



MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE**

Lecture № 11

HIV infection and AIDS

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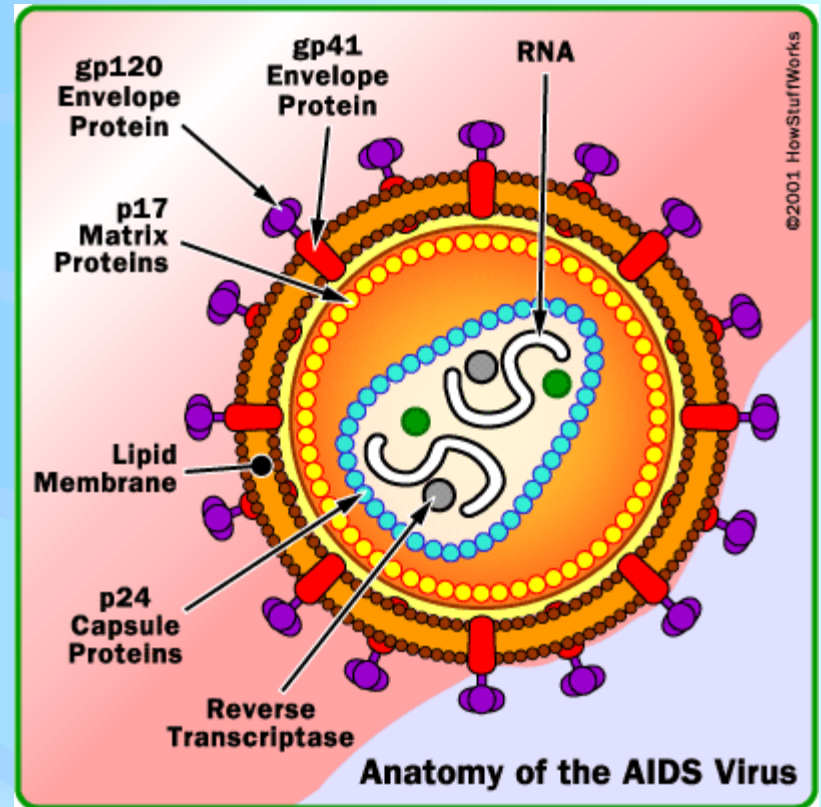
HIV infection and AIDS – definition

- AIDS is the terminal phase of an infectious process that is caused by human immunodeficiency virus (HIV).
- The disease is a complex of clinical manifestations such as opportunistic infections, neoplasms, disorders in all organs/systems but with prominent involvement of the lymph nodes and central nervous system (CNS).

HIV infection and AIDS – etiology

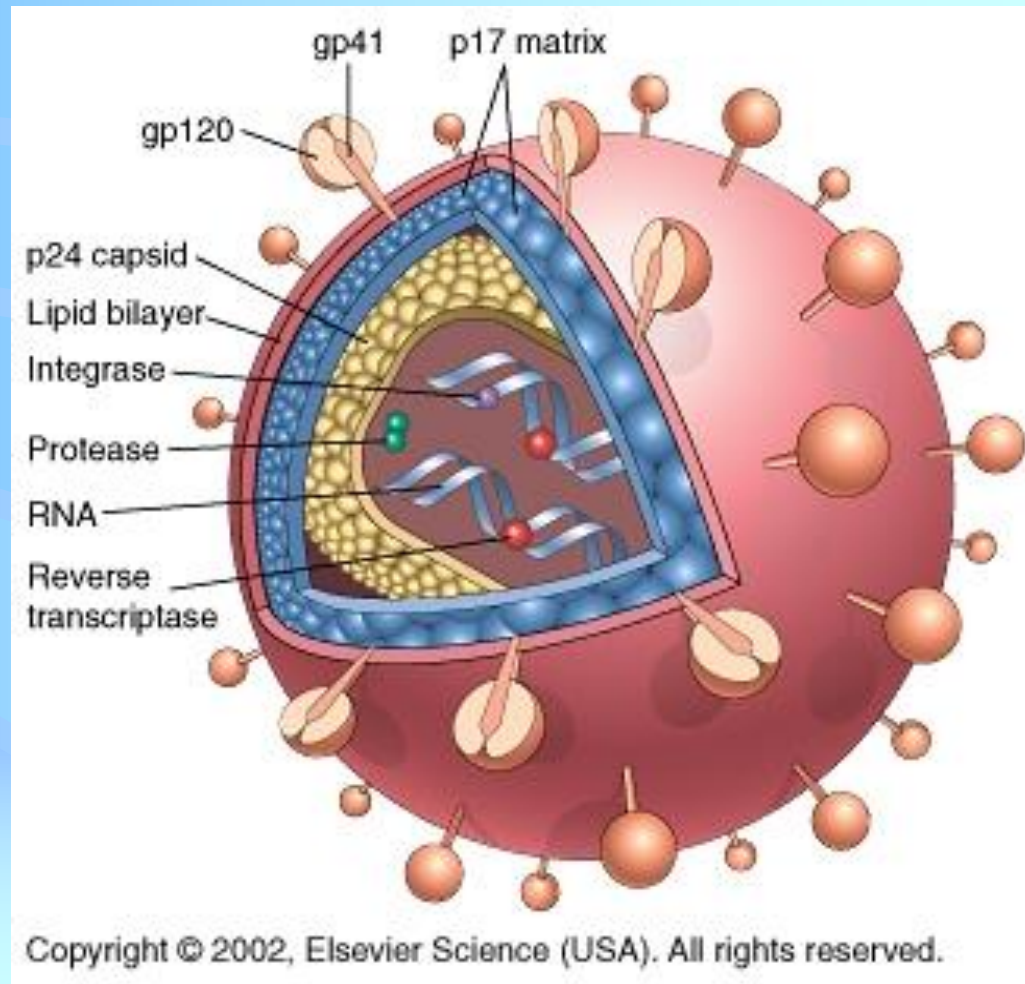
- Causative agent – Human immunodeficiency virus (HIV), belonging to Retroviridae family. It possesses a spherical form, measures 80 to 100 nm and:
 - ❖ outer lipid membrane with spikes of two specific envelope glycoproteins (gp120 и gp41);
 - ❖ matrix, containing viral proteins (p17 и p24);
 - ❖ capsid, containing double-chained RNA and specific viral enzymes – dependent-of-RNA-DNA polymerase, reverse transcriptase, integrase and viral proteases.
- Two types of the virus exist – HIV-1 and HIV-2 (members of Lentiviridae family).
- HIV is unstable on environmental and disinfectants. More stable on UV-rays and radiation.
- HIV is with fast speed of mutations and great genetic variability.

