent and the transmission is higher during primary infection and in end-stage, terminal disease.

Blood-transmitted HIV infection needs a much higher dose than hepatitis B virus (HBV). For HIV infection, 1 microliters of infected blood is required, compared to 0.004 microliters of infected blood needed for HBV infection). The risk for infection after an incidental prick with an HIV-infected needle is 0.5%, versus 7 to 30% in case of a needle used by HBV-infected patients. Susceptibility to infection is higher in case of deep wounds, extended skin lesions exposed to contact with blood or with other biological products containing HIV-infected blood or cells.²

Transfusion of HIV-infected blood or organ transplant from seropositive donors present with the highest risk for infection.²

3. Vertical transmission has a prevalence of 11 to 60%. The prevalence can be decreased to 3% if antiretroviral prophylaxis is applied to the mother in the last month of pregnancy and then to the new-born immediately after delivery. Vertical HIV infection occurs during 1 of 3 periods.⁴

-Prenatally, the fetus can be hematologically infected by means of transmission across the placenta or across the amniotic membranes, especially if the membranes are inflamed or infected.

-Most vertical infections occur during delivery. Usually, the longer and the greater amount of contact the neonate has with maternal blood and cervicovaginal secretions, the greater the risk of vertical transmission. The risk of infection during delivery is higher in premature and low-birth weight babies because of their reduced skin barrier and immunologic defenses.

-Postnatal vertical transmission occurs with the ingestion of HIV in the breast milk.

PATHOGENY OF HIV INFECTION

The pathogeny of HIV infection is multifactorial and the pathogenic mechanisms differ with the infection stage.

Animal studies have shown that in the first 24 hours, at the infection site, the dendritic cells of the skin or of the mucosae proliferate actively. In the following 24 to 48 hours, dendritic cells are mobilized, enter the lymph vessels and reach the regional lymph nodes.¹¹ Dissemination of the virus in the lymphoid organs is a major factor accounting for the persistence and chronicization of the infection because HIV replications occurs mainly within the lymphoid tissues.^{3, 12} The plasmatic viral load actually reflects the production of the virus in the lymphoid organs.

In order to establish infection in a person, the virus must enter cells such as lymphocytes, that display on the outer surface HIV receptors. The genetic material of the virus is incorporated into the DNA of an

infected cell. The virus replicates itself within the host cell, eventually destroys it and new infective virus particles are released. The new virus particles then infect other lymphocytes and can destroy them as well.⁴

Daily, 10^{10} virions are produced, the minimal lengths of HIV-1 life cycle is on average 1.2 days. Time elapsed from the release of a virion to the infection of a target cell and the apparition a new generation of viral particles is estimated to be 2.6 days. The virus can be detected in the peripheral blood within 5 days from the infection; through rapid replication, each virion can generate 5000 new viral particles. The level of viremia at one year from infection is an important prognostic factor for disease progression (low levels correlate with slow progression to AIDS).²

During HIV infection, the immune system reacts by synthesizing specific antibodies and cytotoxic T lymphocytes.¹⁵

The humoral immune response consists in the activation of B lymphocytes against antigens from the HIV envelope, against internal proteins coded by genes gag and pol as well as against regulatory proteins coded by genes nev and vif. Consequently, IgM-class antibodies are initially synthesized, followed by IgG (IgG1, G2, and G3) and IgA_s class antibodies. Neutralizing anti-HIV antibodies have a low titer and are not able to eliminate the virus. Furthermore, the presence of facilitating antibodies has been demonstrated, antibodies that enhance the infection instead of limiting it and allow HIV fixation on Fc receptors.

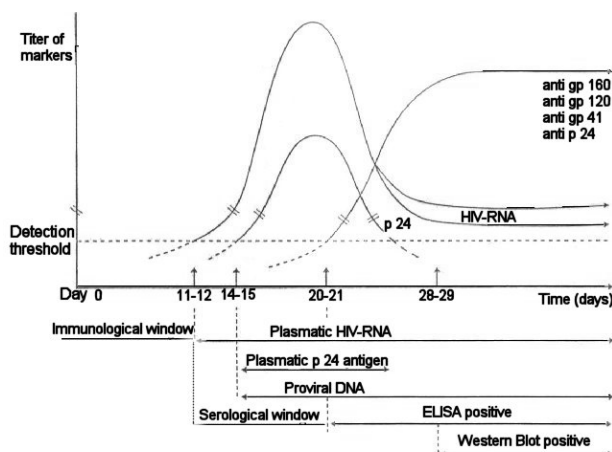


Figure 2. The evolution of viral and serological markers in primary HIV infection

Antibodies against core protein or against envelope proteins allow the serologic diagnosis of HIV infection 3 to 6 weeks after infection. Two types of test are commonly used: ELISA and Western blot.

