

Teaching unit 12

HEPATITIS VIRUSES. RETROVIRUSES AND PRIONS

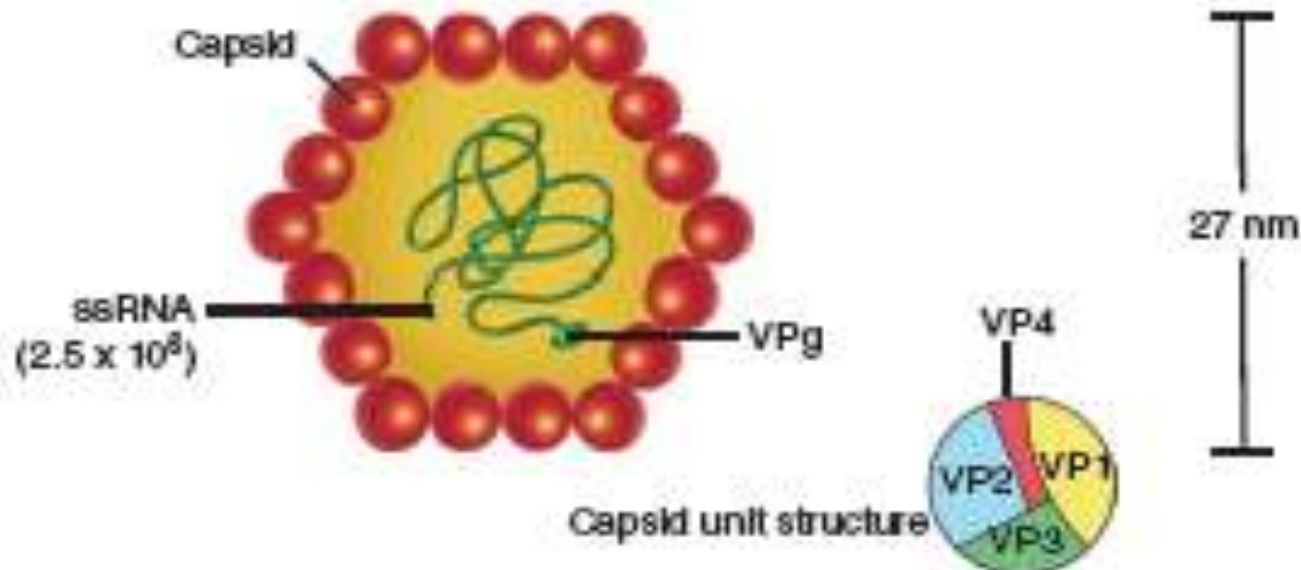
Hepatitis viruses

Comparative characteristics of hepatitis A, B, C, D and E viruses

Feature	A	B	D	C	E
Virus type	Single-stranded RNA	Double-stranded DNA	Single-stranded RNA	RNA	RNA
Incubation (days)	15-45 (average 25)	30-180 (average 60-90)	28-45	15-150 (average 50)	21-56 (average 40)
Beginning	Usually sudden	Gradual	Variable	Insidious	?
Age of most common occurrence	Children, young people	All ages	All ages	All ages	Younger people
Fecal-oral transmission	+++	±	±	-	+++
Sexual transmission	+	++	++	+	+?
Parenteral transmission	-	+++	++	+++	
Chronic infection (%)	No	10	50-70	85	Rarely
Carriers	No	Yes	Yes	No	No
Protective serum antibodies	Yes	Yes	Yes	No	No
Vaccine	Yes	Yes	Yes	No	No

Hepatitis A virus (HAV)

- HAV belongs to *Picornaviridae* family and genus *Hepatovirus*, is nonenveloped virus with icosahedral symmetry
- HAV genome is made of single-stranded RNA to which the VPg protein is bound, and each capsid unit contains 4 proteins VP1, -2, -3 и -4
- VP1 binds to a receptor on host cells
- There is only one serotype of HAV virus



