Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 110 (2018) 129-146 EISSN 2392-2192

A review of current literature on the diagnosis, prophylaxis and treatment of HIV/AIDS

Mateusz Sobieski[1], Dawid Przystupski[1], Aleksandra Korzeniewska[2], Stanisław Kwiatkowski[1,*], Agata Górska[3], Krzysztof Kotowski[1], Dagmara Baczyńska[4]

[1] Faculty of Medicine, Wroclaw Medical University, J. Mikulicza-Radeckiego 5, 50-345 Wroclaw, Poland

[2] Faculty of Clinical Psychology, SWPS University of Social Sciences and Humanities, Ostrowskiego 30b, 53-238 Wroclaw, Poland

[3] Department of Biological Sciences, Institute of Experimental Biology, University of Wroclaw, Kanonia 6/8, 50-328 Wroclaw, Poland

[4] Department of Forensic Medicine, Molecular Techniques Unit, Wroclaw Medical University, J. Mikulicza-Radeckiego 4, 50-345 Wroclaw, Poland

*E-mail address: stkwiatek@gmail.com

ABSTRACT

Acquired immunodeficiency syndrome (AIDS) is a spectrum of various diseases associated with the human immunodeficiency virus (HIV) infection. AIDS is one of the most common infectious illness with 1.8 million of new cases and approximately 36.7 million living with HIV. AIDS becomes a worldwide problem and due to rising number of HIV-positive patients, the appropriate medical care is needed. This article takes into consideration the current information about pathogenesis of HIV infection, clinical and biochemical symptoms, diagnosis, prophylaxis and treatment the disease. Furthermore, the article describes the side effects of the treatment, the methods of their diagnosis and prevalence, and focuses on the psychological problems of HIV-positive people.

***Keywords*:** AIDS, HIV, cART, AIDS-related cancers

(Received 30 August 2018; Accepted 14 September 2018; Date of Publication 15 September 2018)

1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a spectrum of various conditions caused by the human immunodeficiency virus (HIV). AIDS is one of the most common infectious diseases with 1.8 million of new cases and approx. 36.7 million living with HIV1. Despite the fact that methods to control the infection are well known, non-specific symptoms of the initial phase of infection can be misinterpreted, and then the patient, who becomes a virus reservoir, can transmit the infection to other people. It is also a social problem, which is particularly evident in developing countries and some social groups, but it affects people from every population around the world. Thus, it is highly important to broaden constantly the knowledge about AIDS and HIV, among the clinicians, specialists of the health service and the whole society.

2. HIV TRANSMISSION, STRUCTURE AND REPLICATION

The virus can be transmitted through unprotected sexual contacts, blood transfusion and needles used for drug injection, from a mother to a child during pregnancy and delivery as well as after a birth with breastfeeding (1). The main causes of infections are risky sexual behaviors, risky sexual partners, use of contaminated drug injection equipment, accidental or intentional injury with a knife stained with blood of a person with HIV and mother infected by virus (2).

HIV is a lentivirus with a lipid bilayer envelope including transmembrane glycoprotein gp41 and outer membrane gp120, which are necessary to penetrate the human cells (3). In a core, single-stranded RNA is bounded to nucleocapsid proteins and enzymes such as reverse transcriptase, proteases and integrases.

There are two types of HIV – HIV-1 (which occurs all over the world) and HIV-2, less pathogenic occurring only in West Africa. Virus penetrates CD4+ cells such as Th lymphocytes but also macrophages, monocytes, microglia or dendritic cells (4). Cell penetration is based on the presence of CD4 receptor (which is a receptor for viral gp120 glycoprotein) and the co-receptors like CCR5 (for β-chemokines) and CXCR4 (for α-chemokines) (5). R5 strains (which display tropism to CCR5) are responsible for new infections and predominate in the initial phase of infection, X4 strains (which display tropism to CXCR4) appear later. CCR5 co-receptor is used by almost all subtypes of HIV-1, regardless of the genetic subtype of virus. As a result homozygotes that have *CCR5* gene mutations are less susceptible to infection with certain virus strains (6).

After penetration, an enzyme called the reverse transcriptase (RT) copies ssRNA genome into complementary DNA, which is incorporated into the host's DNA by integrases. The process of reverse transcription leads to many errors resulting in drug resistance or allowing to evade the immune system (7). Thus, there is created HIV reservoir which is an invulnerable to anti-retroviral drugs. However, it can be activated and turn into a source of replicating viruses under favorable conditions. The HIV virus is not only multiplying rapidly, but it also puts numerous host proteins (adhesive, MHC) on its envelope, protecting it against the immune system (8).

A chronic infection leads to a gradual decrease in lymphocytes CD4+, initially proceeding asymptomatically, while causing a gradual destruction of the microenvironment of

peripheral lymphatic organs, where the replication occurs. As the infection progresses, the immune homeostasis, as well as Th2 cell growth are disturbed and the concentration of pro-inflammatory cytokines increases, leading to the clinical appearance of symptoms (9,10).

3. SYMPTOMS AND CLASSIFICATION

The United States Center for Disease Control and Prevention created a classification system for HIV infection (11). All categories of level 3 and level C (i.e. A3, B3, C1, C2, C3) are basis to recognize to recognize AIDS.

Table 1. United States Center for Disease Control and Prevention classification system for HIV (13).