Structure of HIV



Structure of HIV

The outer shell of the virus is known as the *Viral envelope*. Embedded in the viral envelope is a complex protein known as *env* which consists of an outer protruding cap *glycoprotein* (gp) 120, and a stem gp14. Within the viral envelope is an HIV protein called *p17*(matrix), and within this is the viral core or capsid, which is made of another viral protein *p24*(core antigen).



HIV infection and AIDS – epidemiology

- Infects only humans.
- Source of infection – human – carrier of HIV or patient.
- The infected person sheds the virus from 10th to 100th day after contamination.
- HIV is in high concentration in semen and vaginal secret, and in the blood (more than 1 million viral particles in 1 mL). Patients with neurological manifestations contain HIV in the CSF in same high concentrations. HIV contains in the saliva, tears, bronchial and ear secretas, breast milk and sweat in lower concentrations but the epidemiologic significance of these fluids is not well understood.

HIV infection and AIDS – epidemiology

- Three basic mechanisms for transmission of HIV infection:
- Sexual – at homo- and heterosexual contacts – in North America and Western Europe higher is the significance of homosexual (ratio men : women – 10:1), in Africa, South-Eastern Asia and South America – heterosexual contacts (men : women 1:1). Anal sexual contact increases 8 times the risk for HIV transmission.; presence of syphilis in concrete patient increases 7 times the risk and genital herpes – 25 times.
- By transfusions of blood or blood products; manipulations (medical and non medical – in intravenous drug abusers with contaminated needles); by contact of mucosa with HIV-contaminated blood; other – tatoo, piercing, acupuncture, laser therapy, ophthalmological and dentistry manipulations, cosmetic – manicure, pedicure, epilatio, shaving etc.; professional – medical staff.
- Vertical – in child from mother with HIV/AIDS. The risk for baby is to 15-20%, in treated pregnant women – to 2%.

HIV infection and AIDS – epidemiology

- The epidemic process is worldwide distributed – the **pandemia** exists. Victims of HIV/AIDS: the first case was in USA during 1981. To this moment more than 60 millions people were infected. More than 25 millions were died. At the end of 2016 more than 36 millions people are alive with HIV/AIDS. Every day 8500 die due to AIDS. Every day 16000 infects by HIV.
- HIV infection is important as **nosocomial infection** – at conditions out of the rules of good medical practice, use of contaminated instruments or syringes etc. There are certain described nosocomial epidemics (in Kinshasa – Congo, Bengazi – Libia, Elysta – Kalmutia etc.) and above 1000 children in Romania with non sterile needles and instruments.
- United Nations Program on HIV/AIDS (UNAIDS) has a strategy “90-90-90” – to 2020 90% of all infected with HIV to know their HIV-status, 90% of all diagnosed with HIV to receive HAART and 90% of received HAART to reach undetectable viral load.

HIV infection and AIDS – epidemiology

- All humans are at risk for HIV infection but in certain the risk is higher – they are the **risk groups**:
 - ❖ Homosexual people, prostitutes, people with promiscuity etc.
 - ❖ Intravenous drug abusers using same syringes
 - ❖ People with frequent manipulations, performed with non sterile instruments, at non sterile conditions, at tattoo, at haemophiliacs, with frequent blood transfusions etc.
- In Bulgaria the epidemic process is slow, but “iceberg phenomenon” exists – more of infective are not clear.

