

# Immunodeficiencies

*Diseases caused by insufficient  
immune response*

# *Immunodeficiencies are disorders of one or more components of the immune system*

## **Primary (congenital)**

**group of congenital  
diseases**

## **Secondary (acquired)**

**they are caused by the  
action of  
environmental factors**

**HIV**

**chemotherapy  
radiation  
malnutrition**

# Physiological immunodeficiencies

- **physiological immunodeficiency in newborns**
- **Physiological selective IgA immunodeficiency in children**
- **physiological immunodeficiency in elder people**

# **Congenital (primary) immunodeficiencies**

**Congenital immunodeficiencies are the consequences of genetic disorders that are the cause of interruptions in the maturation or functioning of various components of the immune system.**

**One in every 500 people suffers from some immunodeficiency**

# Characteristics of immunodeficiencies and their manifestations

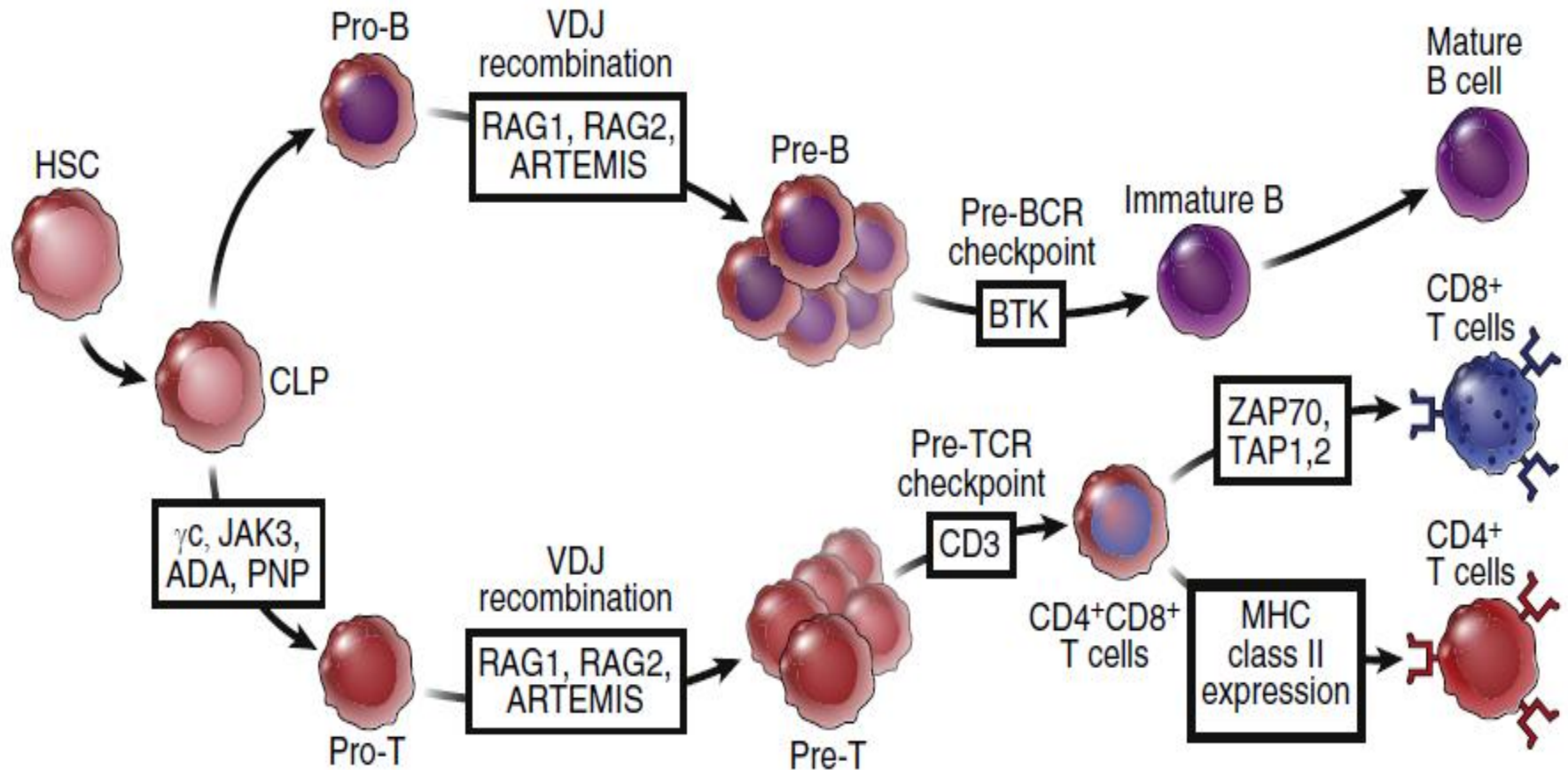
Type of immunodeficiency	Histopathology and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Often absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections, enteric bacterial and viral infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens in vitro	Viral and other intracellular microbial infections (e.g., <i>Pneumocystis jiroveci</i> , other fungi, nontuberculous mycobacteria) Some cancers (e.g., EBV-associated lymphomas, skin cancers)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable; pyogenic bacterial and viral infections

Severe forms of immunodeficiency open the door to infections with microorganisms that are not usually considered virulent, including many members of the body's normal microflora or environmental microorganisms.

# Defects in innate immunity

Disease	Functional deficiencies	Mechanisms of defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutations in genes of phagocyte oxidase complex; phox-91 (cytochrome <i>b</i> <sub>558</sub> $\alpha$ subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion to endothelial cells and migration into tissues linked to decreased or absent expression of $\beta_2$ integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the $\beta$ chain (CD18) of $\beta_2$ integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling on endothelium and migration into tissues because of decreased or absent expression of leukocyte ligands for endothelial E- and P-selectins; recurrent bacterial and fungal infections	Mutations in gene encoding GDP-fucose transporter-1, required for transport of fucose into the Golgi and its incorporation into sialyl-Lewis X
Chediak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, NK cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutations in gene encoding LYST, a protein involved in fusion of vesicles (including lysosomes)
Toll-like receptor signaling defects	Recurrent infections caused by defects in TLR signaling	Mutations in TLR3 and MyD88 compromise NF- $\kappa$ B activation and type I interferon production in response to microbes

# Disorders in the maturation of lymphocytes





## Severe combined immunodeficiency (SCID)

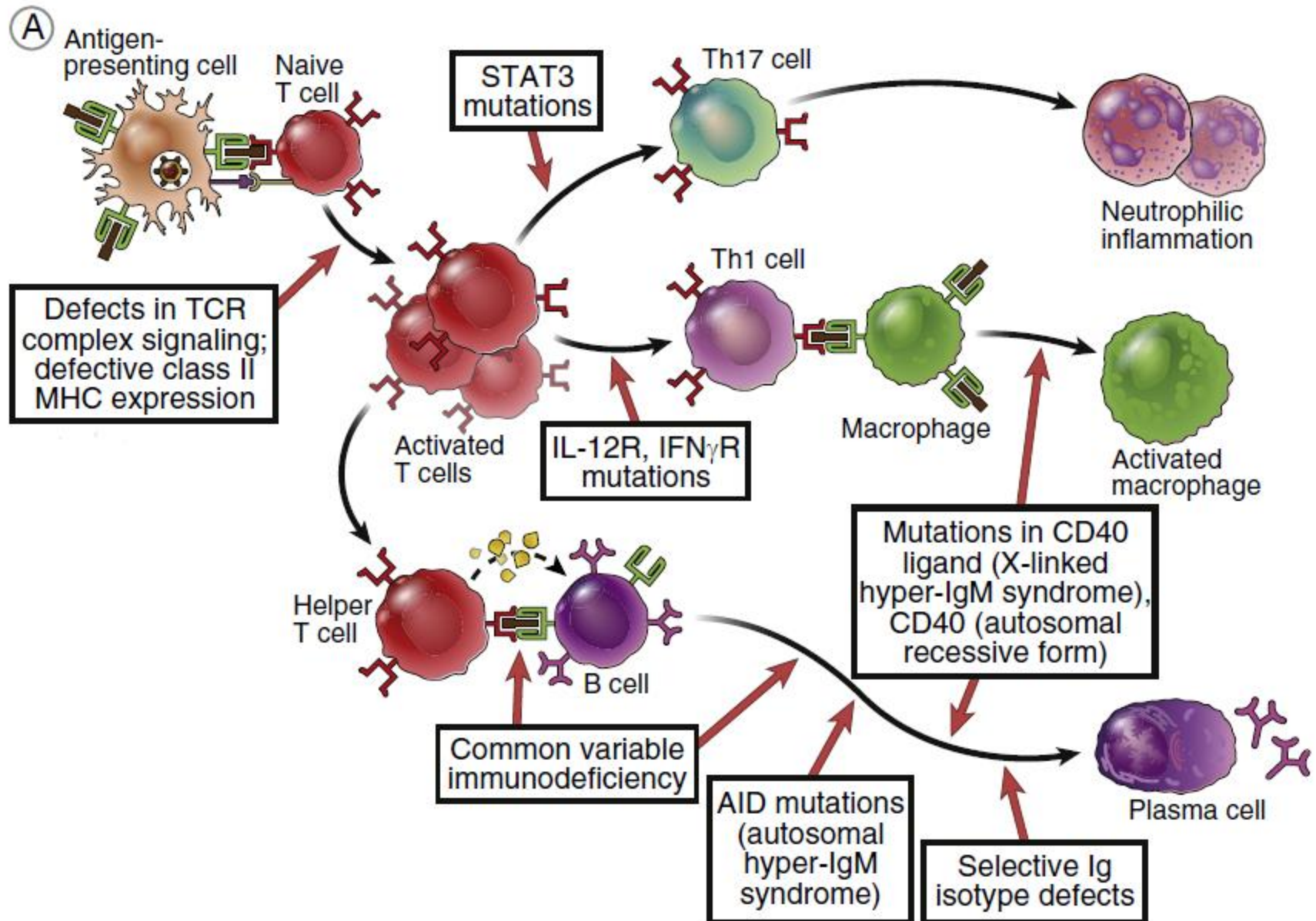
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common $\gamma$ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; may be mutations in <i>RAG</i> genes and other genes involved in VDJ recombination or IL-7R signaling
DiGeorge syndrome	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia

## B cell immunodeficiencies

Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in Bruton tyrosine kinase (BTK)
Ig heavy chain deficiencies	IgG1, IgG2, or IgG4 absent; sometimes associated with absent IgA or IgE	Chromosomal deletion involving Ig heavy-chain locus at 14q32



# Disorders of lymphocyte activation and function



# Disorders of lymphocyte activation and function

B

Disease	Functional deficiencies	Mechanisms of defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective Ig deficiency	Reduced or no production of selective Ig isotypes; susceptibility to infections or no clinical problem	Mutations in Ig genes or unknown mutations
Common variable immunodeficiency	Reduced immunoglobulins; susceptibility to bacterial infections	Mutations in receptors for B cell growth factors, costimulators
Defective class II MHC expression: The bare lymphocyte syndrome	Lack of class II MHC expression and impaired CD4 <sup>+</sup> T cell activation; defective cell–mediated immunity and T cell–dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of CD4 <sup>+</sup> and CD8 <sup>+</sup> subsets; decreased cell–mediated immunity	Mutations or deletions in genes encoding CD3 proteins, ZAP-70
Defects in Th1 differentiation	Decreased T cell–mediated macrophage activation; susceptibility to infection by atypical mycobacteria and other intracellular pathogens	Mutations in genes encoding IL-12, the receptors for IL-12 or interferon- $\gamma$ , STAT1
Defects in Th17 differentiation	Decreased T cell–mediated inflammatory responses; mucocutaneous candidiasis, bacterial skin abscesses	Mutations in genes encoding STAT3, IL-17, IL-17R
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation and CTL activation; defective NK cell and CTL function and antibody responses	Mutations in gene encoding SAP (an adaptor protein involved in signaling in lymphocytes)

**Immunodeficiency can be one of the components of some systemic diseases that affect a number of organ systems**

***Wiskott-Aldrich syndrome:***

- eczema
- reduced number of thrombocytes
- immunodeficiency

***Ataxia-telangiectasia :***

- gait disorders (ataxia)
- malformations of blood vessels (telangiectasia)
- immunodeficiency