Immunological categories (CD4 cells' count range)	**Clinical categories**		
	A	**B**	**C**
≥500 μl	A1	B1	C1
200–499 μl	A2	B2	C2
<200 μl	A3	B3	C3

The clinical category A consists of three variants:

1) acute HIV infection;
2) chronic generalized lymphadenopathy;
3) asymptomatic infection.

The acute HIV infection occurs among 40-90% patients after 2-6 weeks from exposure to infection (but it can occur up to 6 months after that moment) and lasts for about 14 days. In some cases the disease is prolonged up to 10 weeks. It runs uncharacteristically and is reminiscent of mononucleosis. Symptoms of acute HIV infections are:

- Fever (80-90% of patients)
- Lymphadenopathy (40-70%)
- Pharyngitis (50-70%)
- Erythematous or maculopapular rash (40-80%)
- Arthralgia, myalgia (50-70%)
- Diarrhea and vomiting (30-60%)
- Headache (32-70%)
- Ulcers of oral mucosa or external genitalia (10-20%)
- Weight reduction (50%)
- Hepatosplenomegaly

- Candidiasis of the oral cavity
- Neurological symptoms
    - Meningitis (24%)
    - Encephalitis
    - Peripheral neuropathy
    - Guillain–Barré syndrome

During the acute HIV infection leukopenia, thrombocytopenia, anemia and increased values of transaminases and OB are often observed (12,13).

The acute HIV infection must be suspected when:

1) the patient has "re-mononucleosis";
2) there is promiscuous sexual behavior or the possibility of blood-borne infection;
3) the patient has symptoms of other sexually transmitted diseases.

A significant severity of symptoms and their prolongation are correlated with a faster progression of infection (12). An early diagnosis of HIV infection is crucial in order to limit the spread of infection (due to large viremia and high infectivity). When the symptoms of the acute HIV infection and seroconversion have subsided, the stabilization period of changes begins. It means a return to apparent health, a decrease in viremia to the level of set point in laboratory tests and an increase in the number of CD4 lymphocytes after their previous decrease. The set point, or the average level of viral load after the infection stabilizes, is a recognized and important prognostic indicator of disease progression.

Acute HIV infection is an indicator for the antiretroviral therapy (ARV). The optimal situation is to start the treatment before seroconversion (i.e. 8 weeks prior to exposure) - PCR-HIV diagnosis (or Elisa IV gene); a very early intervention enables to obtain an undetectable HIV-RNA/DNA level in peripheral blood mononuclear cells and sigmoid cells and the possibility of "functional cure".

The switched-on scheme without the result of drug resistance should contain drugs with a high genetic barrier. In this case, the inclusion of protease inhibitors (IPs) should be considered. Another group of drugs, recommended for the treatment of an acute retroviral infection, are integrase (II) inhibitors; their advantage is a rapid reduction in the level of HIV-RNA (14,15).

Chronic generalized lymphadenopathy is diagnosed when the lymph nodes are enlarged (more than 1 cm in diameter) in at least two regions of the body (except groin) for 3 months. Splenomegaly and feeling of chronic fatigue may occur (16).

The asymptomatic period appears after the phase of primary viremia as a result of determining the relative balance between HIV replication and the T-cell immune responce; in untreated patients it may last from 1.5 to 15 years (shorter in perinatally infected children, up to 12 months).

The clinical category B consists of diseases or conditions associated with decreased levels of CD4 cells. These conditions are not as specific as opportunistic infections (which create category C), but much more specific than those which are included into A category; hence, they are called “not A-not C”. Diseases and conditions related to category B are shown in Table 2.

Table 2. Diseases and conditions belonging to clinical category B (17).

Infectious diseases	Non-infectious diseases or conditions
Zoster on more than one dermatome or relapse	Thrombocytopenia
Hairy leukoplakia *(EBV infection)*	Fever *(*lasting more than a month)
Recurrent candidiasis of vulva or throat	Peripheral neuropathy
Dysplasia of the cervix *(HPV infection)*	Pelvic inflammatory disease
Bacterial hemangioma *(B. henselae infection)*	
Listeriosis	

The category C consists of coexisting diseases that make up the full-blown AIDS. These diseases are observed much less frequently (or not at all) in immunocompetent people. Diseases and conditions related to category C are presented in Table 3.

Table 3. Diseases and conditions included in clinical category C (18)(19).

Opportunistic infections	AIDS-related cancers	AIDS-related syndromes
Recurrent bacterial pneumonia *(two or more in year)*	Kaposi's sarcoma *(HHV-8 infection)*	Encephalopathy associated with HIV infection
Recurrent Salmonella bacteremia	Lymphomas *(Burkitt's, primary brain lymphoma, immunoblastic lymphoma)*	Exhaustion syndrome due to HIV infection
Tuberculosis *(pulmonary or extrapulmonary)*		
Disseminated mycobacteriosis		
Candidiasis of esophagus, bronchi, trachea or lungs		
Pneumocystis jiroveci *(carinii)* pneumonia *(PCP)*		
Extrapulmonary histoplasmosis		
Extrapulmonary coccidioidomycosis		
Extrapulmonary cryptococcosis		

Isosporosis		
Cryptosporidiosis		
HSV infections – chronic ulcers, pneumonia or esophagitis		
CMV infections *(except liver, spleen and lymph nodes)*		
Toxoplasmosis of internal organs *(brain, lungs, eye, myocardium)*		
Progressive multifocal leukoencephalopathy *(as a result of reactivation of JCV infection)*		