The first 12 days after infection are called the immunological window, and are followed by the serological window (between day 12 and day 20 after infection) when plasmatic HIV and p 24 antigens can

be detected (using polymerase chain reaction -PCR). The serological window superimposes on the acute retroviral syndrome (Fig. 2).

The cellular immune response in HIV infection is accomplished by activation of several types of lymphocytes: natural killer (NK), cytotoxic T lymphocytes (CD8 T-cells), helper T lymphocytes (CD4 T-cells). The cytotoxic immune response is performed by CD8 T lymphocytes which destroy HIV-infected cells. Target antigens for the action of cytotoxic T lymphocytes are represented by the proteins of the viral envelope, the proteins coded by gag and pol genes, as well as by the regulatory proteins coded by nef.¹⁴⁻¹⁶

During primary HIV infection, cytotoxic T lymphocytes exert a favorable action by decreasing the number of infected cells and thus reducing the viral load.¹⁴ However, with the progression of infection, HIV changes its antigenic structure in order to avoid the immune response. The repeated changes of the viral antigenic structure leads to the development of a population of antigenic variants of the infective HIV strain. Under the pressure of the immune response, resistant viral strains are selected from this population.¹⁷ Furthermore, since HIV is hosted in the immune system cells, cytotoxic T lymphocytes and specific antibodies directed against viral antigens will destroy the infected immune cells (especially CD4 T-cells), therefore antiviral mechanisms become self-destroying.³ Another subpopulation of lymphocytes (CD8 and CD28 T-cells) play a role in inhibiting viral replication without cellular lysis.

THE CLINIC OF HIV INFECTION

The incubation period lasts on average 2 to 4 weeks, ranging from 5 to 150 days, depending on the infection route (transfusion, parenteral treatment, sexual intercourse), infective dose, the virulence of infective strain, and on the host mechanisms of immune defence.²

The primary infection (the acute retroviral infection) is clinically recognized only in a minority of patients and lasts on average 1 to 2 weeks. The primary infection can present as a mononucleosis-like syndrome (fever, swollen lymph nodes, congestive macular rubeola-like or urticaria-like rash, erythematous angina, myalgia, arthralgia, headache, anorexia, nausea, liver and spleen enlargement). Additional manifestations are: meningitis or meningoencephalitis, cranial nerves palsies, or peripheral neuropathies, and myopathy.¹⁸

During primary infection, anti-HIV antibodies can not be detected (patients are seronegative). In case of high suspicion (known infective contact) the diagnosis

can be established by detecting viral RNA using the PCR technique and/or by evidentiating p24 antigen.

A strong humoral and cellular immune response is triggered during the primary infection, however not powerful enough to dispense the virus from the body.¹³

Primary infection is followed by **the clinical latency period** that lasts from several months to more than 10 years. During this period, HIV-infected subjects are asymptomatic but can spread the infection. Serologic tests (ELISA and Western Blot) are positive during this period.

Symptomatic HIV infection refers to HIV-infected patients who develop symptoms: persistent fever, nocturnal sweat, moderate weight loss, lymph node enlargement more than 1 cm in more than two extrainguinal areas. Other symptoms that may appear are chronic diarrhoea, buccopharyngeal candidiasis, herpes zoster infection, hairy leucoplakia and are indicative of HIV infection progression to AIDS. In this stage, serologic tests ELISA and Western Blot are positive, and antibodies against proteins coded by gag, env and pol can be identified.

In this stage of HIV infection, viral replication is active resulting in an increase of the viral load, the infection of macrophages and of the “sanctuaries” (central nervous system, gonads).

AIDS

The patient status is progressively and evidently worsening, with the appearance of opportunistic infections, neoplasia, HIV encephalopathy, wasting syndrome (marked weight loss, extreme fatigue). CD4 cell count decreases to less than 200/mm³.