# Therapy of congenital immunodeficiencies

- Transplantation of hematopoietic stem cells (SCID)
- IV injection of pooled immunoglobulin -IVIG  
(selective disorders of B lymphocytes)
- Gene therapy

# HUMAN RETROVIRUSES

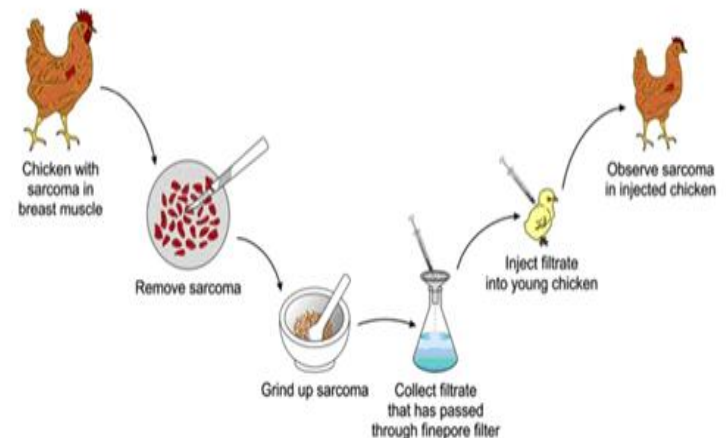
<b>HTLV-1</b>	<b>HTLV-2</b>
<b>HIV-1</b>	<b>HIV-2</b>

# History of retrovirology

- The complex relationship between viruses and tumors - the role of viruses in the development of tumors
- The first retrovirus discovered in 1911 - RSV (Rous sarcoma virus) - the cause of tumors in chickens that can be transmitted via tumor extract
- Peyton Rous – Nobel Prize in 1966



Peyton Rous: discovery of the chicken sarcoma virus



The filtration step proved that the tumorigenesis was not due to a primitive transplantation-like effect.

# History of retrovirology

## Reverse transcriptase

*Contrary to the basic principles of molecular biology*

**Genetic information  
written in the RNA molecule**



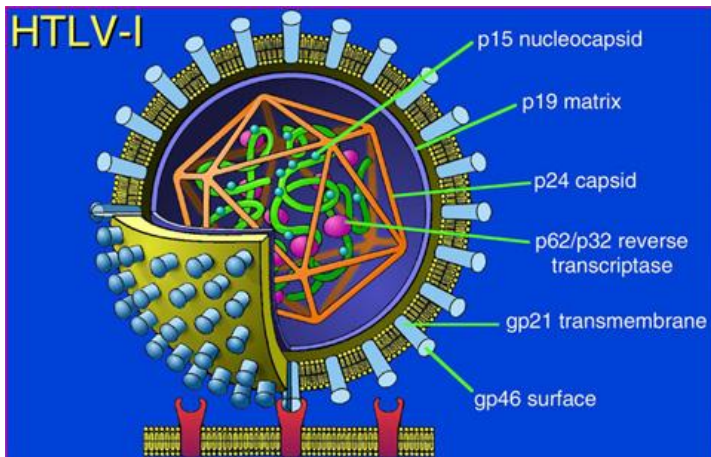
**Synthesis of complementary DNA that eventually  
integrates into the genome of the host cell  
(provirus), a transitional form in the replicative  
cycle of the virus**



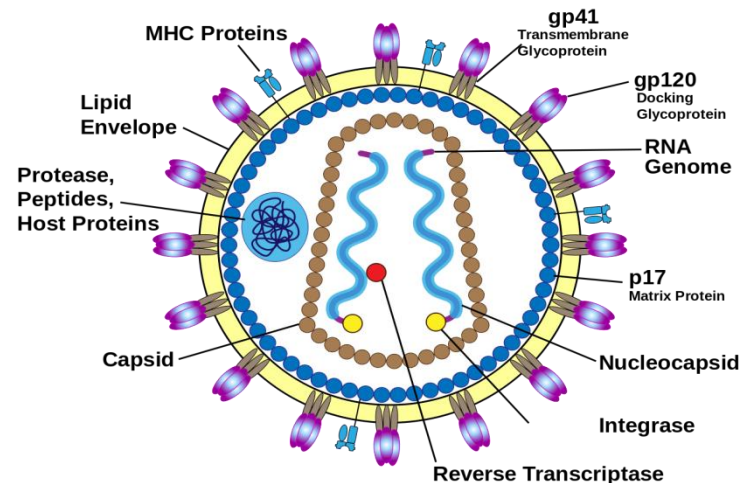
# History of retrovirology

- Early 1960s - feline leukemia virus
- 1986 - feline immunodeficiency virus - similar to HIV
- Since 1980 - two groups of retroviruses capable of causing disease in humans have been isolated and described

## HTLV-1 and HTLV-2

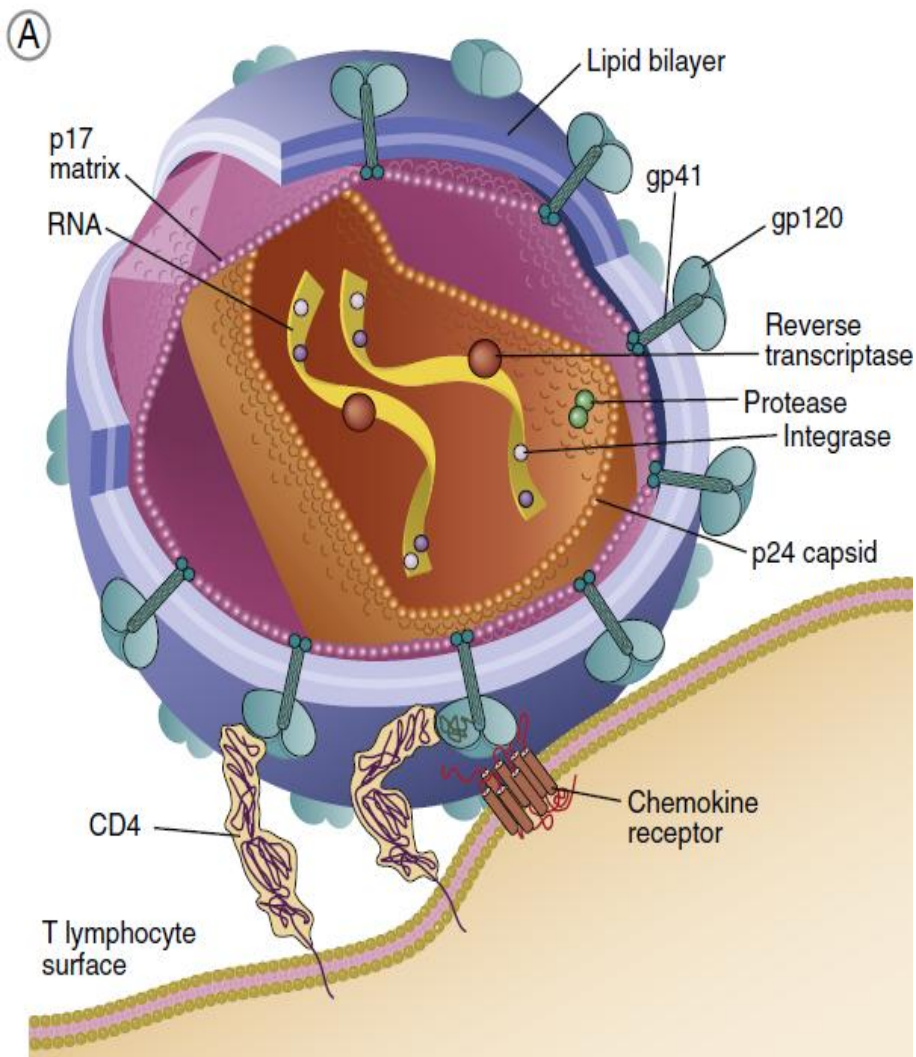


## HIV-1 and HIV-2



# HIV

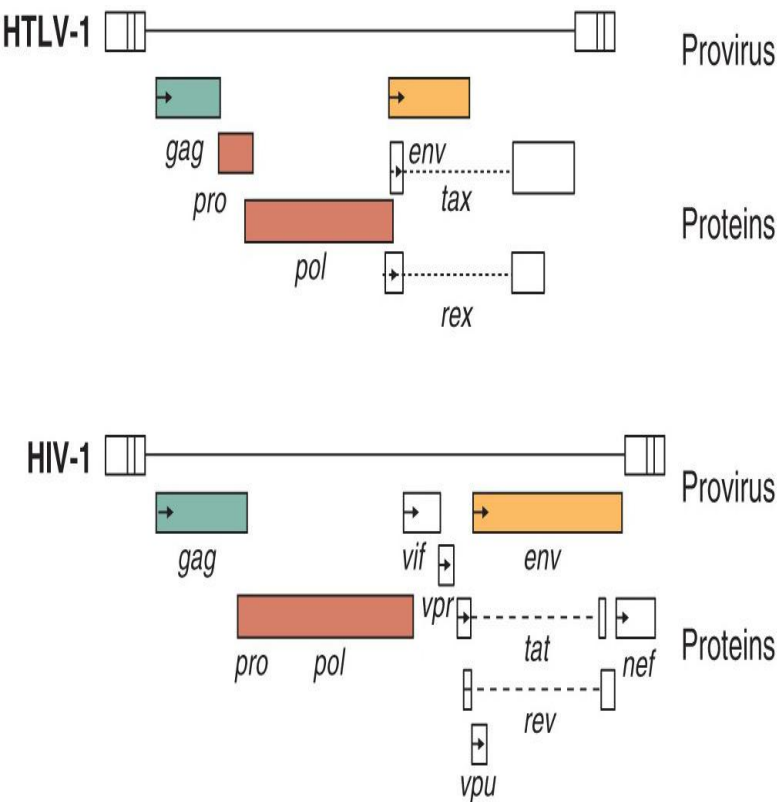
## Structure of the virion



- A small, spherical virus surrounded by a lipid envelope
- Glycoproteins of the viral envelope : **gp120** and **gp41**
- An icosahedral capsid : **p24** and matrix protein **p17**
- The genome contains two identical RNA molecules
- The enzymes **reverse transcriptase**, **integrase** and **protease** are attached to the genome

# HIV

## Structure of genom



Four viral genes are essential for retrovirus replication:

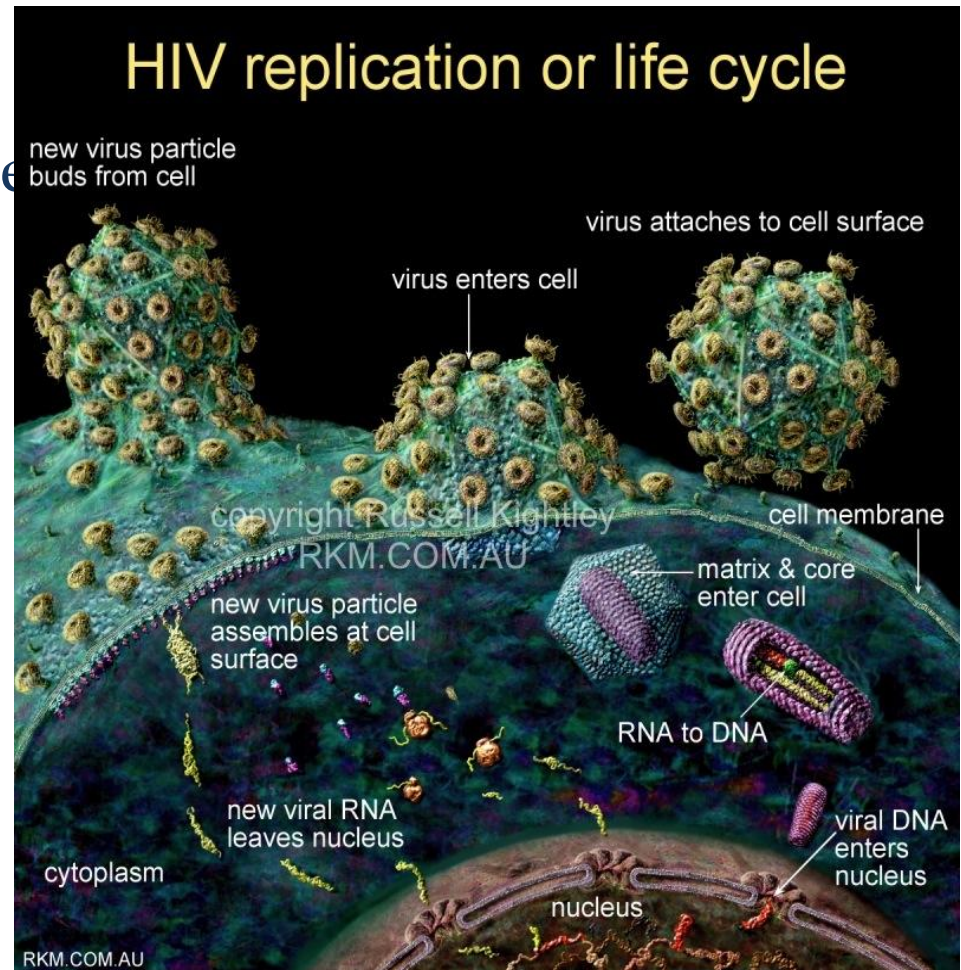
- **Gag gene** encodes several core (Gag) proteins of the viral envelope
- **Pol gene** encodes **reverse transcriptase** or RNA-dependent DNA polymerase (Pol), an enzyme responsible for genome replication, as well as **integrase**, an enzyme required for the integration of viral DNA into the host cell genome
- **Env gene** encodes two viral envelope glycoproteins **gp120** and **gp41**
- **Pro gene** encodes a **protease** necessary to cleave Gag and Pol proteins and create their active form