The occurrence of particular diseases is also dependent on the patient's immunity (CD4 cell level). Thus, they can be divided into several categories (20):

- Primary HIV infection may be asymptomatic, associated with acute retroviral syndrome or include generalized lymph node enlargement;
- Stage I (200-500 CD4 cells/µl) includes pneumonia (especially pneumococcal), zoster, tuberculosis, candidiasis of mouth and throat, cryptosporidiosis, Kaposi's sarcoma and hairy leukoplakia;
- Stage II (<200/µl) includes pulmonary pneumocystis, disseminated histoplasmosis, coccidioidomycosis and extrapulmonary tuberculosis;
- Stage III (<100/µl) includes disseminated HSV infection, toxoplasmosis, cryptococcosis, chronic cryptosporidiosis, microsporidiosis and candidiasis of esophagus;
- Stage IV (<50/µl) includes disseminated CMV infection and disseminated *Mycobacterium avium complex* (MAC) infections (20).

There are also diseases that do not fit into the categories listed above, but may suggest that the patient has been infected with HIV. Any patient with a sexually transmitted disease (STD) or HAV/HBV/HCV co-infection should be suspected of being infected with HIV (21)(22). Fever, neutropenia and thrombocytopenia also may suggest infection. Other such are:

1) Interstitial pneumonitis;
2) Aspergillosis;
3) Recurrent vaginal candidiasis;
4) Weight loss with unclear etiology;
5) Fever of unknown origin (FUO);
6) Enterocolitis with unclear etiology;
7) Lymphadenopathy;

8) Exhaustion syndrome of unclear etiology;
9) Neurotoxoplasmosis;
10) Cryptococcal meningitis;
11) Progressive dementia;
12) Lung cancer;
13) Seminomas;
14) Retinopathies of unclear origin;
15) Glomerular nephropathy

4. AIDS-RELATED CANCERS

AIDS-related cancer is a complex issue - patients infected with HIV are at an increased incidence of certain types of cancer (as Kaposi's sarcoma, non-Hodgkin's lymphomas and cervical cancer) and their treatment is difficult due to cachexia, drug load, coexisting diseases and, most importantly, the reduced immunity. Importantly, early (and even immediate) implementation of antiretroviral therapy significantly reduces the risk of cancer. However, it should be borne in mind that the longer life of patients infected with the virus causes the increased risk of cancer among older population (similarly as in the uninfected).

Kaposi's sarcoma (KS) is associated with HHV-8 infection (23). The virus can be transmitted by saliva, sexual contacts and blood. It occurs mainly in "men having sex with men" group (MSM), usually with significant immune deficiencies; however, there are cases of patients with a relatively high number of CD4 lymphocytes. Symptoms of sarcoma may also be present in immune reconstitution syndromes.

Kaposi's sarcoma is characterized by a diverse clinical picture. In the benign, cutaneous form, nodules, spots of various colors and ulcerations associated with the possible bleeding and subsequent deposition of hemosiderin are observed. A frequent location is the area of the genital mucous membranes, eyes and very characteristic changes in the oral cavity, where the hard palate is attacked first of all. In cases involving internal organs, the changes may include the digestive tract and the respiratory system. In the latter, the prognosis is very serious. Sarcoma has a severe course in the immune reconstruction syndrome. These are rare incidents, often with a very aggressive course, and a visceral location. The diagnosis is usually symptomatic, and should be confirmed by the immunohistochemistry assay. In the visceral form – X-Ray of the chest, USG, CT scan or endoscopic examination are obligatory. The applied treatment consists of cART and chemotherapy.

Most non-Hodgkin's lymphomas are B-cell tumors. The most common ones (> 90%) are diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma (18). Organ-limited lymphoma are primary central nervous system lymphoma (PCNSL) or primary effusion lymphoma (PEL), which occur only in seropositive population.

When analyzing the lymphoma etiology, it should be noted that DLBCL is usually associated with Epstein-Barr virus (EBV) infection and a low number of CD4 lymphocytes. Burkitt's lymphoma, which is not always accompanied by EBV infection, occurs more often than DLBCL at the level of CD4>200 cells/μl. The last two types of lymphomas, PCNSL and PEL are characterized by extremely low levels of CD4 lymphocytes (in most cases <50 cells/μl). PCNSL is practically 100% associated with the etiology of EBV, while PEL always occurs in the connection with HHV-8 infection and sometimes also EBV (24,19,25).

The most common symptom is the enlargement of the peripheral lymph nodes. They are hard, non-translucent to the ground and painless. At the time of diagnosis the vast majority of patients present an advanced picture of the disease accompanied by rapidly increasing symptoms, such as weight loss, fever, night sweats and general weakness. The characteristic neoplastic changes can be found practically everywhere - in orbits, testes, heart, kidneys, bladder, muscles or bones. The most typical, however, is the involvement of the bone marrow, gastrointestinal tract, liver and central nervous system. In the case of an extra-nodal location, the patient's discomfort is related to the location of proliferative changes: abdominal pain resulting from hepatosplenomegaly, bleeding or symptoms of gastrointestinal obstruction, bone pain due to neoplastic infiltration.

In the case of PCNSL, epileptic seizures may be the first sign of disease. The clinical picture is dominated by headaches, personality changes, neurological disorders and very rapidly progressing cachexia. Similarly dramatic progression of the disease is observed in the primary exudative lymphoma. PEL should be suspected in any HIV-seropositive patient who is rapidly debilitating and who has symptoms of pleural, pericardial effusion or effusion in other location. In the vast majority of cases, there is no tumor mass found.