HIV infection and AIDS – pathogenesis

- Portal of entry – the genital and anal mucosa, and the skin → penetration into the circulation → localization in cells with CD4 receptors – T helpers, monocytes, macrophages, nervous cells (neuroglia), dendrite cells, cardiac, hepatic cells etc.
- **Basic characteristic of the immunogenesis** – at the disease appear:
 - ❖ strong morphologic and functional disorders of the immune system – “immune chaos”;
 - ❖ HIV escapes from the immune response – chronic infection.
- **The basic moment in the pathogenesis** is dynamic colonization and damage of the immune system of infected person followed by immune deficite, oportunistic infections and neoplasms.

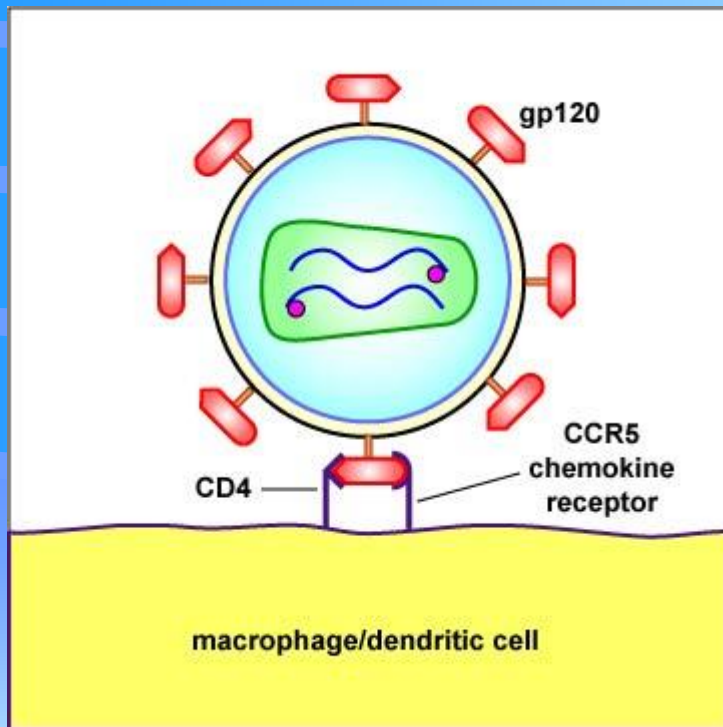
HIV infection and AIDS – pathogenesis

- The involvement of the immune system is determined by **primary lymphotropism of HIV** – it localizes in follicular dendritic cells in the germinative centers of the lymph nodes. These cells are the viral pool.
- In to 60% of infected person has **primary neurotropism of HIV**.
- In to 10% of infected HIV affects directly certain target organs' cells with CD4 receptors resulting in **primary organotropism** – HIV based hepatopathy, cardiopathy, nephropathy, enteropathy etc.

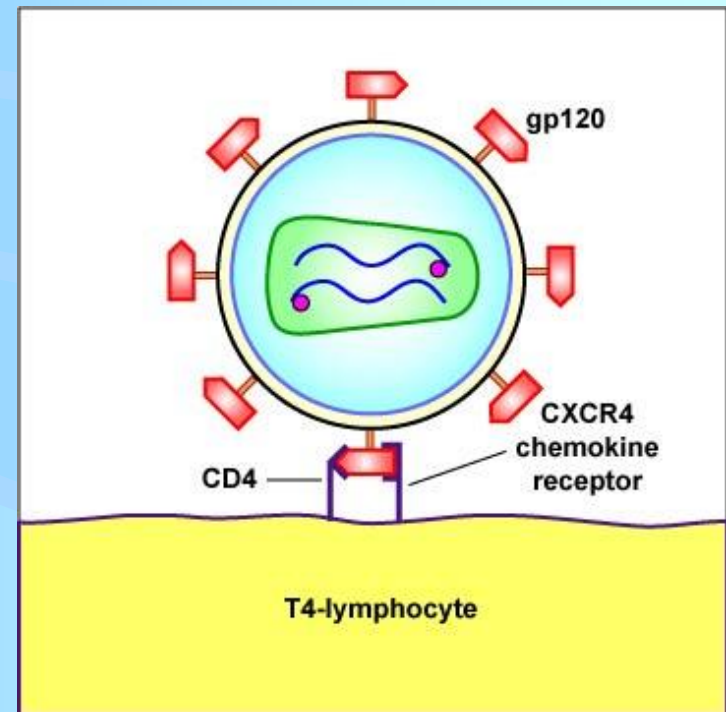
HIV infection and AIDS – pathogenesis

- **The basic pathogenic steps of the infectious process are:**
 - ❖ Viremia.
 - ❖ Specific selected viral adhesion to the target cells:
 - cells of the immune system – T lymphocytes with CD4 receptors (T helpers), monocytes, macrophages;
 - cells of the nervous system – astrocytes, gliocytes, dendrite cells etc.
 - cells of target organs – renocytes, hepatocytes, enterocytes, cardiocytes, Langerhance cells of the skin etc..
 - ❖ Penetration of HIV into the target CD4 cells.
 - ❖ Viral replication.
 - ❖ Cell immune deficit – it progresses during the HIV infection due to progressive decreasing of the CD4 cells – **in the late phase < 50/mm³.**
 - ❖ Autoimmune processes and mechanisms in the course of HIV infection.
 - ❖ Increased production of cytokines.