HIV contains at least six other genes that encode proteins that are important in the regulation of complex viral replication

# HIV

## -entry into the host organism-

- Via infected cells, such as macrophages, lymphocytes or spermatozoids or as a free viral particle
- Through microabrasions on the surface of the mucous membrane, penetration through intact skin after a needle puncture or through undamaged mucosal surfaces



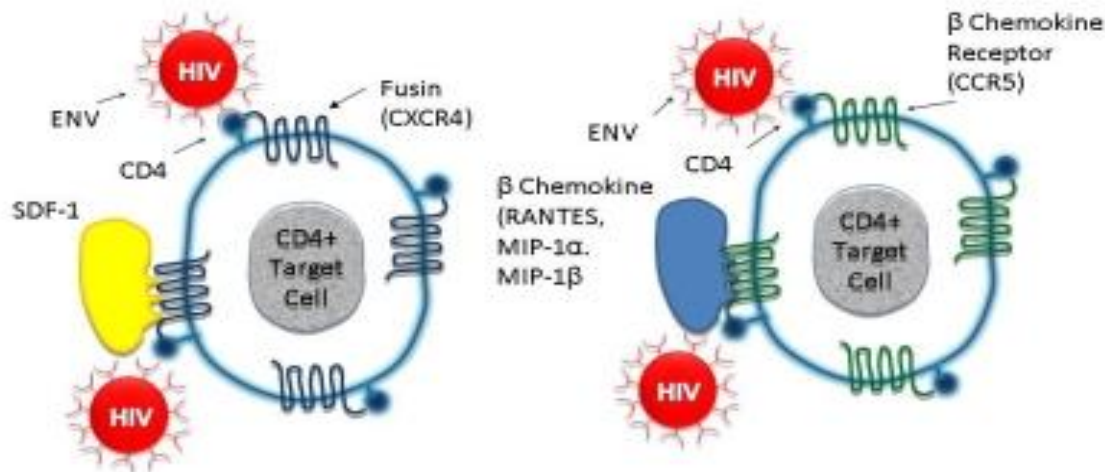


# HIV

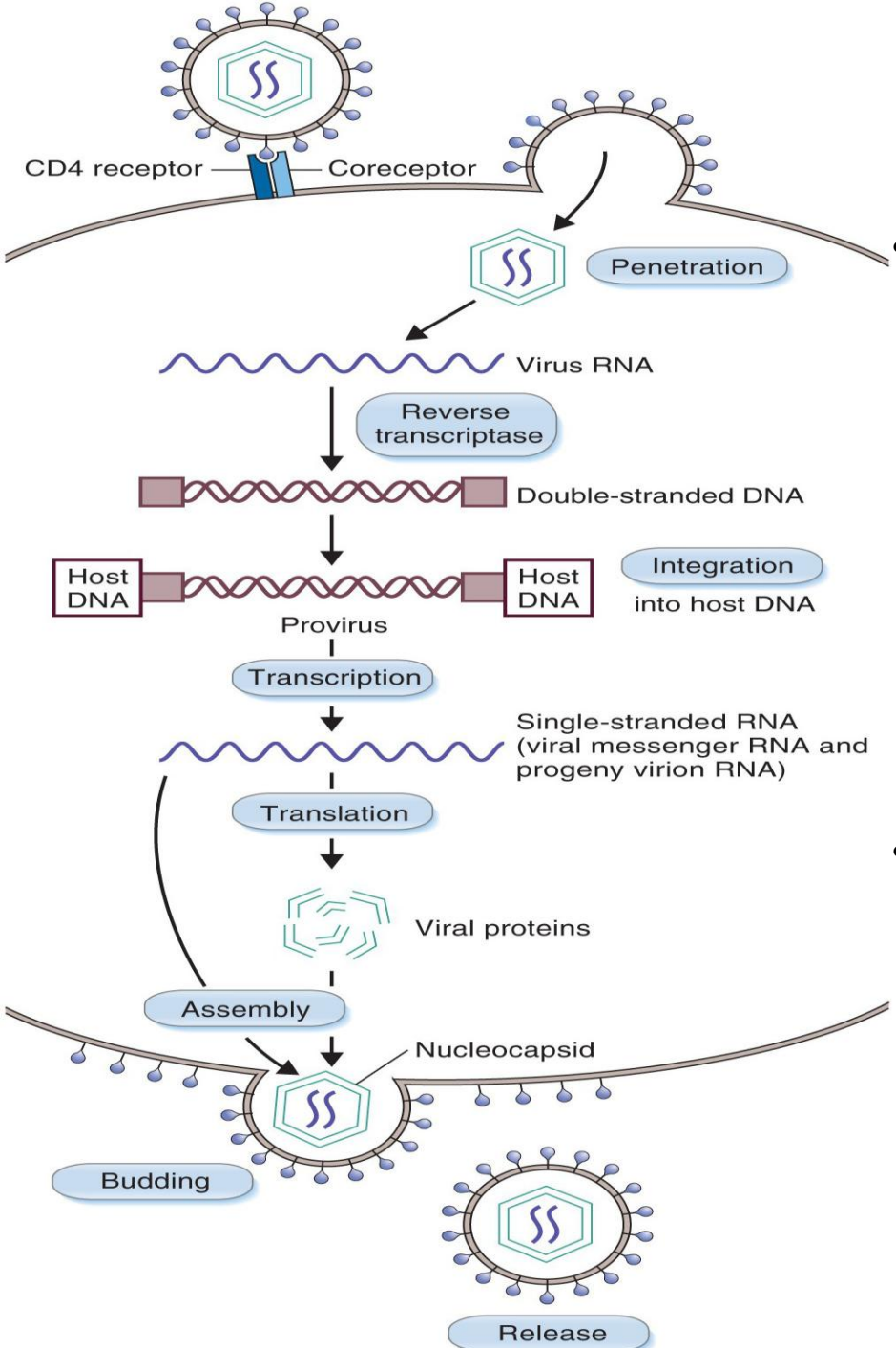
## -spread in the host organism-

- Although HIV can infect many types of cells, two main groups of cells in the body serve as targets for infection: **helper T lymphocytes** and macrophages, which express the **CD4** molecule and the corresponding co-receptors for HIV (chemokine receptors, CXCR4 and CCR5)
- These cells further transport the virus to tissues where they are normally present in large numbers (lymph nodes, spleen, blood and body fluids).

### HIV receptor + coreceptors

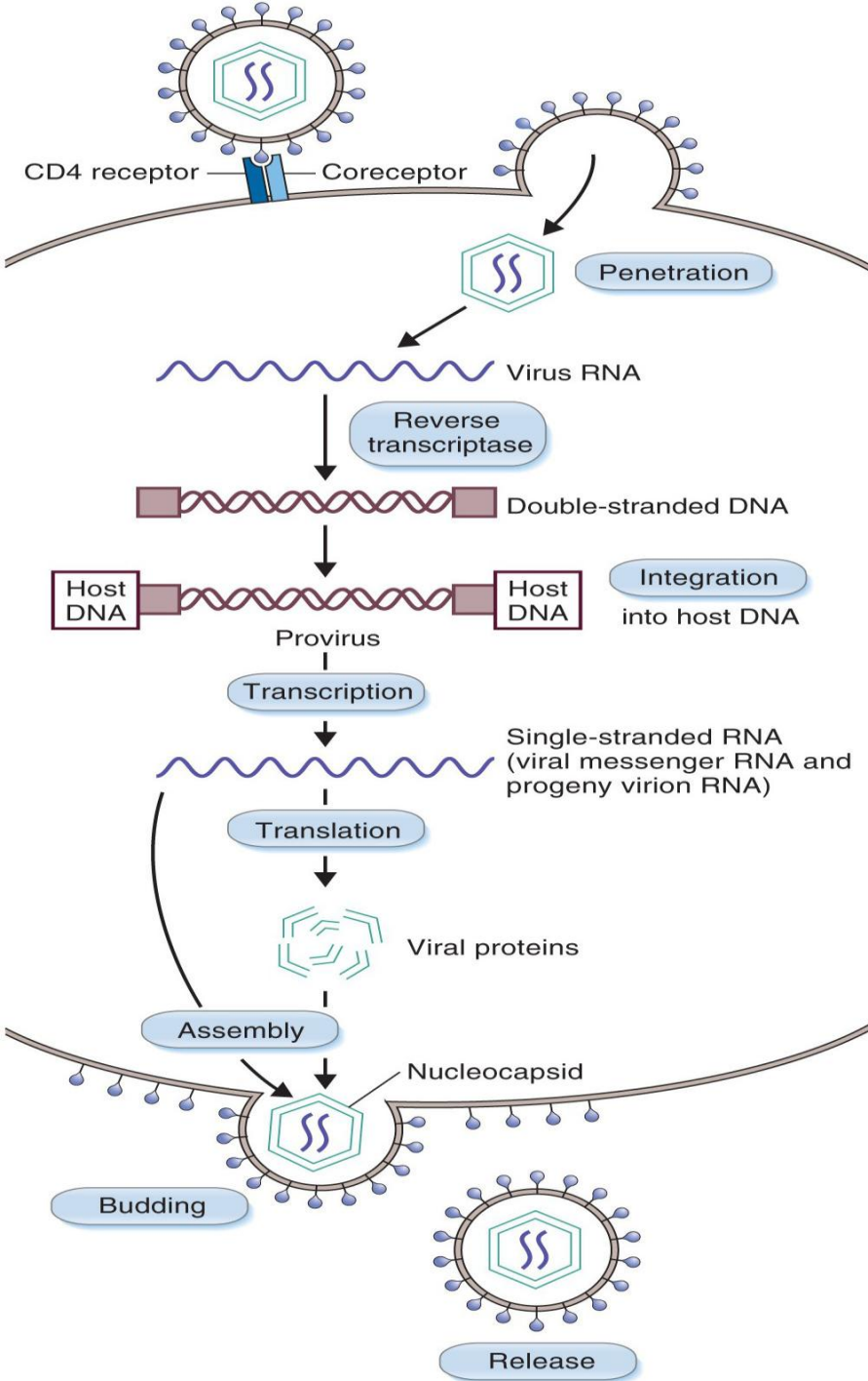


# HIV -replication-



- Binding (adsorption): HIV binds to the **CD4** molecule via the envelope glycoprotein **gp120**. After binding to the CD4 molecule, gp120 binds to one of the two co-receptor molecules (**CCR5** or **CXCR4**), which allows the virus to bind tightly to the cell membrane and the conformational changes of the gp41 protein bringing its hydrophobic domain into contact with the cell membrane
- **The fusion** of the viral envelope with the cell membrane is facilitated by the hydrophobic interaction between the **gp41** protein and the target cell membrane. The viral core, which contains genomic RNA and reverse transcriptase molecules, is released into the cytoplasm