The most reliable diagnostic material is the acquired lymph node, since the biopsy of both the node and the bone marrow may not be sufficient to make an accurate diagnosis. The basic pathomorphological examination should determine the lymphoma subtype based on the immunophenotypization method. The diagnosis of primary brain lymphoma is based primarily on the presence of a pathological mass (solid structure with spreading infiltration) by using MRI. The diagnosis verification excluding brain toxoplasmosis should be performed (MRI image, presence of anti-Toxoplasma antibodies, results of empiric anti-toxoplasmosis treatment). The decisive factor in the diagnosis is the result of the histopathological examination of the brain biopsy material.

The invasive cervical cancer is associated with oncogenic human papilloma virus (HPV) types, especially 16, 18 (types 6 or 11 are known to be benign) (26), women with HIV-positive test results are nine times more likely to have cervical cancer (27). In the first year of observation, female patients should be examined twice a year, then every year. In men, circumcisions have a positive effect on reducing of the risk of transmitting the disease to sexual partners.

5. DIAGNOSIS OF HIV INFECTION

As a part of the laboratory diagnosis of HIV infection, it is recommended to use IV generation serology tests (ELISA), which allow the detection of HIV p24 antigen (which is detectable 2 weeks after infection) and anti-HIV 1/2 and 0 IgG and IgM antibodies (occurs after 4-12 weeks after infection). Currently, the third generation tests are not recommended as these only detect anti-HIV antibodies - it is not possible to detect very early HIV infection.

This test is carried out twice.Negative results of screening test after 12 weeks exclude HIV infection (in most cases specific antibodies are formed already in 6-8 weeks); however, repeating the test after 12 weeks is justified when the patient often displays promiscuous behavior behaviors, there is undoubted exposure to the infectious HIV material or when the patient is a pregnant woman (28).

In the prophylactic treatment of post-exposure HIV, with the simultaneous co-infection of HIV and HCV, EBV or CMV, the period of seroconversion may be prolonged. The tests can be confirmed by Western Blot or INNO LIA assays. When both of generation IV ELISA tests are positive, a verifying test is used due to the low positive prediction value; it cannot be commissioned as the first and only one. Western Blot methods are more specified, but less sensitive – hence they are used as a confirmation of ELISA result. Tests are performed to exclude a false positive result from screening tests since they detect anti-HIV antibodies against more HIV antigens than ELISAs.

The positive result is the presence of antibodies (strips on the nitrocellulose membrane) against ≥2 antigens from various groups of proteins: *env* gene products (envelope proteins: gp160, gp120, gp41), *gag* (core proteins: p24, p17, p55) or *pol* (p68, p52, p34); according to WHO criteria, the presence of antibodies against casing proteins is a necessary condition for a positive result. Only after a positive validation the result is disclosed to the patient. In emergency situations (acute HIV infection, childbirth, etc.) HIV infection can be diagnosed through fast HIV-1 RNA testing. When the first screening test comes out positive and the second one negative, it should be assumed that the result may be false positive, false negative, as well as blood samples of another patient could have been tested and whole diagnostics must be retried. When the two screening tests are positive and the confirmation test - negative again, tests may be false positive or negative or the patients may be in very early phase of HIV infection. When it is assumed to be a very early phase, HIV-1 RNA should be determined and the diagnostics should be repeated after 4 weeks. If HIV-RNA is negative, it is possible to mark p24 antigen in patients' blood. HIV-RNA PCR test could be divided into qualitative and quantitative; qualitative tests are used to exclude or confirm an infection and quantitative – assess prognosis and monitor the effectiveness of treatment.

HIV-DNA PCR tests detect the HIV genome linked to the genome of infected cells and is used to explain uncertain results in newborns and in very early diagnosis – this test has almost 100% specificity and sensitivity (29–31).

A negative test result does not exclude the possibility of HIV infection:

- when antibodies have not been produced by immune system;
- when patient is in advanced phase of AIDS;
- in case of virus mutation;
- in case of infection with different serotype of a virus than HIV-1, M, O and HIV-2 if the test cannot detect them;
- in people with immunodeficiency.

A false positive result occurs:

- in the presence of other infections: T. gondii, CMV, EBV, HAV, HBV, HCV, T. pallidum;
- in the presence of autoantibodies: anti-gag, ANA, RF;
- after vaccination within 1 month before the test;
- when the patient is pregnant;
- after transfusions of blood and immunoglobulins;
- when the patient is after transplantation;
- in the case of handling of test tubes.

6. PRE-EXPOSURE PROPHYLAXIS

Pre-exposure prophylaxis HIV (PrEP) is the use of antiretroviral drugs in HIV-negative people to reduce the risk of acquiring HIV infection. Pre-exposure prophylaxis is highly effective and should be applied in the combination with broad and regular HIV screening, early treatment of all HIV-infected patients, extensive diagnostics and treatment of other sexually transmitted infections, as well as the promotion of prevention and other harm reduction methods. Such combined activities, including PrEP, are the only way to reduce the number of new infections in key populations. PrEP should be used in adults with an increased risk of acquiring HIV infection.