Phases of HIV-infection



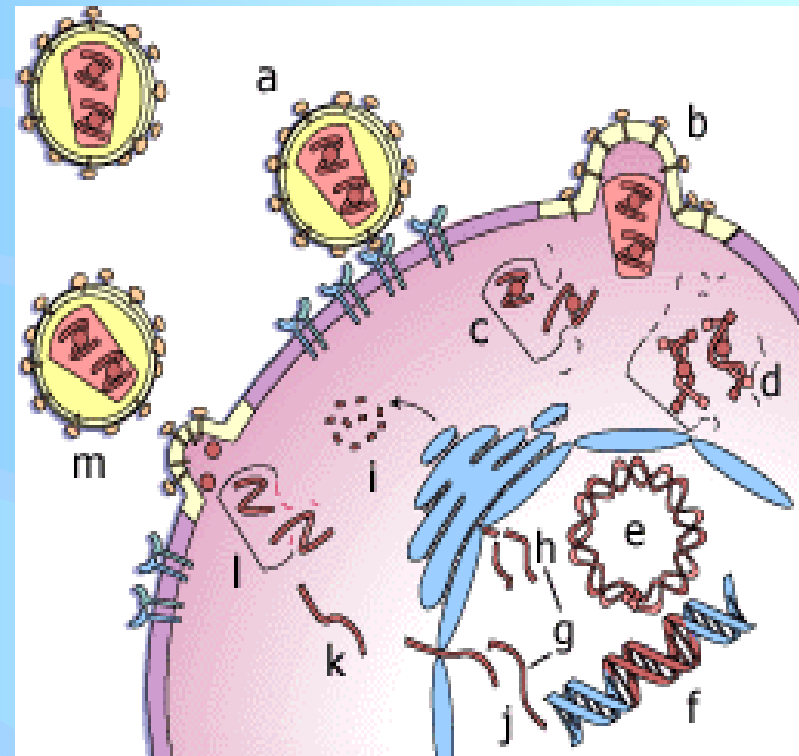
Early phase



Late phases

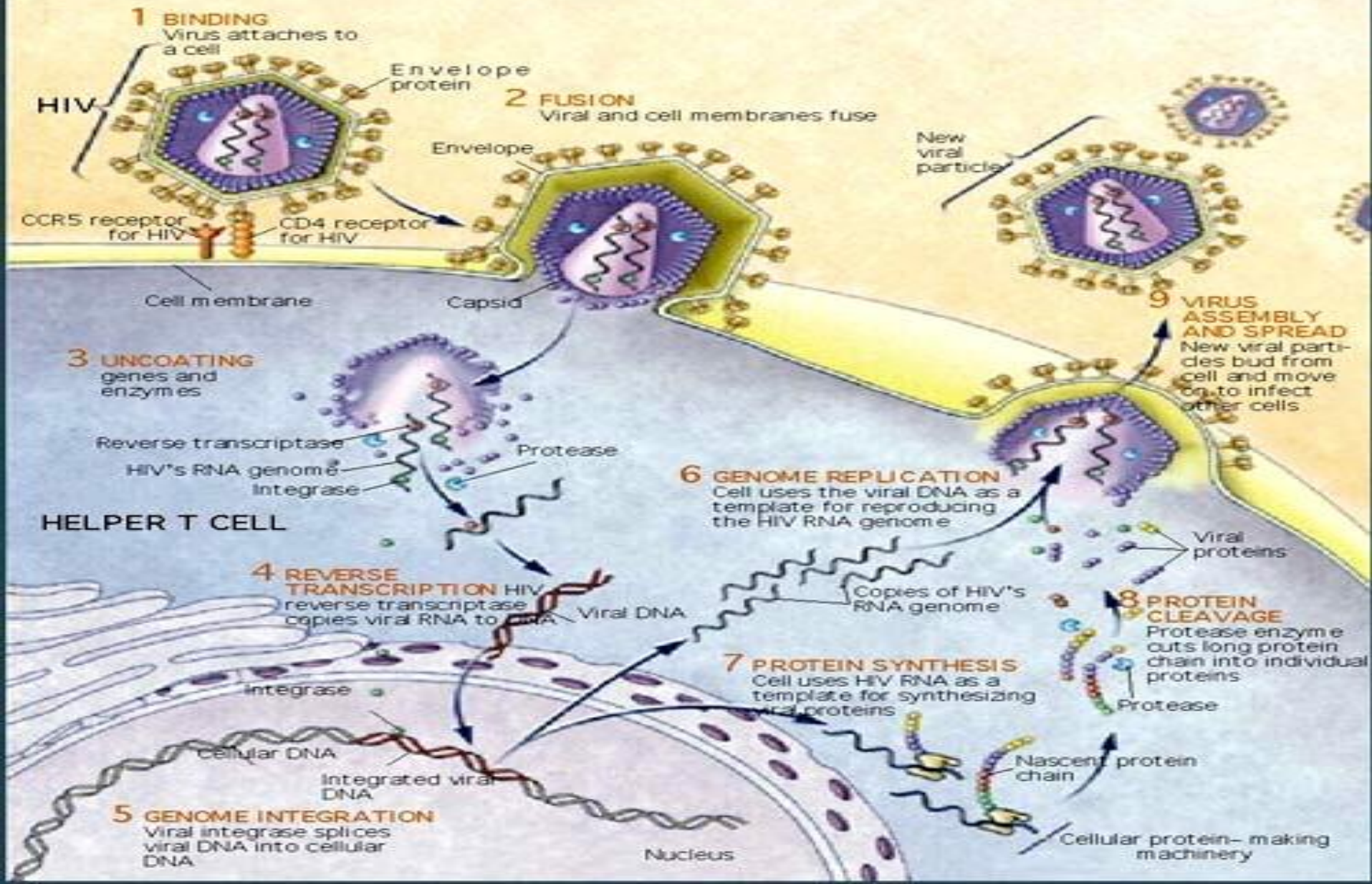
HIV life cycle

- (a) HIV (red) attaches to two cell-surface receptors (the CD4 antigen and a specific chemokine receptor).
- (b) The virus and cell membrane fuse, and the virion core enters the cell.
- (c) The viral RNA and core proteins are released from the virion core and are then actively transported to the nucleus.
- (d) The viral RNA genome is converted into double-stranded DNA through an enzyme unique to viruses, reverse transcriptase (red dot).
- (e) The double-stranded viral DNA moves into the cell nucleus.
- (f) Using a unique viral enzyme called integrase, the viral DNA is integrated into the cellular DNA.
- (g) Viral RNA is synthesized by the cellular enzyme RNA polymerase II using integrated viral DNA as a template. Two types of RNA transcripts shorter spliced RNA (h) and full-length genomic RNA (j) are produced.
- (h) Shorter spliced RNAs are transported to the cytoplasm and used for the production of several viral proteins that are then modified in the Golgi apparatus of the cell (i).
- (j) Full-length genomic RNAs are transported to the cytoplasm (k).
- (l) New virion is assembled and then buds off.
- (m) Mature virus is released.



HIV LIFE CYCLE, deciphered with the help of genomic analyses, is unusually complex in its details, but all viruses undergo the same basic steps to infect cells and repro-