# HIV -replication-



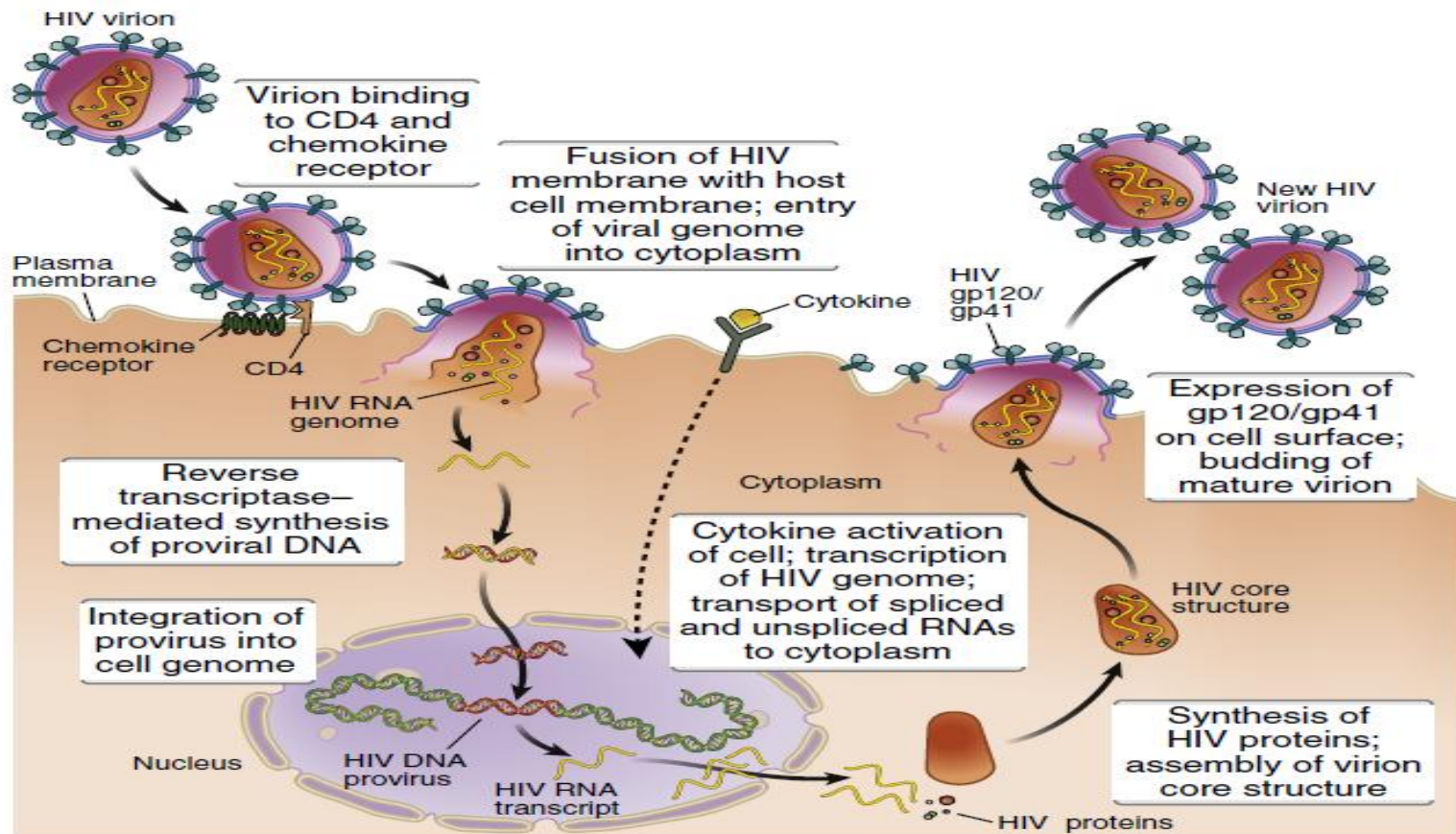
- **DNA synthesis : Reverse transcriptase** is the enzyme responsible for the synthesis of the double DNA strand that is complementary to the RNA molecule of the viral genome. The parts at the ends of the genomic RNA are copied twice, so that at each end of the newly synthesized DNA there are specific sequences **called long terminal repeats** (LTR)
- **Integration** : The DNA is then transported to the nucleus and integrated into the host cell's genome with the help of viral integrase, which joins the ends of the LTR sequence for the host cell's DNA. In an integrated state, the viral genetic material is called a **provirus**. A provirus is analogous to a cellular gene, and is transmitted to daughter cells after division.



# HIV

## - replication -

- **Synthesis of new viruses** - in **“productive phase”** of infection viral DNA is transcribed into mRNA by cellular **DNA-dependent RNA polymerase**. The signals for viral RNA synthesis are found in the LTR sequences. Some of the newly synthesized viral RNA molecules are used as mRNA for the synthesis of viral proteins, while the rest are incorporated into the genome of new virions.
- **Assembly and release of virions**



# HIV

## -latency and reactivation-

- **Latent phase** - infected cells contain provirus but do not express viral RNA or viral proteins

*After infection of lymphocytes with HIV and integration of the provirus, the infectious process can be arrested and reactivated explosively after a certain time by another stimulus*

More precisely, in case of **activation of an infected T lymphocyte, macrophage or dendritic cell** to some external stimulus (infection), the cell responds by transcribing more of its own genes and producing cytokines

An adverse consequence of the normal protective response is the **activation of the provirus**, which induces the production of viral RNA and proteins

The result is explosive virus production and rapid death of the infected cell

# HIV

## -latency and reactivation-

HIV proviruses contain promoters that induce the expression of viral genes when HIV-infected cells are stimulated with antigen or infected with other microorganisms.

HIV expresses macromolecules that regulate the expression of the viral genome and function as soluble factors:

- *Tat protein (transcription activator)* accelerates and enhances transcription of integrated viral DNA with the help of host RNA polymerase
- *Rev protein (regulator of viral gene expression)* promotes the transport of viral RNA from the nucleus to the cytoplasm

# How does HIV evade the host's immune response?

- *Nef protein (negative effector)*  
it reduces the expression of MHC class I molecules on the cell surface, blocks apoptosis, and enhances virus infectivity
- *Vif protein (viral infectivity factor)*  
cancels the inhibitory effects of cellular components
- *Vpu protein (viral protein)* promotes the destruction of CD4 and affects the release of virions

# How does HIV evade the host's immune response?

- Viral gene products can be relatively invisible to the immune system
- 
- A virus can mask or change its antigenic repertoire - **antigenic variation**
- The virus primarily replicates in lymph nodes, where immune system cells specific for virus antigens do not migrate freely

# HIV

## **-antigenic variation-**

*HIV evades the host's immune response by altering large surface antigens*

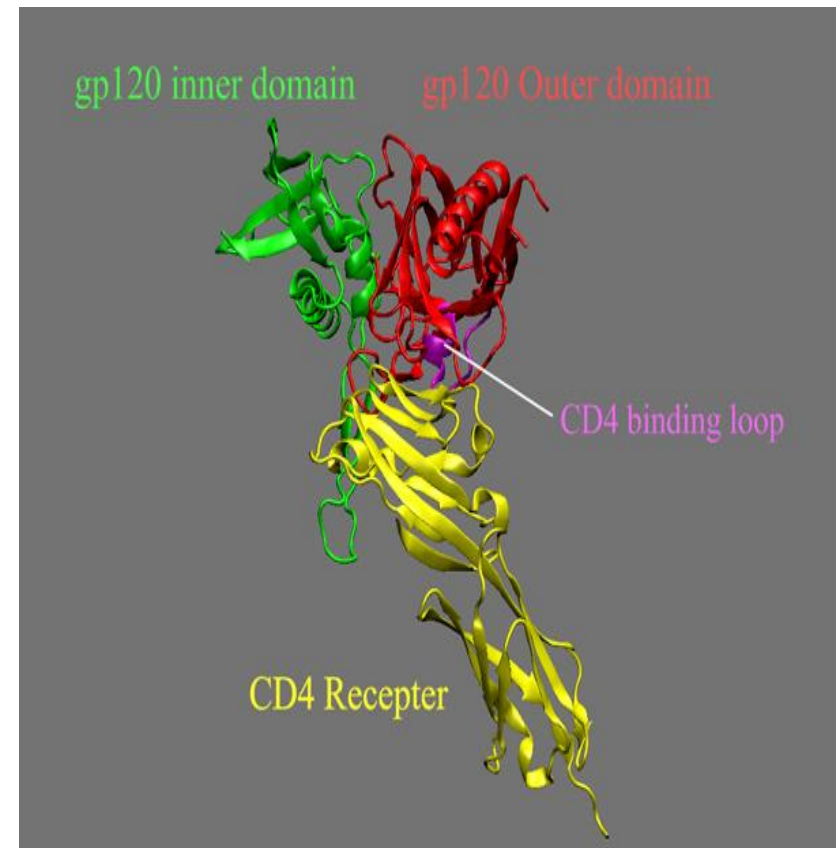
- Genes encoding internal viral proteins (gag and pol) show relative stability
- The env gene is subject to numerous mutations that induce variability in the surface glycoproteins gp41 and gp120



# HIV

## -antigenic variation-

- Sequences of gp120 surface glycoprotein, involved in interactions with cell receptors must be genetically conserved
- Conserved sequences can be hidden and thus protected from neutralizing antibodies by **carbohydrate chains and hypervariable regions**