People with an increased risk of HIV infection who should be offered PrEP include:

- people who have sexual contact with HIV-positive person (untreated or not treated successfully) or with someone of unknown serological status who does not consistently use condoms;
- people using drugs intravenously.

The current prescriptions indicate the application of Tenofovir (300 mg) with emtricitabine (200 mg) administered as a PrEP orally, once per a day, with meal. PrEP achieves efficacy after 7 days of use, when it is used as protection during anal contacts, and after 20 days in the case of vaginal contacts (32).

7. POST-EXPOSURE PROPHYLAXIS (PEP)

Post exposure prophylaxis is used in cases where there has been a situation that carries the risk of virus infection. Such situations include stabbing, sexual contact without a condom, intravenous drug use or any other contact with blood or other body secretions (however, for instance, saliva or tears do not contain the virus) (33).

After stabbing, it is not advisable to stop bleeding or squeeze blood from the wound. The wound needs to be washed under running water with soap (to dissolve the envelope of the virus). After splattering blood or other body secretion on mucous membranes, it is necessary to rinse them several times with water. If the exposure occurred at work, it is obligatory to report it to the supervisor. Then, the source patient's blood needs to be secured for testing. If it is impossible to do so, the source patient should be referred to the examination to a specialist medical center dealing with post-exposure prophylaxis. In case of exposure of medical employees, tests may be performed at the parent workplace, unless it delays the implementation of post-exposure prophylaxis. It is recommended to obtain additional medical information about the source patient, which may affect the decision to implement prophylaxis (keeping medical confidentiality and adequate protection of such data).

The person exposed to the virus should be directed to a specialist medical center to perform tests and qualifications for specific prophylaxis as soon fas possible. Importantly, if the person who is the source of the exposure is conscious, they should give their written consent to the examination. If the source of exposure is a minor under 16 years of age the consent for research is provided by a legal guardians, and in the age of 16-18 - both the legal guardians and minor. If the patient refuses to perform the source of the test - they should be regarded as potentially infected with HIV, HBV and HCV. It is also worth implementing

prophylaxis of hepatitis B, STDs and tetanus. On the first visit qualifying for PEP, the exposed patient should be tested for HIV (HIVAb IV generation), HBV (HBsAg, HBcAb, HBsAb – last one if patient was vaccinated for hepatitis B), HCV (HCVAb). Additionally, a test for syphilis (when there was sexual exposition) and a pregnancy test (to choose the right prophylaxis) should be performed. The source patient should be also tested for HIV (also HIVAb IV generation), HBV (HBsAg only is sufficient), HCV and for syphilis. Prophylaxis should be started within 48 hours; in high-risk cases – it can be started 72 hours after exposure. This is a problem, as patients often report after this time due to various personal reasons (shame, fear, lack of awareness of the threat, etc.).

Regardless of the type of exposure, if the source patient is HIV-positive, prophylaxis should be started - even when the serological status of source patient is unknown, but there was sexual contact without condom, with condom damage or oral sex with ejaculation. If there is a transcutaneous exposure, depending on the situation (visible blood on the tool, needle after intramuscular/intravenous injection) when the source is unknown or with an unknown serological status, prophylaxis is not recommended (especially if the tool was exposed to external environment factors), and it is only used when the source is at high risk of HIV infection (e.g. the source patient is drug addicted, engages in promiscuous behavior etc.). In the case of splashing, the situation is analogous - however, depending on the volume of infectious material, prophylaxis may not be necessary or implemented (when the volume of infectious material is large). Basically, PEP consist of three drugs: 2 NRTIs (tenofovir + emtricitabine or zidovudine + lamivudine or lamivudine + tenofovir) with PI or InI (raltegravir or lopinavir or darunavir). In the case of drug resistance or contraindications, the basic scheme can be changed (33).

8. PSYCHOLOGICAL HELP FOR PEOPLE LIVING WITH AIDS

Being HIV-positive is associated with specific psychological functioning. The problem begins even before the moment of diagnosis (34). The time between the hazardous situation and HIV test results is about 4 weeks. Patients waiting for results suffer from restlessness and high level of anxiety in regard to being infected. After that, the patient has to face up tof disease which tends to result in psychological crisis. This, in turn, may be connected with many cognitive, emotional and behavioral dysfunctions and when, untreated, may turn into chronic mental illness, e.g. depression or anxiety disorders. Hence, people infected with HIV virus require well-organized and professional psychological help.

Every patient has different „pattern" of reaction to illness – related stress, so they need different individual approach. The first step in providing help is defining the space of patient's difficulties and resources. HIV-positive patients can express various emotions such as huge anxiety, panic, depression or happiness of their state. Still, the psychologists or different specialists should normalize patient's feelings; every emotion felt by person with AIDS is a part of long internal process, which can alter in any moment of illness. Subsequently, after interventions directed at facing with AIDS disease, the specialists should supervise the patient's daily functioning. It is recommended to consider creating the net of social support (35). Like many research have reported, the social support is substantially connected with people's well-being. Furthermore, this tendency is noticeable among people suffering from diseases.

Due to the mentioned facts psychologists should support the patient in this area of life. It's easier to build social support with people who understand patient's experiences, which is reflected in some psychological recommendations such as taking part in therapeutic groups. For example there is a "Life-steps" group associated with cognitive-behavioral therapy. The patients can find mental support of other people suffering from AIDS. It has been proved that taking part in that kind of assistance is connected with fewer depression symptoms (36).