The clinical picture in AIDS is dominated by major immune disfunctions, especially those of cellular immunity, and by progressive neurological alterations, deriving from the primary HIV infection of immune and nervous cells.²

In AIDS, the opportunistic infections (severe or relapsing infections with commensal pathogens due to decreased immunity) are associated with autoimmune or hypersensitivity disorders (due to immune regulation deficits) as well as with tumours such as Kaposi sarcoma and non-Hodgkins lymphomas.^{2, 4, 18, 19}

The involvement of central nervous system is produced by:

- direct HIV action
- opportunistic infections of the central nervous systems
- neoplasia
- vascular disorders

Neurological disorders include acute HIV meningitis that can accompany the primary infection,

peripheral neuropathies of various types, encephalopathy with convulsions, focal motor or/and sensorial lesions, and gait disorders. These can be associated with cognitive disfunctions progressing to dementia.

Hematologic manifestations are relatively frequent and consist of anemia and thrombocytopenia, immune-mediated or secondary to other concomitant conditions.

Gastro-intestinal involvement is also a frequent feature of AIDS, with abdominal pain, nausea and vomiting, prolonged or relapsing diarrhoea that contribute to weight loss and to development of the wasting syndrome.

Opportunistic infections and tumors can involve the oropharynx but also the esophagus, the stomach, the bowel or even the biliary tract. Furthermore, pancreatic and liver lesions can develop secondary to antiretroviral medication.

Cutaneous and mucous involvement is found during primary infection (acute retroviral syndrome) in the form of rubella-like or urticaria-like congestive rash, facilitating confusion with mononucleosis syndrome. Generalized lymphadenopathy is also a frequent finding during primary infection.

In all HIV infection stages, patients can present muco-cutaneous candidiasis (thrush), transient, relapsing, hard to treat, as well as allergic rash (prurigo) and Kaposi sarcoma.

The infection with varicella zoster virus can present as herpes zoster infection of multiple dermatomes with a tendency to generalization and can be the clinical sign that raises the suspicion of a cellular immune deficit.

The most frequent pulmonary involvement is represented by tuberculosis that can have an atypical presentation (hilar lymph node involvement, miliary tuberculosis or infiltrates of the lower pulmonary lobes that rarely progress to cavern). The diagnosis is difficult because the intradermal reaction to tuberculin is often negative due to decreased cellular immunity.

Frequent pulmonary opportunistic infections are represented by fungal infections such as *Pneumocystis carinii*, *Cryptococcus neoformans*, *Histoplasma neoformans*, *Aspergillus*.

Bacterial pneumonia are severe, prolonged and can be caused by pneumococcus, haemophilus, pyocyanic. Mediastinal lymph node involvement is suggestive for carcinoma, Kaposi sarcoma, B-cell lymphoma, tuberculoma.

Cardiovascular involvement can manifest through dilative cardiomyopathy with progression to congestive heart failure or through bacterial endocarditis, myocarditis, and pericarditis.

HIV infection progresses to AIDS in approximately 10 years. Subjects who survive 10 to 15 years from

the primary infection are called long-term survivors and represent about 13% of all HIV-positive persons. Most of these subjects have significant deficits of the defense mechanisms, some have overimposed opportunistic infections. Their survival is conditioned by the favorable effect of the antiretroviral therapy. Different from long-term survivors, approximately 5 % of HIV-infected patients with a duration of the

disease of 10 years or more, do not present any evidence of alteration of the immune status, in the absence of antiretroviral therapy. Since the infection is present but has not progressed to AIDS, these individuals are called long-term non-progressors.²⁰

In 1993, CDC Atlanta has established the definition of HIV infection and has released the clinical and evolutive classification of HIV infection