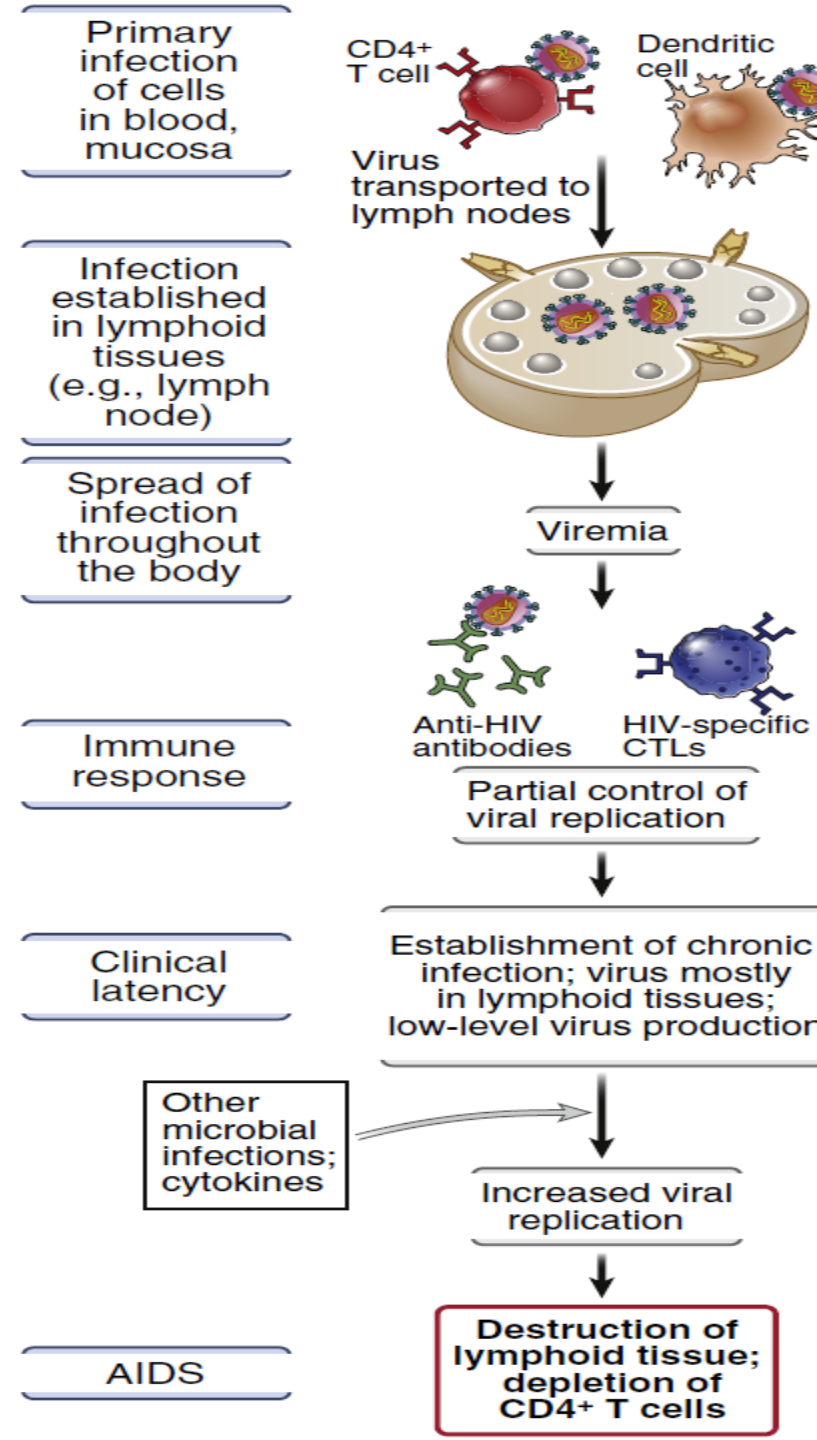


# HIV

## - disease pathogenesis -

### *Infection and depletion of helper T lymphocytes*

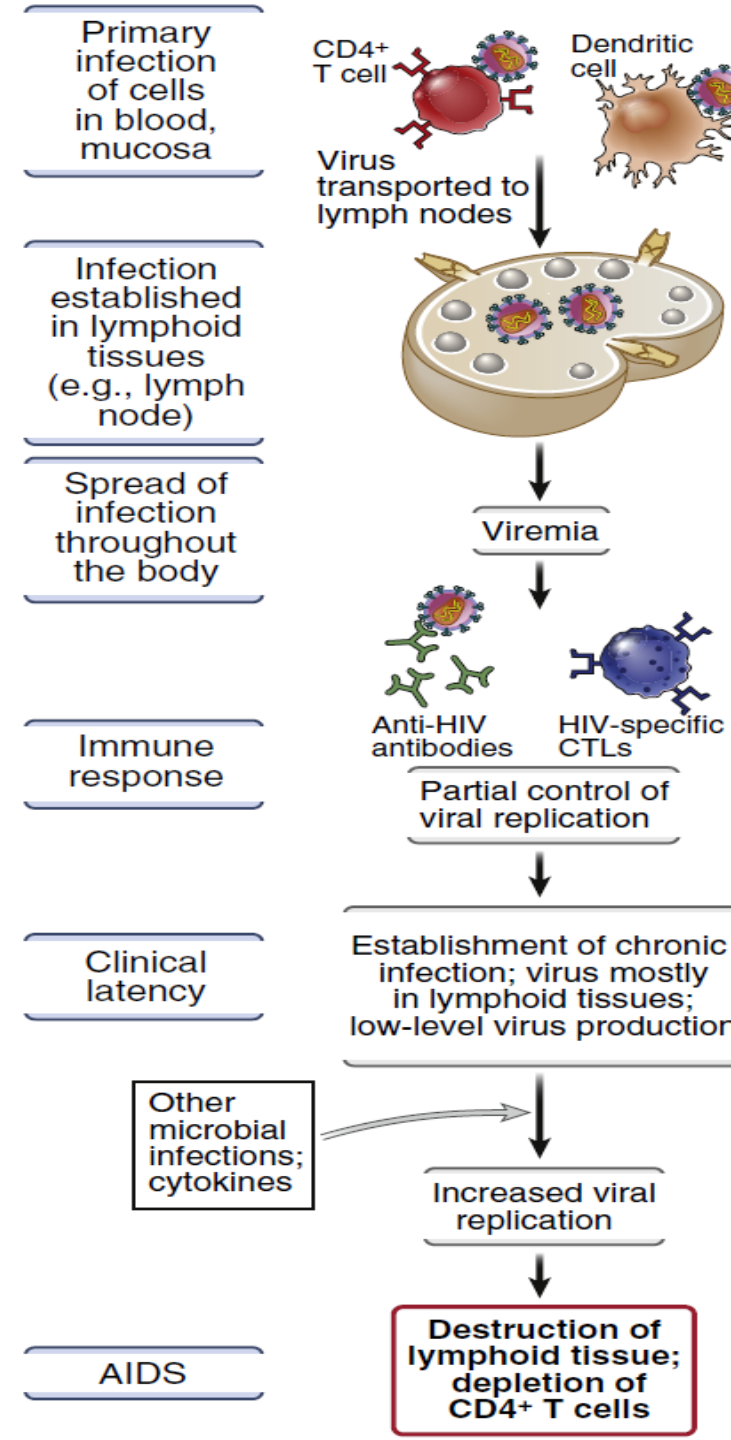
- The CD4 molecule can also be found on the membranes of other cells: monocytes and macrophages (disorders of phagocytosis), NK cells, some B lymphocytes, glia cells and Langerhans cells (important for the establishment of infection)
- These cells can also be infected by the virus and be destroyed in the process of virus replication or serve as a reservoir for virus latency



## Tissue damage

### Acute HIV infection

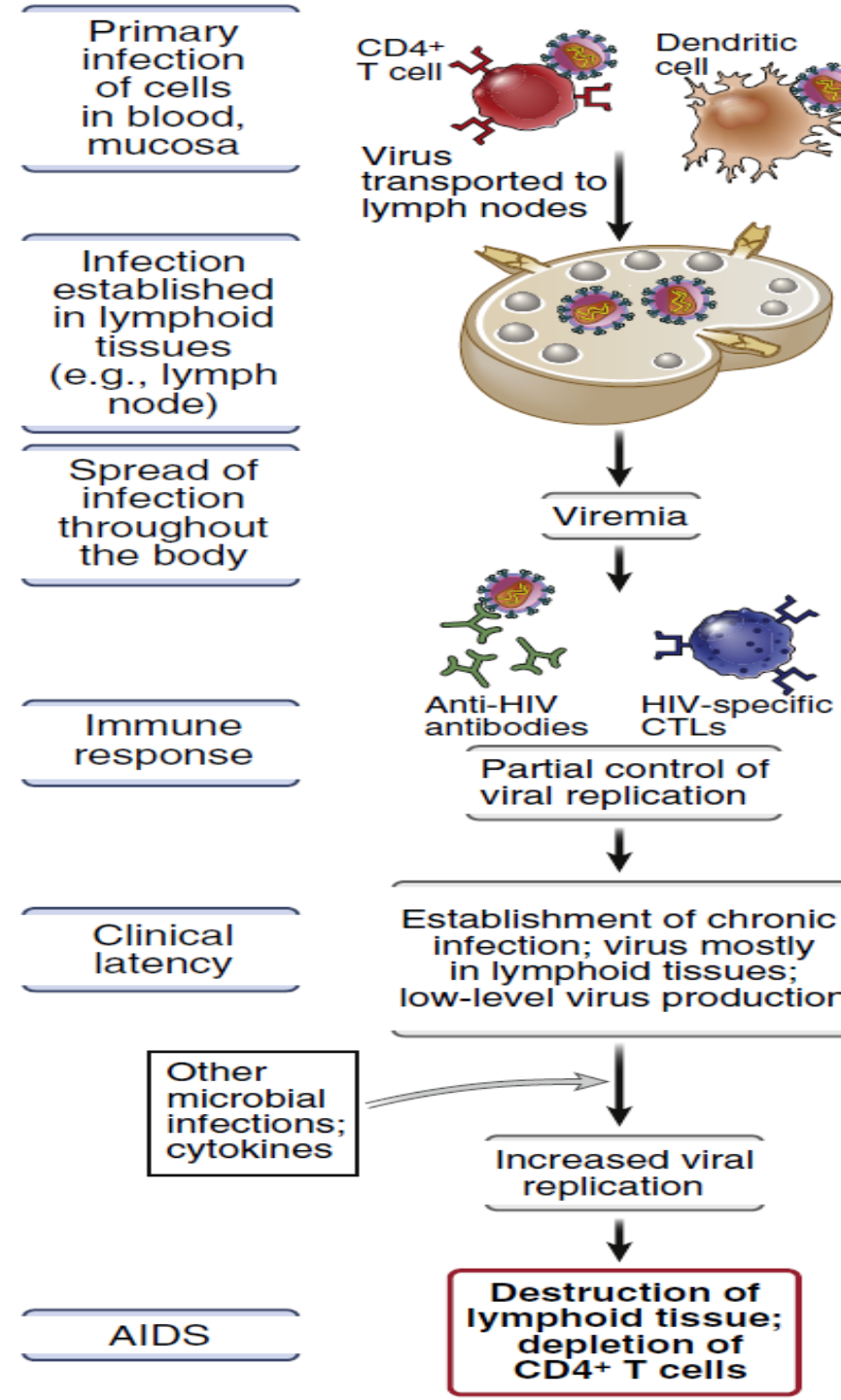
- The virus infects cells that express the CD4 molecule in local mucous membranes, and then rapidly establishes infection in local lymphatic tissues.
- During the next few days, **local replication** is limited to cells present at the site of viral entry. In most cases, the number of local susceptible cells decreases and the infection "dies" at the site of initial inoculation
- However, cytokines and chemokines, produced as part of the primary immune response, recruit additional components of the immune system
- If local viral replication is still ongoing at the time of immune system cell migration, the conditions for further viral replication are created, and the infection spreads and becomes self-sustaining.



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After infection at the site of entry, **the virus spreads rapidly systemically**, to distant organs of the lymphatic tissue and the central nervous system (CNS). In this phase, **the virus shows the highest level of replication in the entire course of the disease** and appears in genital secretions - the possibility of transmission is high

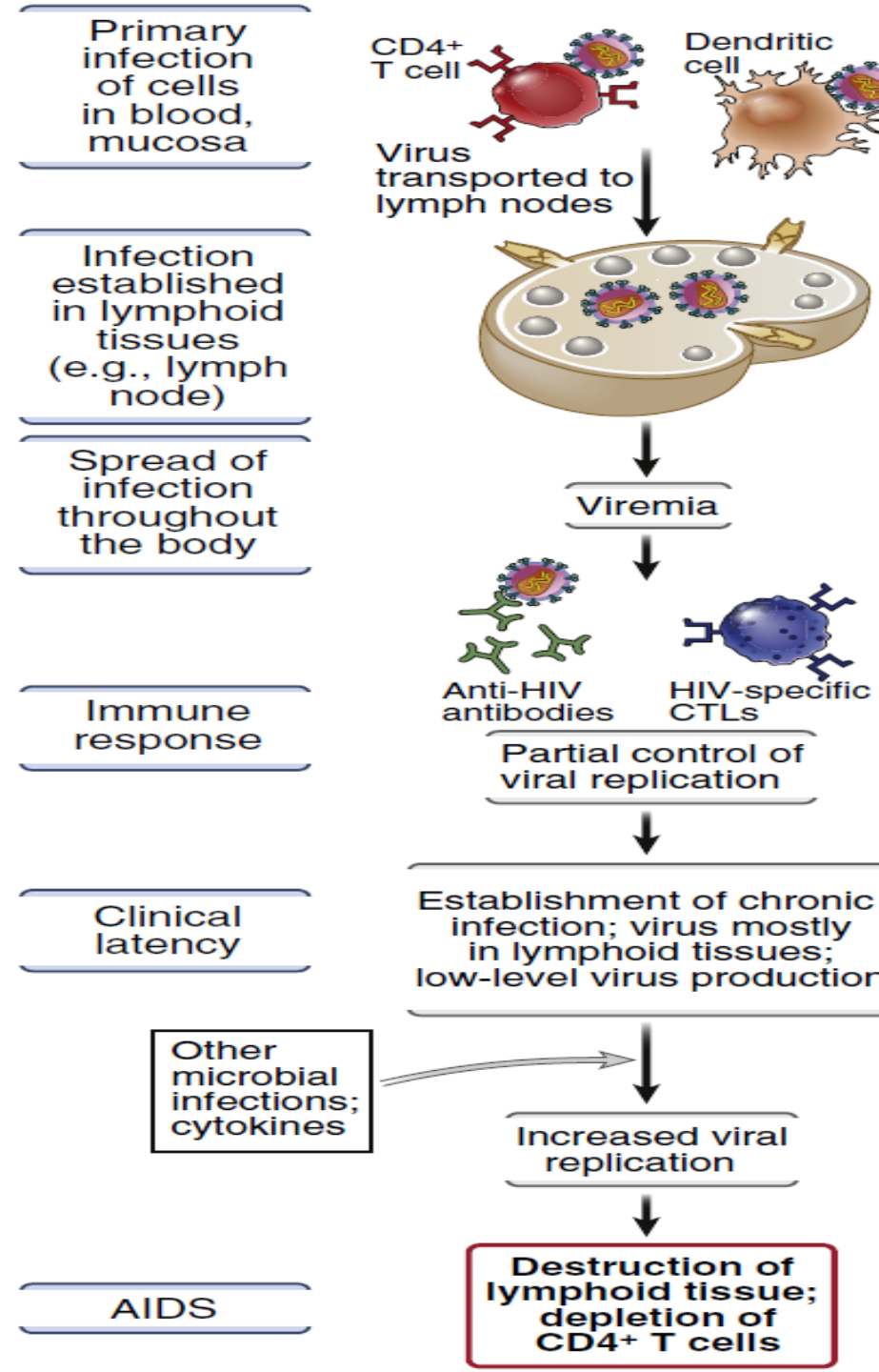
In the first weeks after the onset of infection, specific cytotoxic T lymphocytes appear in the peripheral blood and lymph tissue, and soon after, neutralizing antibodies can be detected in the plasma. During this period of rapid viral replication, the lifelong process of generating viral diversity is initiated, and **the host is faced with the challenge of developing an immune response against a rapidly changing pathogen**