9. TREATMENT OF HIV

HIV treatment is based on cART (*combined antiretroviral therapy*) (formerly HAART - *highly active antiretroviral therapy*). Antiretroviral drugs block the activity of enzymes responsible for the replication and inhibition of fusion with cells. The use of several drugs with a synergistic effect results in a quick inhibition of multiplication and enables the partial reconstruction of the immune system.

The indications for cART protocole (3):

- Symptomatic infection (B or C clinical category) regardless of CD4 lymphocytes level;
- Patients with CD4 cells level lower than 350/µl;a
- Acute HIV infection;
- Pregnant women after 14 weeks of pregnancy;
- Women planning to get pregnant;
- Patients over the age of 50;
- Risk of cardiovascular diseases;
- Diabetes;
- Neurological symptoms;
- HIV RNA level higher than 100,000 copies per ml;
- Nephropathy associated with HIV infection;
- Co-infection with HBV, HCV;
- Prevention of HIV infection in the patient's partner(s);
- Impaired cognitive functions.

It is recommended to start treatment when CD4 cells level is lower than 500/μm^3 or when CD4 decrease is greater than 100/μm^3 per year. The treatment should be considered when the patient is ready to start taking medication.

Drugs used in the cART scheme are:

- *Reverse-transcriptase inhibitors* (RTI) – *nucleoside analog RTIs* (NRTIs) or *nucleotide analog RTIs* (NtRTIs);
    - RTI competitively inhibit HIV reverse transcriptase activity by blocking the synthesizing active center of the enzyme;
    - examples of NRTIs are zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine;
    - example of NtRTIs is tenofovir;
- *Non-nucleoside reverse-transcriptase inhibitors* (NNRTIs)

  - NNRTIs block HIV reverse transcriptase outside the active center which prevents the formation of conformations necessary for the enzyme to work;
  - examples of NNRTIs: nevirapine, efavirenz, etravirine;
- *Protease inhibitors* (PI)
  - by competitive blocking of the active protease center (the enzyme that cleaves HIV polyproteins into the structural components of the virus envelope) PI inhibits the formation of complete progeny HIV virions and stops the replication cycle;
  - examples of PI: indinavir, saquinavir, nelfinavir, fosamprenavir, lopinavir, tipranavir, darunavir;
- *Integrase inhibitors* (InI)
  - blocking the action of integrase necessary to integrate HIV genetic material with human DNA;
  - examples of InI: raltegravir, elvitegravir, dolutegravir;
- *Entry inhibitors*
  - inhibiting the process of HIV penetration into CD4+ cells by blocking changes in the gp41 structure or blocking the co-receptors necessary for the entry of HIV;
  - examples: maraviroc (inhibitor of CCR5 co-receptor), enfuvirtide (fusion inhibitor).

As the first cART scheme 2 NRTI + NNRTI or PI or InI is recommended. It is necessary to select the appropriate set of medication for the patients based on their lifestyle and concomitant diseases. Treatment should be monitored - after two weeks from the beginning of treatment HIV RNA should be marked and laboratory tests assessing whether the selected drugs are safe for the patient should be performed.

Every three months CD4 and CD8 lymphocytes and HIV RNA levels should be marked and basic laboratory tests (morphology, AST, ALT, bilirubin, creatinine, lipid, glucose, urinalysis) performed. Every year, the patient should undergo chest X-ray, abdominal ultrasound examination, ECG and gynecological examination.

The treatment is considered as an ineffective when sufficient reduction of viraemia is not detectable, HIV RNA is measurable in blood after 4-6 months long treatment, HIV RNA re-appeared in the blood plasma after declining to indeterminate values and when the disease is clinically progressive.

9. 1. cART side effects

Like every pharmacotherapy, cART also involves side effects after the use of antiretroviral drugs that depend on the type of substance applied.

The side effects of cART include:

1) skin lesions – rash, erythema, hyperpigmentation;
2) gastrointestinal symptoms – nausea, diarrhea, pancreatitis;
3) fatty liver, hepatitis, elevated level of alanine and aspartate transaminase in serum;
4) osteopenia, myopathy, ischemic heart disease;
5) renal failure;
6) immune reconstitution syndromes;

7) lipodystrophy syndromes;
8) lactic acidosis;
9) insulin resistance;
10) dyslipidemia - hypercholesterolemia, hypertriglyceridemia, elevated level of LDL and VLDL in serum; caused by both PI and RTIs.

Lipoatrophy is most often associated with the use of NRTI, characterized as the disappearance of subcutaneous fat tissue within the limbs, buttocks and face. No changes in lean body mass (mainly muscle mass) distinguishes lipoatrophy from the wasting syndrome associated with AIDS. Fat loss on face is one of the most stigmatizing symptoms of HIV infection. Lipoatrophy of subcutaneous tissue significantly reduces the quality of life and self-esteem of the patient and may adversely affect compliance with the cART treatment (37).

Lipohypertrophy is most often associated with the use of PI and efavirenz; it also occurs in HIV-positive untreated patients. It is characterized as the accumulation of fat in the abdominal cavity and on the abdomen (with increasing its circumference), around the neck and the upper part of the neck and/or in the breast glands (gynecomastia) and internal organs. Fat accumulation has also been reported in HIV-positive patients in the form of a suprapubular fat pad and a fat band extending from the breast to the axillary pits (38).