Table 1. CDC Clinical Categories for HIV-Infected Children²¹

Category	Manifestation
N - Asymptomatic	One of the manifestations in category A or no symptoms listed in the other categories
A - Mildly symptomatic	Two or more: dermatitis, hepatomegaly, lymphadenopathy (>5 mm at multiple sites), splenomegaly, parotitis Recurrent or persistent sinusitis, otitis, or upper respiratory infection (URI)
B - Moderately symptomatic	Invasive bacterial infection Persistent (>2 months) oropharyngeal candidiasis (patients aged >6 months) Cardiomyopathy Congenital CMV infection (onset before patient aged 1 mo) Chronic or recurrent diarrhea Persistent (>1 mo) fever Persistent (>1 mo) hematologic disorders Anemia (<8 mg/dL) Neutropenia (<1000/mm ³) Thrombocytopenia (<100,000/mm ³) Hepatitis HSV infection Recurrent (>2 episodes/y) stomatitis Multiple dermatomes or recurrent (>2 episodes) zoster infection Early-onset (patient aged <1 mo) bronchitis, pneumonitis, or esophagitis Leiomyosarcoma Lymphoid interstitial pneumonia Pulmonary lymphoid hyperplasia complex Nephropathy Nocardiosis Congenital toxoplasmosis (patient age a onset <1 mo) Disseminated varicella
C - Late symptomatic	Pulmonary or esophageal candidiasis Coccidioidomycosis Extrapulmonary cryptococcosis Cryptosporidiosis CMV infection Histoplasmosis Chronic mucocutaneous HSV infection Encephalopathy Isosporiasis Kaposi Sarcoma Lymphoma MAC infection <i>Mycobacterium kansasii</i> infection <i>Pneumocystis carinii</i> pneumonia (PCP) Recurrent pneumonia Progressive multifocal encephalopathy Salmonellosis TB Toxoplasmosis
Late disease	MAC infection Disseminated CMV retinitis Cryptococcal meningitis Dementia, histoplasmosis Disseminated CNS lymphoma Progressive multifocal leukoencephalopathy (PML) Wasting syndrome

Table 2. CDC Clinical Categories for HIV-Infected Adults¹

Category	Manifestation
A	<p>One or more of the conditions listed below in an adolescent or adult (13 years or older) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.</p> <ul style="list-style-type: none"> -asymptomatic HIV infection -persistent generalised lymphadenopathy (PGL) -acute (primary) HIV infection with accompanying illness (sometimes known as seroconversion illness) or history of acute HIV infection
B	<p>Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in Category C and that meet one of the following criteria:</p> <ul style="list-style-type: none"> -the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity, or -the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection <p>Includes all such symptomatic conditions, with the exception of those placed in Category C. Examples of conditions in this category include, but are not limited to:</p> <ul style="list-style-type: none"> -bacillary angiomatosis -candidiasis (thrush) in the mouth and/or upper throat -candidiasis of the vagina and/or vulva which is persistent, frequent, or responds poorly to treatment -cervical abnormalites of moderate or severe extent or cervical cancer -constitutional symptoms such as fever (38.5 C) or diarrhoea lasting longer than one month -herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome (skin area) -idiopathic thrombocytopenia purpura -listeriosis -oral hairy leukoplakia -pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess -peripheral neuropathy <p>For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.</p>
C	<p>Includes the following conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.</p> <ul style="list-style-type: none"> -<i>Candida</i> in the oesophagus, trachea, bronchi or lungs -invasive cervical cancer -coccidioidomycosis -<i>Cryptococcus</i> outside the lungs -cryptosporidiosis with diarrhoea lasting for more than one month -CMV disease outside the liver, spleen or lymph nodes -CMV retinitis -herpes simplex virus causing prolonged skin problems or involving the lungs or oesophagus -HIV-related encephalopathy -chronic intestinal isosporiasis lasting longer than one month -Kaposi's sarcoma, Burkitt's, immunoblastic or primary (i.e. not involving other parts of the body) brain lymphoma -Widespread <i>Mycobacterium avium intracellulare</i> (MAI), <i>M kansasii</i> or other species <i>Pneumocystis carinii</i> pneumonia (PCP) -recurrent bacterial pneumonia -progressive multifocal leukoencephalopathy (PML) -recurrent <i>Salmonella</i> septicemia -toxoplasmosis of the brain -HIV wasting syndrome

depending on the superimposed pathology occurring in the course of infection. The classification is useful for the follow-up of the seropositive patients, for the adjustment of the antiretroviral therapy as well as of the treatment of associated conditions.

The clinical-evolutive stages differ from children to adults and are presented in Table 1 and Table 2.^{1,21}

Each of the A, B, and C stages are subdivided in three substages (1, 2, and 3) depending on the number of CD4 lymphocytes (Table 3).¹

The fast decrease of CD4 count is an indicator of the progression of HIV infection. When CD4 count decrease to less than 200/mm³, even if the clinical

symptomatology can be classified as stage A or B, the patient reached the AIDS stage.¹

Table 3. The 1993 Revised CDC Classification System for HIV Infection¹

CD4 count/mm ³	Clinical categories		
	A	B	C
	Asymptomatic, acute (primary) HIV or PGL**	Symptomatic, not A or C Conditions	AIDS Indicator Condition
>500	A1	B1	C1
200-499	A2	B2	C2
<200	A3	B3	C3

*Persons in categories A3, B3, C1, C2, and C3 have AIDS under the 1993 surveillance case definition. ** PGL = persistent generalized lymphadenopathy. Clinical Category A includes acute (primary) HIV infection.