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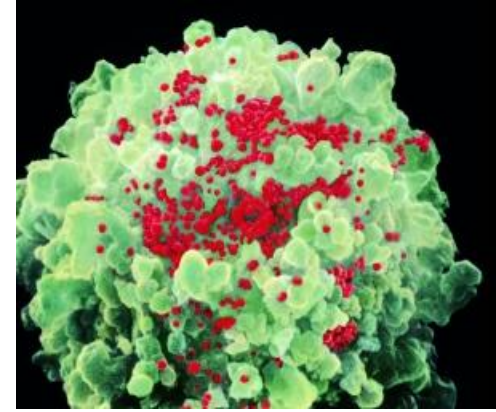
After the first few months of infection, a balance is established between **viral replication, effector immune mechanisms and available cells for viral replication**, and the infection enters a **latent phase** during which the infected person is symptom-free.

After the initial phase of HIV infection, viral replication is limited mainly to lymphoid organs where the main target is activated CD4+ T lymphocytes and 99% of viral replication takes place in them

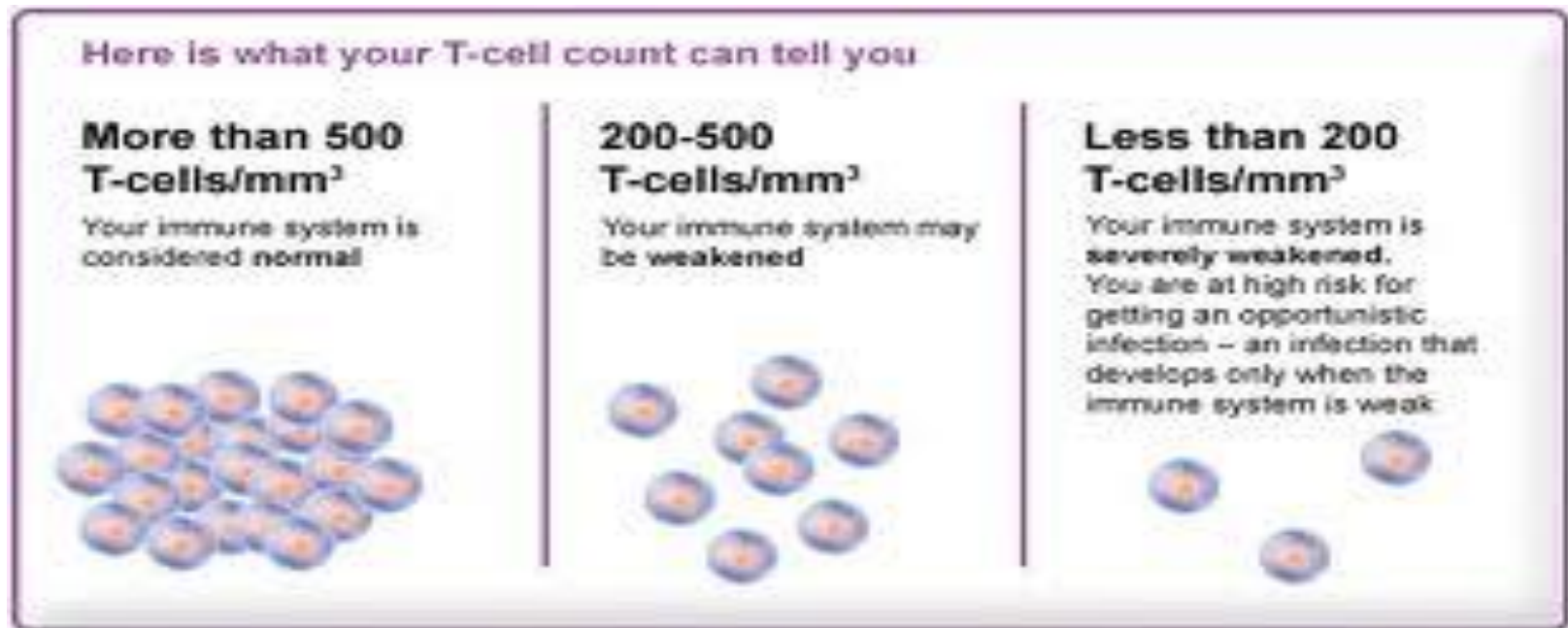




# Tissue damage



- HIV-infected cells can be directly destroyed in the viral process replication or effector specific immune response mechanisms (cytotoxic T lymphocytes or antibody-dependent cytotoxicity)
- The loss of the CD4+ T cell population affects the development of progressive immunodeficiency, which ultimately results in the appearance of opportunistic infections and malignancies.
- Although there is individual variation, the duration of the asymptomatic period before the onset of AIDS is about 10 years



- People with **advanced AIDS** usually have **fewer than 200 CD4+ T lymphocytes per mm<sup>3</sup>**
- The risk of infections is greatest in the **terminal stages of AIDS**, when the CD4+ T lymphocyte count falls **below 50 cells/mm<sup>3</sup>**
- Serial measurements of the number of CD4+ T lymphocytes serve to assess the risk of infections and are a guide for the implementation of antiretroviral therapy



**Level of viral replication**



**Number of HIV RNA copies in plasma**



**Disease progression**

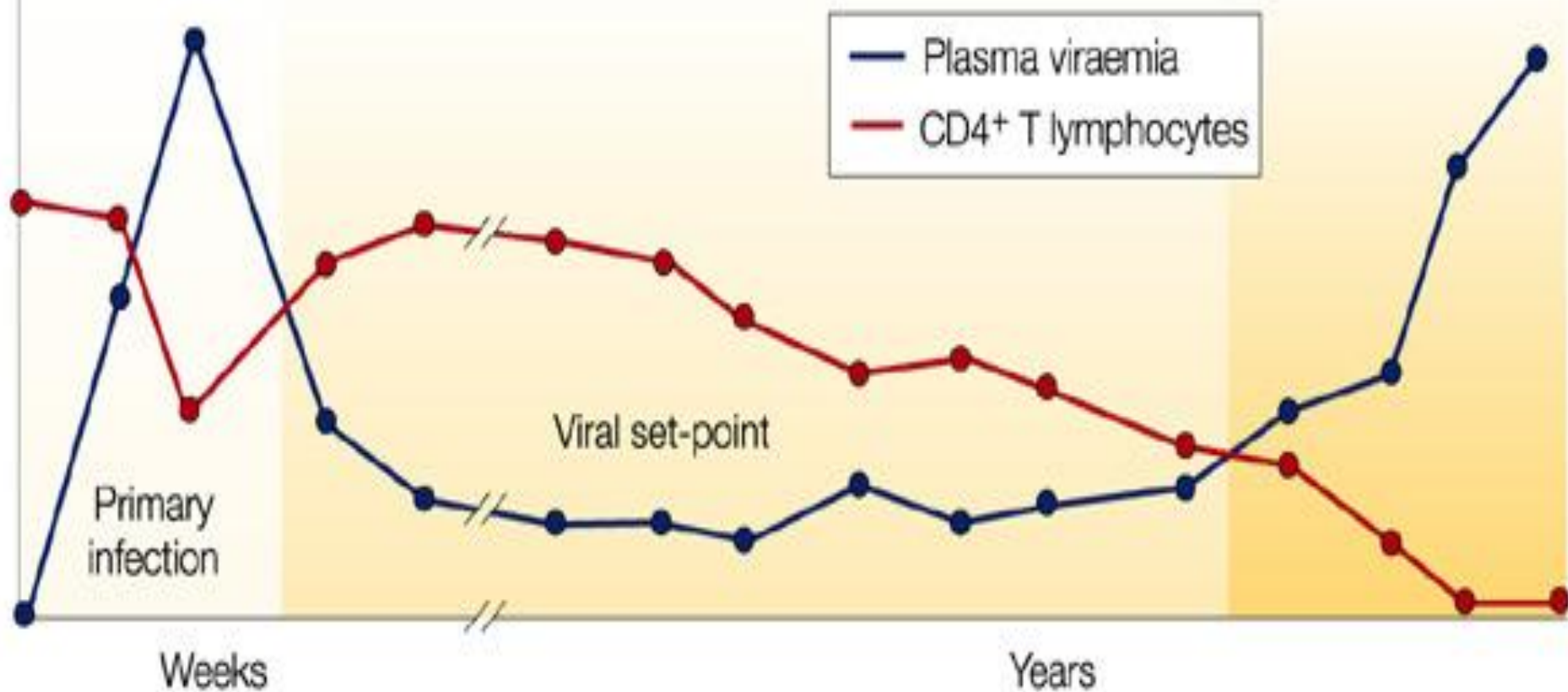
People with **high levels of viral RNA** ( $10^5$  copies/ml or more) are at **greater risk of disease progression** within a few years, while infected people with lower levels ( $<10^4$  copies/ml) remain asymptomatic for 10 years or longer

Increasing viral diversity →

**Acute**

**Chronic**

**AIDS**



# **Acquired Immunodeficiency Syndrome (AIDS)**

**Two characteristics make AIDS unique among  
infectious diseases:**

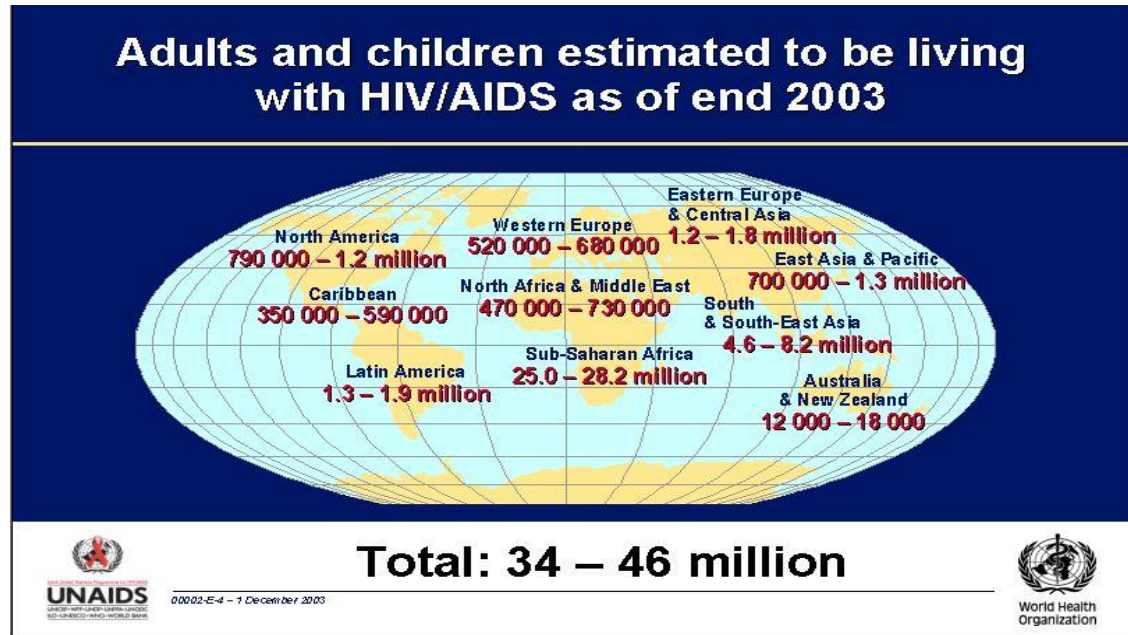
**it is a deadly disease  
and most of its devastating symptoms are not the  
result of the direct action of the causative agent of  
the disease**

**AIDS is a set of clinical diseases, primarily opportunistic infections and malignancies, which occur as a result of the destruction of the immune system by HIV.**

**The syndrome is a terminal manifestation of HIV infection that occurred many years earlier (10 or more years).**

# AIDS - PANDEMIC

- It is estimated that there are more than 34 million people infected with HIV in the world, about 70% are in Africa and 20% in Asia
- The disease has been attributed to the death of more than 30 million people worldwide, and the annual death rate now reaches around two million.