Pathological hyperplasia of the fat tissue on the neck is not only an aesthetic defect; it causes postural disorders and pain, while the pathological accumulation of visceral fat causes a feeling of fullness and pain in the abdomen. The prevention of lipohypertrophy includes low-fat diet, regular physical activity and avoidance of corticosteroids (39–42).

Peripheral lipoatrophy and central lipohypertrophy can occur in alone or in combination with other disorders (43).

10. CONCLUSIONS

This review outlines the current knowledge about AIDS, its course, risks factors and treatment. The most promising seems cell and gene therapy strategies. The recent research and advances based on stem cells anti-HIV therapies, show the ability to genetical and pharmacological targeting of multiple phases of the viral life cycle (44). The promising method in gene delivery seems to be the nanocarriers application (45,46) or electroporation method (47,48) which was applied as an intradermal protocol and well tolerated. The enhancement methods additionally stimulate cell- and antibody-mediated immune responses provoked by the HIV-DNA treatment (49-51). The application of the cell and gene therapy approaches seems to be fundamental to rebuild and strengthen an effective immune response. However, the available data indicate that AIDS is still uncontrollable disease and requires further and thorough studies.

Acknowledgments

The work was created as part of the activity of the Student Research Group "Biology of Cancer Cell" at the Wroclaw Medical University (SKN No. K 148). Authors would also like to thank Ms. E. Przydatek for the correction of the English language in the manuscript.

References

[1] Rom W, Markowitz S. Environmental and occupational medicine (4th ed.). Wolters Kluwer/Lippincott Williams & Wilkins (2007) 745.

[2] European Centre for Disease Prevention & Control. HIV Testing: increase uptake and effectiveness in the European Union (2010) 1-34.

[3] Foley B, Apetrei C, Mizrachi I, Rambaut A, Korber B, Kuiken C, et al. HIV Sequence Compendium 2010 (2010).

[4] Arrildt KT, Joseph SB, Swanstrom R. The HIV-1 Env protein: A coat of many colors. *Current HIV/AIDS Reports* 9(1) (2012) 52-63.

[5] Chan DC, Fass D, Berger JM, Kim PS. Core structure of gp41 from the HIV envelope glycoprotein, *Cell* 89(2) (1997) 263-273.

[6] Tang J, Kaslow R. The impact of host genetics on HIV infection and disease progression in the era of highly active antiretroviral therapy, *AIDS* 17(Suppl 4) (2003) 51–60.

[7] Zheng YH, Lovsin N, Peterlin BM. Newly identified host factors modulate HIV replication, *Immunology Letters* 97(2) (2005) 225-234.

[8] Pollard VW, Malim MH. The hiv-1 rev protein, *Annu Rev Microbiol* 52 (1998) 491-532.

[9] Aliberti J. Control of Innate and Adaptive Immune Responses During Infectious Diseases, *Springer Verlag* (2011) 145.

[10] Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences, *J Pathol* 214(2) (2008) 231-241.

[11] Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged, *MMWR Recomm Rep* 57(RR-10) (2008) 1-12.

[12] Kassutto S, Rosenberg ES. Primary HIV type 1 infection, *Clin Infect Dis* 38(10) (2004) 1447-1453.

[13] Kahn JO, Walker BD. Acute Human Immunodeficiency Virus Type 1 Infection, *N Engl J Med* 339(1) (1998) 33-39.

[14] Brenner BG, Roger M, Routy J, Moisi D, Ntemgwa M, Matte C, et al. High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection, *J Infect Dis* 195(7) (2007) 951-959.

[15] Pao D, Fisher M, Hue S, Dean G, Murphy G, Cane P, et al. Transmission of HIV-1 during primary infection: relationship to sexual risk and sexually transmitted infections, *Aids* 19(1) (2005) 85-90.

[16] Abrams DI, Kaplan LD, McGrath MS, Volberding PA. AIDS-related benign lymphadenopathy and malignant lymphoma: clinical aspects and virologic interactions. *AIDS Res* 2(Suppl 1) (1986) S131-40.

[17] Ertunc B, Kaya S, Koksal I. Clinico-Epidemiological Analysis of HIV/AIDS Patients. *Eurasian J Med* 48(3) (2016) 157–61.

[18] Knowles DM. Etiology and pathogenesis of AIDS-related non-Hodgkin's lymphoma, *Hematology/Oncology Clinics of North America* 17(3) (2003) 785-820.

[19] Chen Y-B, Rahemtullah A, Hochberg E. Primary effusion lymphoma, *Oncologist* 12(5) (2007) 569-576.

[20] World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children, *World Health* (2007).

[21] Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, *MMWR Recomm Rep* 64(RR-03) (2015) 1-137.

[22] Saag MS, Chambers HF, Eliopoulos GM, Gilbert DN. The Sanford Guide To HIV/AIDS Therapy, *Antimicrobial Therapy* (2015).

[23] Cancian L, Hansen A, Boshoff C. Cellular origin of Kaposi's sarcoma and Kaposi's sarcoma-associated herpesvirus-induced cell reprogramming, *Trends in Cell Biology* 23(9) (2013) 421-432.

[24] Kirk O. Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy, *Blood* 98(12) (2001) 3406–12.

[25] Simonelli C, Tedeschi R, Gloghini A, Bortolin MT, Spina M, Bidoli E, et al. Characterization of Immunologic and Virological Parameters in HIV-Infected Patients with Primary Effusion Lymphoma during Antiblastic Therapy and Highly Active Antiretroviral Therapy, *Clin Infect Dis* 40(7) 2005 1022-7.