duce. They enter a cell (bind to it and inject their genes into the interior), copy their genes and proteins (by co-opting the cell's machinery and raw materials), and pack



Attachment of HIV to T lymphocyte



HIV infection and AIDS – clinical manifestations

CD4/mm ³	Clinical category		
	A	B	C
	Asymptomatic or acute HIV infection, persistent generalized lymphadenopathy	Symptomatic state (non A, non B), chronic infection	State suggestive for AIDS
1. > 500	A1	B1	C1
2. 200 – 499	A2	B2	C2
3. < 200	A3	B3	C3

Since 1993 WHO postulated a classification of HIV/AIDS that includes three groups based on clinical manifestations and T CD4 count. This scheme is working and has been used in the documents of WHO

HIV infection and AIDS – clinical manifestations

1. **Acute HIV infection** – leads to transient symptomatic illness in 40 to 90% of individuals and continues to 2-3 months. **Acute retroviral syndrome includes:**
 - Fever (96%)
 - Lymphadenopathy (74%)
 - Pharyngitis (70%)
 - Rash (70%) – erythematous, maculopapulous with lesions on the face and the trunk, uncommonly on the limbs; ulcerations on the mouth, oral cavity, esophagus, genitals.
 - Myalgia and arthralgia (54%)
 - Diarrhea (32%)
 - Headache (32%)
 - Nausea and vomiting (27%)
 - Hepatosplenomegaly (14%)
 - Devastating syndrome (loss of body weight) (13%)
 - Oral candidosis (13%)
 - Neurologic symptoms (12%) – meningoencephalitis or aseptic meningitis, peripheral neuropathy or radiculopathy, facial palsy; Guillain-Barre syndrome.