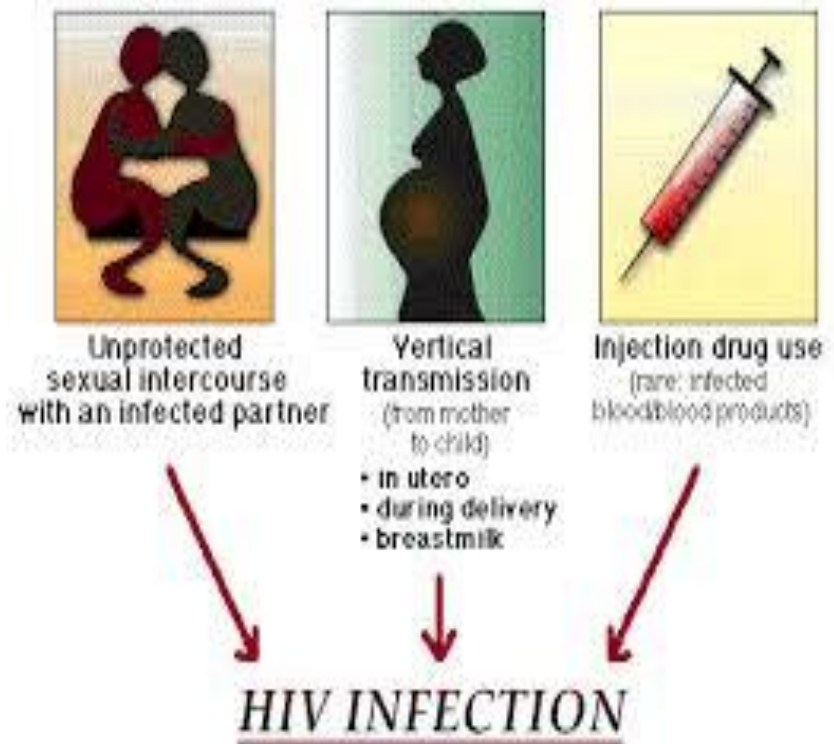


- Unfortunately, only 10% of people living with HIV in the world have access to antiretroviral therapy

# HIV transmission

**HIV is primarily transmitted by direct inoculation of infected blood or body fluids into the host's body**

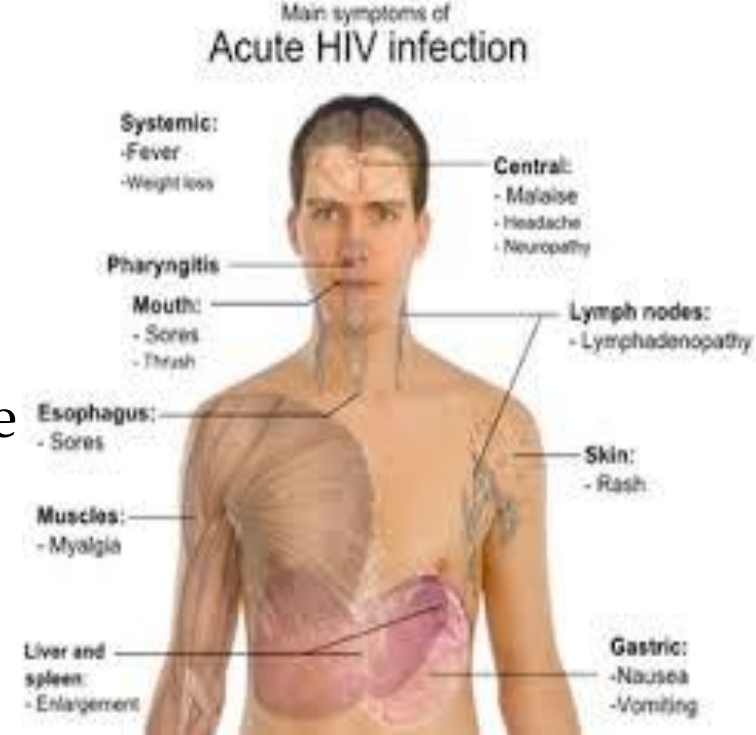
- Sexual contact - other sexually transmitted diseases, especially genital ulcers, are associated with an increased risk of HIV transmission, possibly as a result of compromised skin or mucosal integrity
- Transmission through infected blood and blood products
- Intravenous drug abuse
- Vertical transmission
- Occupational exposure – healthcare workers





# Early acute HIV infection

- ✖ In 50 to 90% of people, the acute disease occurs 2 to 4 weeks after infection
- ✖ In most cases, the only symptoms are fever and mild sore throat
- ✖ Fewer patients may have fever, myalgias, lethargy, pharyngitis, arthralgias, lymphadenopathy, maculopapular rash, or aseptic meningitis.
- ✖ The acute illness usually lasts from 3 to 14 days and, as a rule, complete recovery occurs, even in patients with neurological complications.



# Diagnosis of HIV infection

- **By determining the viral RNA, using the PCR method,** HIV infection can be detected early in the course of the infection, but due to the cost, it is not used as a screening test, unless the doctor suspects an acute infection.
- Instead, HIV infection is usually diagnosed by **detecting circulating antibodies to viral antigens**

**Any presence of anti-HIV antibodies must be considered an active infection that can be transmitted to others**

# Diagnosis of HIV infection

## -serological tests-

*Specific anti-HIV antibodies usually appear 6 to 12 weeks after infection*

In rare cases, infected persons do not develop antibodies for several months or years after exposure to the virus - **false-negative HIV serological tests**

- In addition, some patients in the terminal stages of AIDS may have **negative serological tests** (probably due to **severe B lymphocyte dysfunction**)

# Diagnosis of HIV infection

## -serological tests-

### ELISA test:

- very sensitive test ( $> 99\%$ ), but not completely specific, so false-positive results are possible - verification of a positive finding is necessary

### *Western blot:*

- sensitive and specific method for the detection of anti-HIV antibodies, but it is expensive and requires a lot of time for basic screening needs

# Diagnosis of HIV infection PCR test



*A sensitive and specific method for early detection of infection when specific anti-viral antibodies have not yet appeared*

## It is most often used for:

- assessment of the need and effectiveness of antiretroviral therapy
- identification of HIV-infected children born to HIV-positive mothers, when the presence of maternal antibodies may complicate serological diagnostic tests

# Diagnosis of HIV infection

## -other diagnostic tests-

- **P24** is an antigenic protein of the viral core, and its presence indicates active viral replication. However, in an already established infection, this antigen cannot be detected in the serum of all patients and is therefore less useful
- HIV can be cultured from the lymphocytes of most infected persons, but this test is technically difficult to perform and is mostly used only for research purposes.



# Consequences of HIV infection

HIV infection is a state of activation of the immune system with high turnover between the virus and CD4+ T lymphocytes, which occurs daily until the lymphocyte reserve of the organism is depleted.

**The condition of patients during the progression of HIV infection and the decision to start antiretroviral therapy are routinely evaluated in three ways:**

- clinical assessment of conditions related to HIV infection or AIDS
- by determining the number of CD4+ T lymphocytes
- by quantifying the level of viral RNA

# Progression of infection to AIDS

- **Latent period** (from a few months to more than 15 years) - infected people usually do not have any symptoms of the disease and feel healthy

## Possible manifestations:

- localized or generalized lymphadenopathy
- recurrent mucocutaneous candidiasis
- aphthous ulcers in the mouth, hairy leukoplakia (EBV)
- hematological cytopenias
- viral hepatitis
- skin changes - dry skin or itching, seborrheic dermatitis, eczema, folliculitis, psoriasis, herpes zoster

# Clinical manifestations of AIDS

- "AIDS-associated diseases" are the most common **infections caused by intracellular pathogens** controlled by the cellular immune response
- These infections are more often the **result of endogenous reactivation** of the focus of infection than newly acquired infections

# Diseases associated with AIDS

- Multiple or recurrent bacterial infections (two in a 2-year period) in children under 13 years of age: septicemia, pneumonia, meningitis, bone or joint infection, or internal abscess caused by *H. influenzae*, streptococcus, or other pyogenic bacteria
- Candidiasis of the esophagus, trachea, bronchi or lungs
- Disseminated coccidioidomycosis
- Extrapulmonary cryptococcosis
- Chronic cryptosporidiosis, with diarrhea lasting more than 1 month
- Cytomegalovirus infection
- Mucocutaneous infection caused by herpes simplex viruses that persists for more than 1 month
- HIV encephalopathy
- Disseminated histoplasmosis
- Isosporiasis, with diarrhea lasting more than 1 month

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- Kaposi's sarcoma
- Primary brain lymphoma
- Non-Hodgkin lymphoma of V lymphocytes or unknown phenotype, including Burkitt's lymphoma
- Lymphoid interstitial pneumonia in children younger than 13 years
- Disseminated mycobacterial infection (not caused by M. tuberculosis)
- Extrapulmonary tuberculosis
- Pneumocystis jiroveci infection
- Progressive multifocal leukoencephalopathy
- Recurrent infections caused by salmonella
- Toxoplasmosis of the brain

*Each of these diseases indicates the diagnosis of AIDS in the presence of laboratory evidence of the presence of HIV infection*



# Lung infections

## Pneumonia caused by *Pneumocystis jiroveci* (PCP)

- The most common opportunistic infection associated with AIDS and occurs in 25 to 60% of patients
- 
- Typical symptoms are fever, cough and shortness of breath
- It is associated with a mortality rate of 10 to 20% of cases that develop irreversible respiratory failure.
- The use of specific antiretroviral therapy and anti-PCP therapy has improved quality of life and length of survival



# Gastrointestinal infections

- Oral and pharyngeal **candidiasis**, esophageal candidiasis, accompanied by pain and difficulty swallowing with consequent weight loss
- **CMV** typically causes disseminated disease accompanied by viremia. Involvement of the large intestine can result in intense abdominal pain and diarrhea
- Gastrointestinal symptoms can also be caused by malignancies such as **Kaposi's sarcoma** or **lymphoma** of the stomach or colon



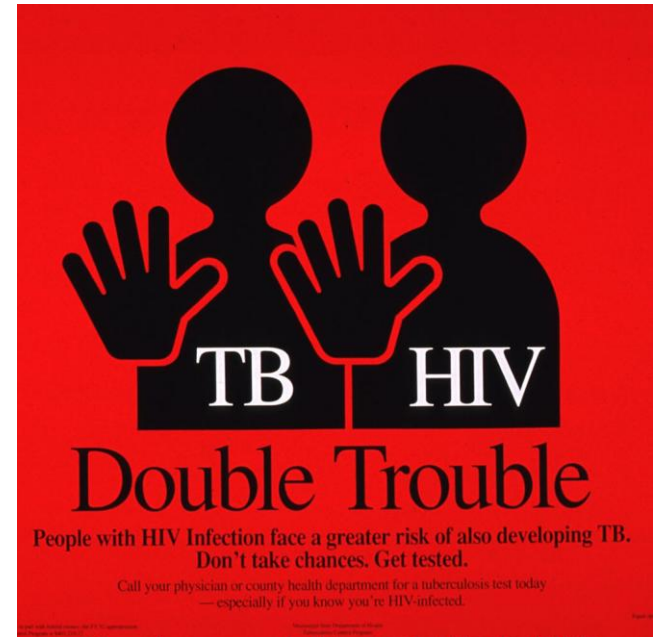
**Diarrhea is a common problem in patients with advanced AIDS and can be serious and difficult to diagnose and treat.**

**It can be caused by a large number of agents:**

- CMV and other viruses
- intestinal Gram-bacteria such as *Salmonella* and *Shigella* spp. (with accompanying bacteremia)
- hospital infections - *Clostridium difficile*
- mycobacterial infections (especially *Mycobacterium avium* complex) primarily of the small and large intestine, followed by malabsorption and diarrhea
- intestinal parasites such as *Giardia*, *Isospora*, *Cryptosporidium* and *Microsporidium* spp.