[26] Sun XW, Kuhn L, Ellerbrock T V, Chiasson M a, Bush TJ, Wright TC. Human papillomavirus infection in women infected with the human immunodeficiency virus, *N Engl J Med* 337(19) (1997) 1343-9.

[27] Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS, *J Acquir Immune Defic Syndr*. 32(5) (2003) 527–33.

[28] Bhatti AB, Usman M, Kandi V. Current Scenario of HIV/AIDS, Treatment Options, and Major Challenges with Compliance to Antiretroviral Therapy. *Cureus* 8(3) (2016) e515.

[29] Cornett JK, Kirn TJ. Laboratory diagnosis of HIV in adults: A review of current methods, *Clinical Infectious Diseases* 57(5) (2013) 712-8.

[30] Arora DR, Maheshwari M, Arora B. Rapid Point-of-Care Testing for Detection of HIV and Clinical Monitoring, ISRN AIDS 2013 (2013) 287269.

[31] WHO. Consolidated guidelines on HIV testing services 2015. *World Heal Organ*. 2015.

[32] Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men, *N Engl J Med.* 363 (2010) 2587-2599.

[33] Sultan B, Benn P, Waters L. Current perspectives in HIV post-exposure prophylaxis. *HIV AIDS (Auckl)* 6 (2014) 147–58.

[34] Weitz R. Uncertainty and the Lives of Persons with AIDS, *J Health Soc Behav* 30(3) (1989) 270-281.

[35] Gonzalez JS, Penedo FJ, Antoni MH, Durán RE, Fernandez MI, McPherson-Baker S, et al. Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. *Health Psychol.* 2004 Jul; 23(4): 413-418

[36] Safren SA, O'Cleirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: A randomized controlled trial, *J Consult Clin Psychol* 80(3) (2012) 404-415.

[37] Dos Santos AP, Navarro AM, Schwingel A, Alves TC, Abdalla PP, Venturini ACR, et al. Lipodystrophy diagnosis in people living with HIV/AIDS: prediction and validation of sex-specific anthropometric models. *BMC Public Health* 18(1) (2018) 806.

[38] Saint-Marc T, Partisani M, Poizot-Martin I, Rouviere O, Bruno F, Avellaneda R, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study, *AIDS* 14(1) (2000) 37-49.

[39] Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors, *AIDS* 12(7) (1998) F51-8.

[40] Calza L, Manfredi R, Chiodo F. Dyslipidaemia associated with antiretroviral therapy in HIV-infected patients, *J Antimicrob Chemother* 53(1) (2004) 10–4.

[41] Chen D, Misra A, Garg A. Clinical review 153: Lipodystrophy in human immunodeficiency virus-infected patients, *J Clin Endocrinol Metab* 87(11) (2002) 4845-56.

[42] Oh J, Hegele RA. HIV-associated dyslipidaemia: pathogenesis and treatment. *Lancet Infectious Diseases* 7(12) (2007) 787-96.

[43] Lichtenstein KA. Redefining lipodystrophy syndrome: Risks and impact on clinical decision making, *Journal of Acquired Immune Deficiency Syndromes* 39(4) (2005) 395-400.

[44] Huyghe J, Magdalena S, Vandekerckhove L. Fight fire with fire: Gene therapy strategies to cure HIV, *Expert Rev Anti Infect Ther* 15(8) (2017) 747–58.

[45] Apostolopoulos V. Vaccine Delivery Methods into the Future, *Vaccines* 4(2) (2016) 9.

[46] Zakeri A, Kouhbanani MAJ, Beheshtkhoo N, Beigi V, Mousavi SM, Hashemi SAR, et al. Polyethylenimine-based nanocarriers in co-delivery of drug and gene: a developing horizon, *Nano Rev Exp* 9(1) (2018) 1488497.

[47] Jakutavičiūtė M, Ruzgys P, Tamošiūnas M, Maciulevičius M, Šatkauskas S. Physical Methods for Drug and Gene Delivery Through the Cell Plasma Membrane. In: *Advances in anatomy, embryology, and cell biology* (2017) 73–92.

[48] Rosazza C, Meglic SH, Zumbusch A, Rols M-P, Miklavcic D. Gene Electrotransfer: A Mechanistic Perspective, *Curr Gene Ther* 16(2) (2016) 98–129.

[49] Nilsson C, Hejdeman B, Godoy-Ramirez K, Tecleab T, Scarlatti G, Bråve A, et al. HIV-DNA Given with or without Intradermal Electroporation Is Safe and Highly Immunogenic in Healthy Swedish HIV-1 DNA/MVA Vaccinees: A Phase I Randomized Trial. *PLoS One* 10(6) (2015) e0131748.

[50] Miracle A. Adesina, Kehinde K. Kanmodi, Physiotherapeutic Management of People Living with HIV/AIDS. *World News of Natural Sciences* 20 (2018) 238-247

[51] Kojom Loick Pradel, Tuileu Tchamake Sorelle Kelly, Assokom Eliane Vanessa, Kouemo Motse Francine Dorgelesse, Kamgain Mawabo Lugarde, Improvement in CD4 cells counts in newly diagnosed HIV infected Cameroonian patients under HARRT is counterbalanced by the mild deleterious effects of antiretroviral therapy on liver function: a longitudinal study. *World News of Natural Sciences* 20 (2018) 215-225