HIV infection and AIDS – clinical manifestations

2. **Chronic HIV infection** – the infected people are clinically “health” – without complaints and clinical manifestations. The immune investigations reveal gradually decreasing of CD4 cells bellow their reference ($< 500/\text{mm}^3$). This asymptomatic phase is from some months to 1-2 or more years, after then appear characteristic symptoms:
- Unclear persistent fatigue
 - Shivering and continuous low-grade fever
 - Night sweats
 - Diarrhea – continuous, without pathologic admixtures
 - Persistent generalized lymphadenopathy
 - Anorexia
 - Loss of body weight more than 10%
 - Seborrheal dermatitis
 - Hairy leucoplakia
 - Oral and esophageal candidosis
 - Aphtous stomatitis
 - Herpes zoster
 - Vaginal candidosis.

HIV infection and AIDS – clinical manifestations

- **Opportunistic infections** appear in this phase dependent of CD4 cells. They are not with maximal severity but are persistent for long time:
 - ❖ Pneumocystic pneumonia
 - ❖ Mycosis (candidosis, cryptococcosis, hystoplasmosis, coccidiomycosis)
 - ❖ Infections caused by protozoa/parasites (toxoplasmosis, cryptosporydiosis, laischmaniosis, microsporidiosis)
 - ❖ Infections caused by Mycobacteria (tuberculosis, mycobacteriosis)
 - ❖ Viral infections (cytomegalovirus, herpes symplex, herpes zoster, Epstein-Barr, Papilloma virus)
 - ❖ Bacterial infections (reccurent pneumococcal pneumonia, bartonellosis).

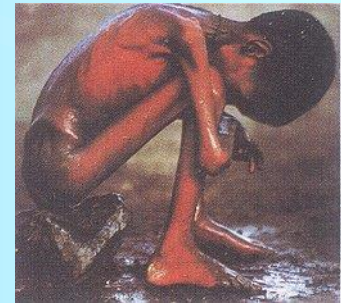
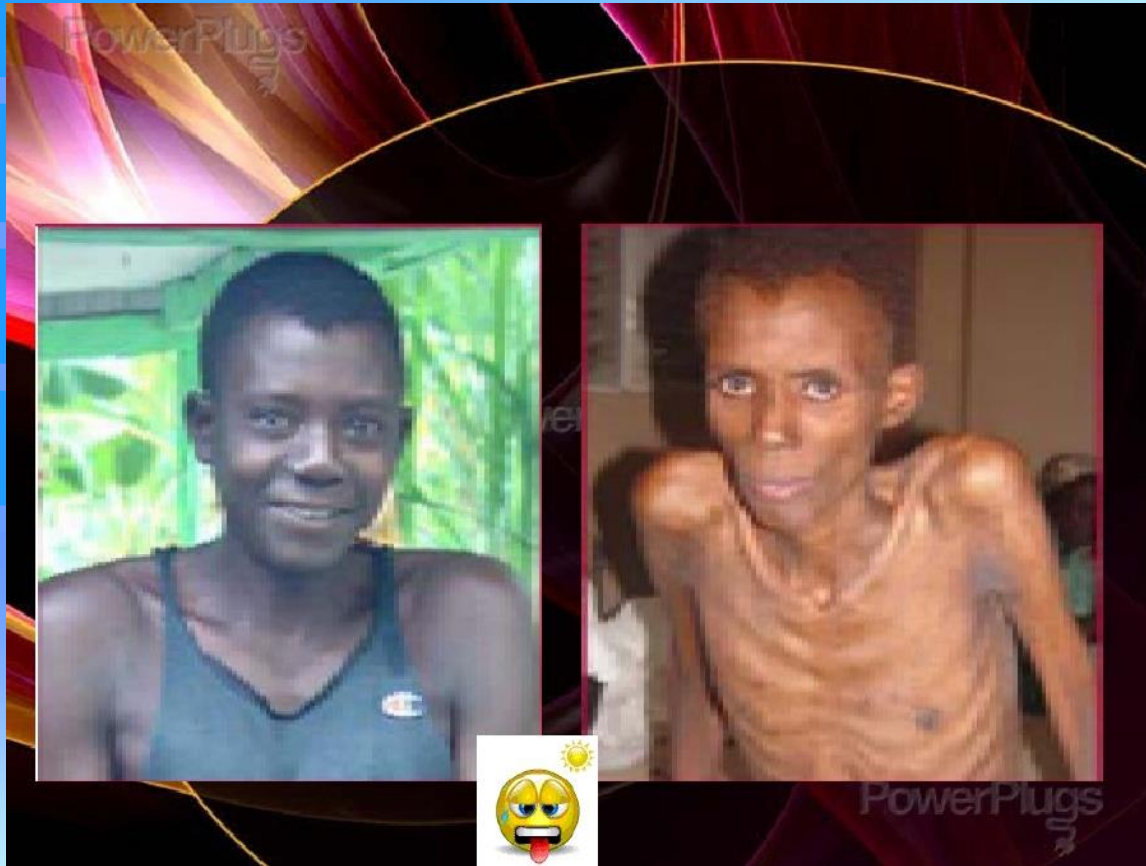
HIV infection and AIDS – clinical manifestations