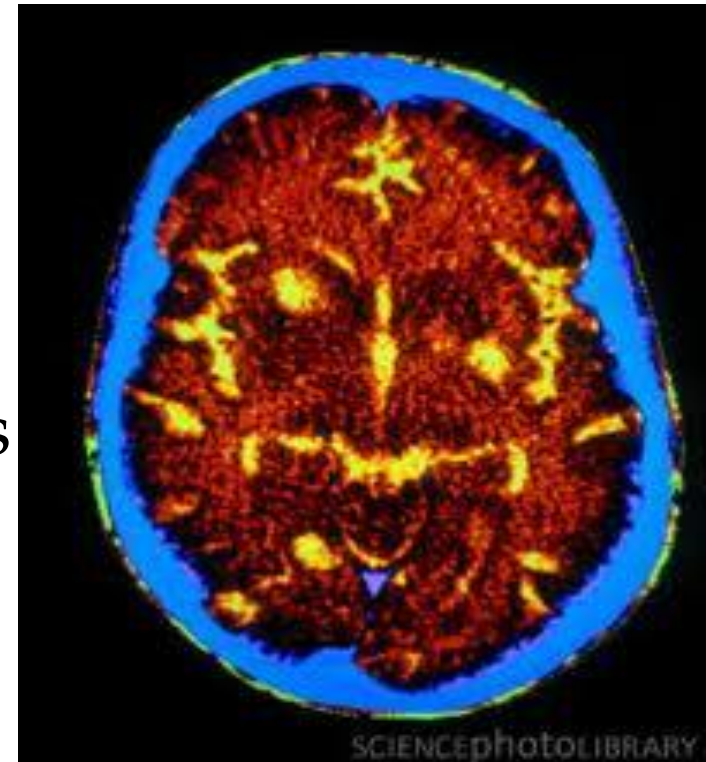
# Mycobacterial and fungal infections

- **Tuberculosis** of the lungs that can spread and manifest as lymphadenitis, hepatitis or meningitis
- Disseminated infection caused by *M. avium* complex (MAC): fever, night sweats, weight loss, splenomegaly, hepatomegaly, and diarrhea
- Similar symptoms are seen in patients with disseminated fungal infections, such as histoplasmosis and coccidiomycosis.



# Infections of the nervous system

- *Cryptococcus neoformans* – meningitis
- Reactivation of infection with the parasite *T. gondii* typically causes multifocal brain infection. Patients may experience headache, confusion, or seizures
- CMV causes retinitis and occasionally encephalitis



# Direct manifestations of HIV infection

- **HIV nephropathy** - proteinuria, nephrotic syndrome and renal failure
- **Myopathy and myositis**
- **Cardiomyopathy**
- **Weight loss**



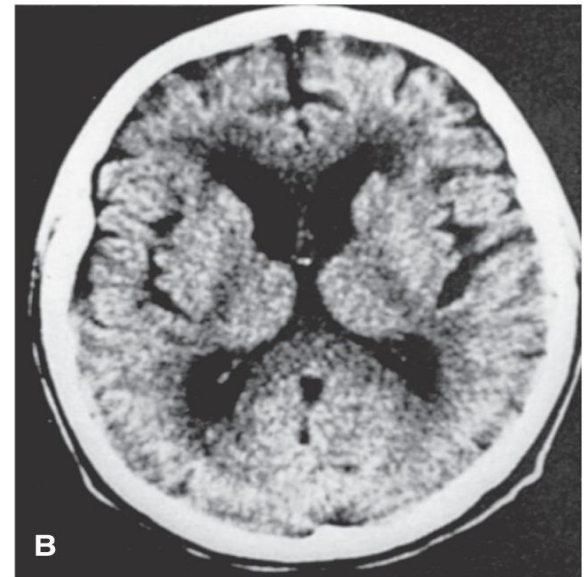
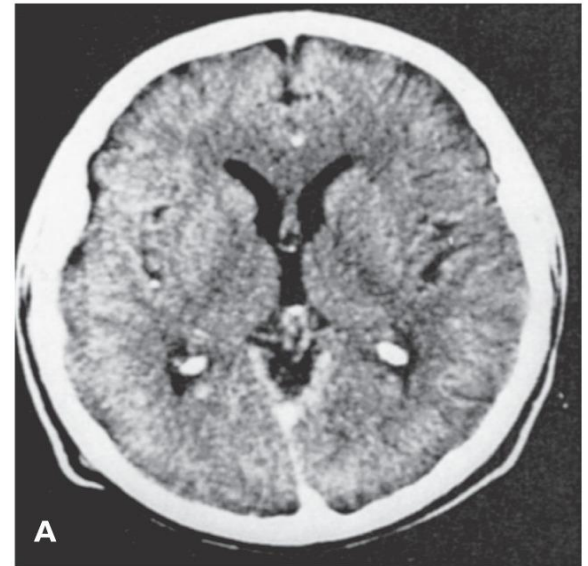
# Oncological manifestations of advanced AIDS

- **Kaposi's sarcoma** (HHV-8) - a localized skin lesion without significant symptoms. Severe cases of Kaposi's sarcoma manifest as widely disseminated lesions, with involvement of the lymph nodes, gastrointestinal tract, and lungs.
- Hodgkin's and non-Hodgkin's lymphoma (EBV infection)
- Malignant transformations associated with HPV infection



# Neurological manifestations in advanced AIDS

- The most common neurological problems are caused by HIV itself
- **Acute primary infection** may be associated with complications such as **aseptic meningitis, encephalitis, myelitis or inflammatory neuropathies** such as *Guillain-Barré* syndrome.
- In the later stages of the disease, patients may have **peripheral neuropathies, motor or sensory neurological deficits**
- **The most common form of neurological disease is HIV-associated encephalopathy followed by progressive dementia**



# HIV infection in children

- Transmission is usually vertical (from mother to fetus), and 13 to 40% of babies born to HIV-positive mothers are infected.
- 
- Combination antiretroviral therapy during the last two trimesters of pregnancy and during delivery can reduce transmission rates to less than 2%
- HIV infection in children has a similar course with progressive immunodeficiency, recurrent opportunistic infections and neurological manifestations. However, disease progression can be much faster in infants

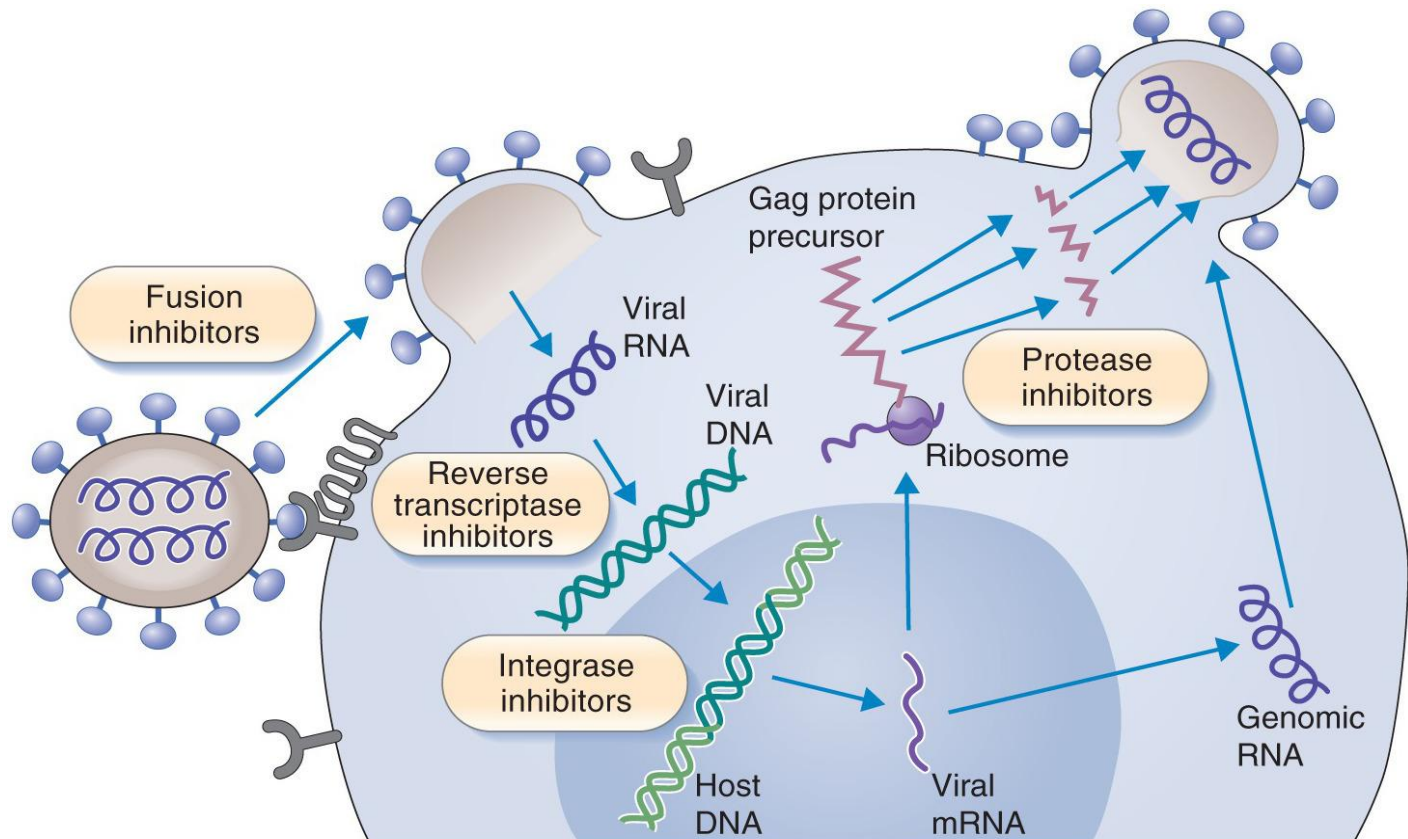


# Treatment of HIV positive patients

- Antiretroviral therapy has changed HIV infection from a fatal to a chronic disease
- Education of the patient and the environment
- Support

# Antiretroviral therapy

Effective drugs that act at different points in the viral life cycle: binding to CCR5 (coreceptor), viral envelope fusion, retrovirus-specific DNA polymerase, integration into the host genome, and viral protease



# Antiretroviral therapy

*Treatment of HIV infection involves a combination of drugs with the aim of achieving synergism and delaying the emergence of resistance*

**“Highly active antiretroviral therapy ” (HAART)**

for example. two reverse transcriptase inhibitors and one protease inhibitor

Prophylaxis of infections - antibiotics





# HIV - Prevention

- The best approach to controlling AIDS is to prevent HIV transmission
- Regular screening of persons at risk of HIV infection
- HAART therapy – reduced risk of transmission
- Development of an effective vaccine