Since CD4 count can vary with the counting assays used, moment of blood sampling and the presence of concomitant conditions, the CD4:CD₈ ratio can be used (normal range 0.83 to 3.41). A low CD4:CD8 ratio indicates severe immune depression.²²

DIAGNOSIS

Epidemiologic diagnosis is made by the appartenance to a high-risk group.

Clinical diagnosis is difficult due to the large array of manifestations of HIV infection, ranging from asymptomatic carrier or with minor clinical signs possibly evoking (prolonged fever, generalized lymph node involvement, asthenia, lack of appetite, weightloss, persistent candidiasis) to severe clinical manifestations (tuberculous meningitis, systemic cryptococcosis). In HIV-positive children in Romania infection was frequently suspected and then confirmed with the occasion of occurrence of herpes zoster infection, knowing that this manifestation of varicella-zoster herpes virus infection usually develops in the circumstances of immune deficit.¹⁸

Laboratory diagnosis relies mainly on detecting anti-HIV antibodies. The importance of serological window must be reemphasized (time between infection and positivation of ELISA and Western Blot) when patients are a source of infection, the virus is actively replicating but the diagnosis can not be established unless viral proteins are evidenced (p24 antigen) or viral nucleic acid using PCR (HIV-RNA). Quantitative measurement of HIV-RNA (viral load) is used for monitoring antiretroviral therapy.¹⁹

ANTIRETROVIRAL THERAPY

The aims of antiretroviral therapy are the following:¹⁹

- clinical: life prolongation and improvement of the quality of life;
- virological: long-term reduction of the viral load to less than 20 copies/ml;
- immunological: restoration of the immune response;
- epidemiological: decrease of the spread of HIV infection.

Antiretroviral therapy should be started in patients with CD4 count equal to or less than 500 cells/mm³ and a high seric level of HIV-RNA (viral load greater than 10,000 copies/ml detected by PCR).²²

Effective treatment consists in association of two or three antiretroviral drugs, from different classes, in order to block viral replication in multiple stages. Antiretroviral drug arsenal consists of: reverse

transcriptase inhibitors (nucleozidic and non-nucleozidic) and protease inhibitors. Main representants of each class are presented in Table 4.^{19,23,24}

Table 4. Antiretroviral drugs^{19,23,24}

Generic name	Trade name
I. Reverse transcriptase inhibitors	
1. Nucleoside inhibitors:	
-Zidovudine (ZDV, AZT)	Retrovir
-Didanosine (ddi)	Videx
-Zalcitabine (ddc)	Hivid
-Stavudine (d4T)	Zerit
-Lamivudine (3TC)	Epivir
-Abacavir	Ziagen
2. Non-nucleoside inhibitors	
-Nevirapine	Viramun
-Efavirenz	Stocrin
-Delavirdine	Rescriptor
II. Protease inhibitors	
-Indinavir	Crixivan
-Ritonavir	Norvir
-Nelfinavir	Viracept
-Saquinavir	Invirase
-Atazanavir	Reyataz

The success of antiretroviral therapy depends on patient compliance (correct and uninterrupted self-administration of the drugs) and on avoidance of drug interactions.

Compliance to treatment may be reduced by the large number of medications as well as by the multiple side effects that may appear along the course of antiretroviral therapy. Reverse transcriptase inhibitors may determine elevation of liver enzymes in the serum, pancreatitis, high serum lipids, myopathy, bone marrow suppression, and rarely lactic acidosis. Side effects of protease inhibitors are represented by nausea and vomiting, diarrhea, and abdominal discomfort. Indinavir causes a mild, reversible increase in liver enzymes that does not produce any symptoms and can also cause severe back pain (renal colic) similar to that caused by kidney stones. Ritonavir induces raising and lowering the levels of many other drugs through its effect on the liver. Metabolic changes (such as elevated blood sugar and fat levels) and obvious redistribution of body fat occur in many patients taking any protease inhibitor and less frequently with other HIV drugs.²²

Antiretroviral drugs are also used in the prophylaxis of vertical transmission from mother to the infant and in post-exposure therapy. The latter should be initiated very rapidly, preferably within 1-2 hours after the infective contact. Prophylactic regimen is adjusted depending on: type of exposure (intact or wounded skin, scratch or deep sting) and on the HIV status of the infected contact. In case of high risk of transmission, triple antiretroviral therapy is indicated