3. Late phase of HIV infection – AIDS. It has been defined as a complex of mentioned above symptoms, opportunistic infections, secondary bacterial infections, neoplasms, in any patients – and neurologic manifestations:

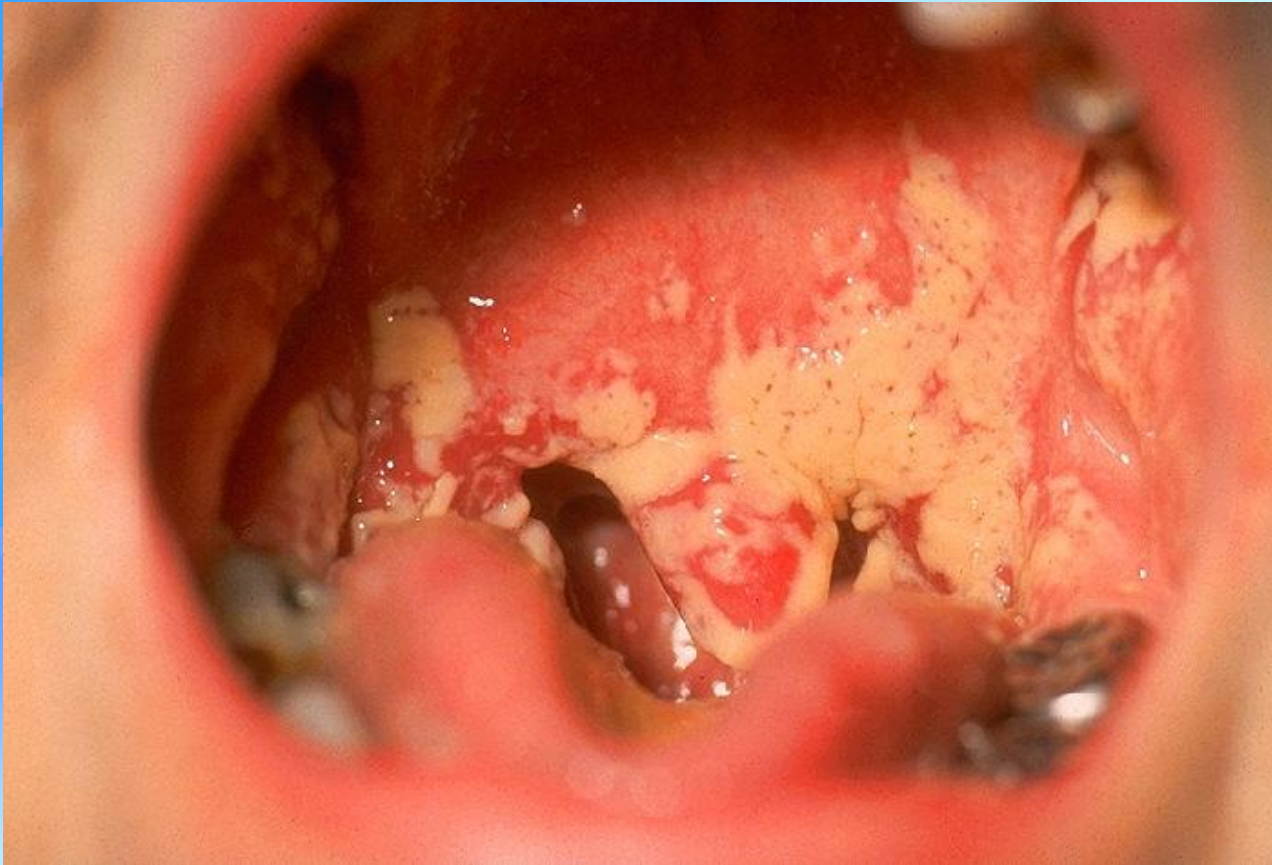
- ❖ Persistent low-grade fever (afternoon, without shivering)
- ❖ Profuse night sweats without fever
- ❖ Severe adynamia to prostration
- ❖ Severe anorexia and loss of body weight >10% within 1-2 months; in terminal state – “slims”.
- ❖ Myalgia and arthralgia
- ❖ Generalized lymphadenopathy
- ❖ Hepatosplenomegaly
- ❖ Persistent diarrhea
- ❖ Bacterial parotitis
- ❖ Mixture of different opportunistic or bacterial infections, neurologic manifestations, neoplasms – lymphoma, carcinoma, Kaposhi's sarcoma

The state is very severe and the patient dies to weeks, months or one year. **Important question: when HIV infection will enter in the late stage of AIDS – from 7 months to more than 20 years.**

AIDS – slims



AIDS – oral candidosis



*AIDS –
hairy leucoplakia*



AIDS – Kaposhi's sarcoma



AIDS – lypodystrophy



HIV infection and AIDS – laboratory findings

- In acute phase – normocytosis, rarely mild leucocytosis or leucopenia] left shift, neutropenia, hypo- or aneosinophilia, monocytosis, normal or slightly elevated number of lymphocytes. In 40% of cases – atypical lympho- and monocytes.
- In the following stages – decreasing of the number of leucocytes and lymphocytes, especially T CD4, less in T CD8, resulting in decreased ratio $T\ CD4 / T\ CD8 < 1,0$; rarely $< 0,5$. B lymphocytes – normal or slightly elevated. At generalized bacterial infections leucocytosis with neutrophilia and left shift. In last stage – anemia, thrombocytopenia. Erythrocytes sedimentation rate – increased. Hypoproteinemia, hypoalbuminemia with hypergammaglobulinemia.

HIV infection and AIDS – diagnosis

- From clinical and epidemiologic data.
- Laboratory – progressive anemia, leucopenia, markedly increased erythrocytes sedimentation rate, thrombocytopenia, hypoproteinemia, **decreased number of T CD4 lymphocytes, ratio T CD4/ T CD8 < 1,0.**
- Serologic:
 - ❖ ELISA – positive after 14-60 days after infection. False (-) results are possible!!!
 - ❖ The confirmation by Western blot is obligatory!!!
 - ❖ In the onset before appearing of antibodies but when has viremia, the virus has been found and its quantity estimates by viral load – by PCR or by its antigens (e.g. p24).

HIV infection and AIDS – prognosis

- **Serious.**
- **At patients with regular HAART the lethal outcome is two years earlier than at health people!!!**
- Without regular HAART the death is to 1-2 years since the onset of AIDS, in recent years – to 5-6 years.

HIV infection and AIDS – management and treatment

- The treatment is complex and depends of the clinical stage and comorbidity with opportunistic infections and neoplasms. It includes:
 - ❖ Free regimen. Admission in hospital only in the onset and severe cases.
 - ❖ **Diet** – caloric, with high protein intake. At diarrhea, hepatic and renal disorders – concrete limitations.
 - ❖ **Medicamentous tretment – 2 components:**
 - Treatment of major disease – HAART (high active anti retroviral therapy)
 - Treatment of the opportunistic infections and neoplasms.

HIV infection and AIDS – management and treatment

- The principles of antiretroviral therapy are based on the pathogenic mechanisms.
- **Basic antiretroviral groups:**
 - ❖ Nucleoside inhibitors of reverse transcriptase (NRTIs) – zidovudine, didanosine, lamivudine, stavudine, abacavir, tenofovir, emtricitabine and combined – combivir, trizivir, kivexa etc.
 - ❖ Protease inhibitors (PIs) – saquinavir, ritonavir, indinavir, nelfinavir, lopinavir/ritonavir, atazanavir, fosamprenavir, tipranavir, darunavir
 - ❖ Non nucleoside inhibitors of reverse transcriptase (NNRTIs) – nevirapine, delavirdine, efavirenz, etravirine, rilpivirine, doravirine etc.
 - ❖ Inhibitors of the fusion (FIs) – enfurvitide (fuseon)
 - ❖ Entrance inhibitors (EIs) – maraviroc, cenicriviroc, vicriviroc
 - ❖ Integrase inhibitors – raltegravir, dolutegravir, elvitegravir, cabotegravir

HIV infection and AIDS – management and treatment

Usually different triple combination administers (see below) for prevention of mutations and resistant viral strains:

- ❖ Two NRTIs + 1 IIs
- ❖ Two NRTIs + 1 PIs
- ❖ Two NRTIs + 1 NNRTIs

FIs and EIs are saving therapy – add to non effective (to the concrete moment) therapy

The treatment of opportunistic infections and neoplasms is same as at patients without HIV/AIDS, the supportive and symptomatic treatment also.

HIV infection and AIDS – prophylaxis

Two types of prevention – social and medical.

- **Social** – education of students, adolescents, risk groups, medical staff etc.
- **Medical – defense of the medical staff. The basic principle is – each patient is potential threatening. The basic rule is – each keeps him/her self.** Important rules:
 - Work with vacutainers.
 - Use of hard containers for medical waste.
 - Use of glass, gloves, mask, isolation wear.
 - ❖ **Pre-exposure prophylaxis (for groups with risk)** – truvada (combination of 2 NRTIs)
 - ❖ **Post-exposure prophylaxis** – after pricking, splashing with blood etc.
 - **Press on the wound to result in bleeding more than 2 minutes**
 - **Wash with water**
 - **Deep disinfection with iodine with maximally opening of the wound**
 - **Initiation of therapy is 4 hours after exposure and no later than 72 hours. With 3 (or more) antiretroviral drugs.**

HIV infection and AIDS – prophylaxis

❖ Defense of the patients:

- Transfusions of the blood products investigated for HIV.
- Use only materials for once usage.
- Use of surgical and dentistry instruments after central autoclaving.
- Cleaning and disinfection of the surfaces, floors, handles of the doors etc. , working at these activities with gloves.

❖ Intensive work for manufacturing of a vaccine.

**THANK YOU
FOR THE ATTENTION !**