(Zidovudine + Lamivudine + Indinavir or Nelfinavir) with a duration of 1 month.¹⁹

Prophylactic treatment against opportunistic infections is usually prescribed in AIDS patients. To prevent pneumocystis pneumonia and toxoplasmic brain infections in patients with CD4 cells less than 200/mm³, the combination of sulfamethoxazole and trimethoprim is highly effective. In patients people with CD4 lymphocyte counts less than 75 to 100 cells/mm³, weekly azithromycin or daily clarithromycin or rifabutin are given to prevent *Mycobacterium avium* infections. In cryptococcal meningitis or in subject with repeated bouts of buccopharyngeal candidiasis, prolonged fluconazole therapy may be needed. Acyclovir is given in patients who experience recurrent episodes of herpes simplex infections to prevent relapses.⁴

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Self-Assessment Examination

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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- Human immune deficiency virus:
 - is a DNA virus
 - is a retrovirus
 - does not need a host cell to replicate
 - has an envelope made solely of a lipid bilayer
 - infects target cells after binding to CD4 receptors
- What are the most frequent modes of HIV transmission in USA and Europe:
 - fetal infection during pregnancy
 - homosexual intercourse
 - occupational transmission (needle-stick in medical personnel)
 - needle-sharing by intravenous drug users
 - infant infection during breast feeding
- Select true statements about sexual HIV transmission:
 - risk for infection is higher in case of concomitant sexual transmitted diseases.
 - HIV infection does not take place in case of anal intercourse
 - HIV transmission from an infected man to a woman is more frequent than viceversa
 - condoms do not completely eliminate the risk of infection
 - HIV transmission is greater during asymptomatic period than in the primary infection
- Humoral immune response during HIV infection is characterized by:
 - activation of macrophages
 - synthesis of antibodies directed against HIV structures
 - anti-HIV antibodies are effective in eliminating the virus
 - facilitating antibodies have been identified
 - allow serological diagnosis of HIV infection
- Early diagnosis of primary HIV infection (during serological window) is done using:
 - ELISA
 - Western Blot assay
 - Clinical symptoms that are highly specific
 - PCR technique for RNA-HIV
 - CD4 cell count
- Which symptoms may appear during the primary HIV infection:
 - herpes zoster infection
 - primary infection is always asymptomatic
 - lymphadenopathy
 - tuberculosis
 - Kaposi sarcoma
- During AIDS, the most frequent pulmonary involvement is represented by:
 - tuberculosis with atypical presentation
 - acute bronchitis
 - sarcoidosis
 - asthma
 - fungal infections
- The category "AIDS- Late disease" in HIV-infected children is suggested by:
 - disseminated varicella
 - persistent oro-pharyngeal candidiasis
 - chronic or recurrent diarrhea
 - persistent lymphadenopathy
 - wasting syndrome
- An HIV-infected adult is considered to have AIDS if:
 - asymptomatic, with CD4 count of $800/\text{mm}^3$
 - clinical category B conditions with CD4 count of $400/\text{mm}^3$
 - clinical category C conditions with CD4 count of $600/\text{mm}^3$
 - CD4 count of less than $200/\text{mm}^3$
- Clinical category C conditions in an HIV-infected adult include:
 - Pneumocystis carinii pneumonia
 - Kaposi sarcoma
 - idiopathic thrombocytopenia purpura
 - peripheral neuropathy
 - HIV-related encephalopathy
- Antiretroviral therapy:
 - is always given in monotherapy
 - has few if any side effects
 - aims to long-term decrease the viral load to less than 20 copies/ml.
 - is indicated for prophylaxis of vertical transmission
 - usually associates two or three drugs from different classes
- True statement about antiretroviral drugs include:
 - Lamivudine and Abacavir are nucleoside inhibitors of reverse transcriptase
 - Nevirapine and Efavirenz are protease inhibitors
 - Indinavir and Ritonavir are non-nucleoside inhibitors of reverse transcriptase
 - Post-exposure therapy is given in triple association for one month in case of high risk of infection
 - Metabolic side effects are more frequent in case of therapy with protease inhibitors.

To complete the examination for CME evaluation turn to page 329 for instructions and the response form.

Correct answers for CME: Sepsis (II). (TMJ 2003;2:185-9): 1-abd; 2-ce; 3-d; 4-ce; 5-abd; 6-bd; 7-a; 8-abce; 9-de; 10-bde; 11-cd; 12-abc.