HAV

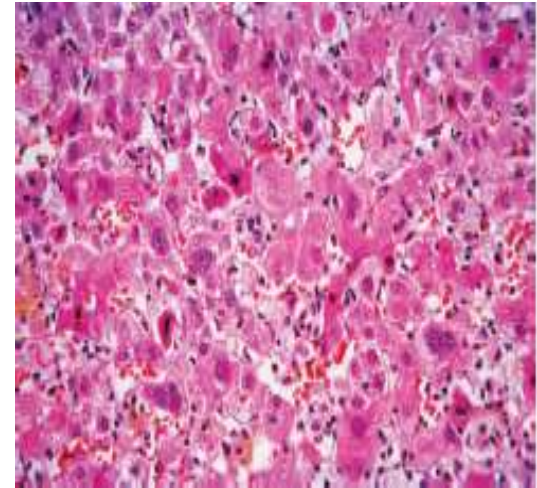
- epidemiology-

- The infection is subclinical in 50% of infected adults, and when it is symptomatic, it is usually manifested by fever and jaundice, **chronic hepatitis is very rare**
- The most important source of HAV are humans, it is **transmitted feco-orally**, transmission by transfusion is possible, but rather uncommon
- Carrier state is possible, but uncommon
- Mostly sporadic cases occur, epidemics are rare
- The person is most contagious during the two weeks before the onset of clinical manifestations of the disease

HAV

- pathogenesis -

1. **Initial replication in the intestinal mucosa**
(with the onset of symptoms, the virus can no longer be found in the feces)
2. **Viremia with spread of the virus to the liver**
3. **Viral replication in liver and inflammation** –
Virus and cytotoxic T cells damage hepatocytes
4. **Elimination of infection** (liver damage is reversible)

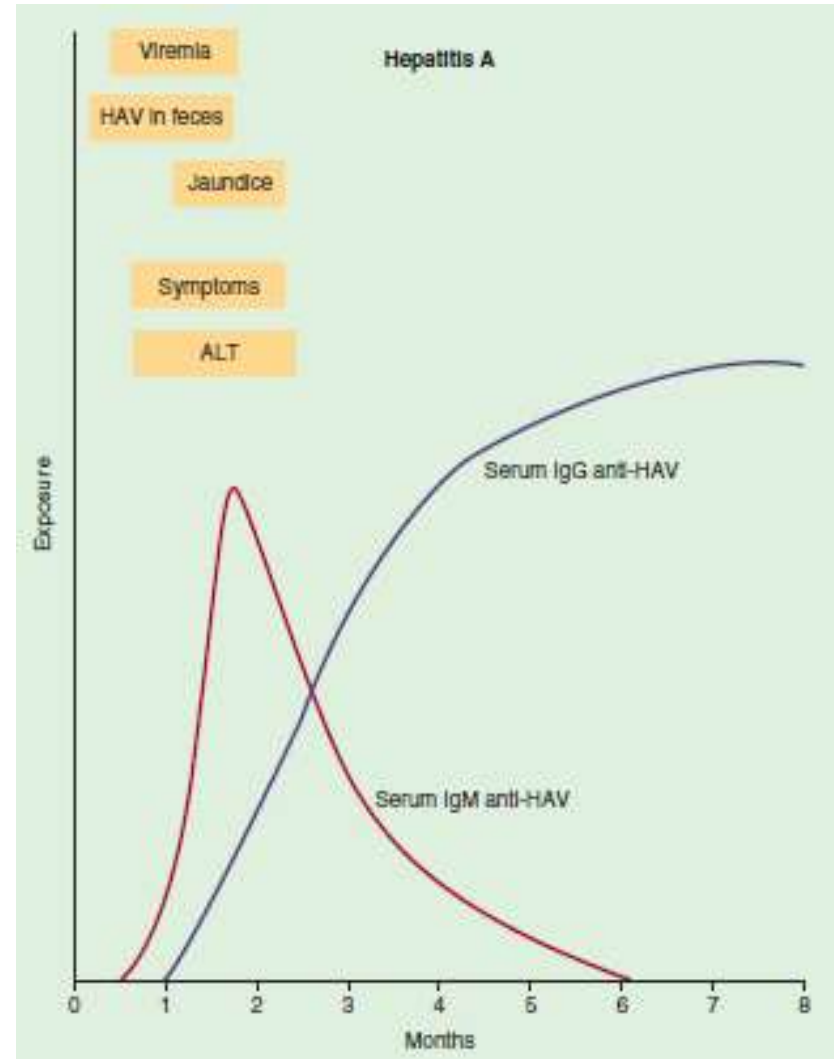


The initial immune response to infection involves the production of HAV-specific **IgM** antibodies, followed by **IgG** in a few weeks. Detected levels of antibodies to HAV permanently persist in serum, so people who have anti-HAV antibodies are immune to reinfection. Although virus-specific IgA antibodies have been detected in the stool, mucosal immunity is not important in protecting against hepatitis A

HAV

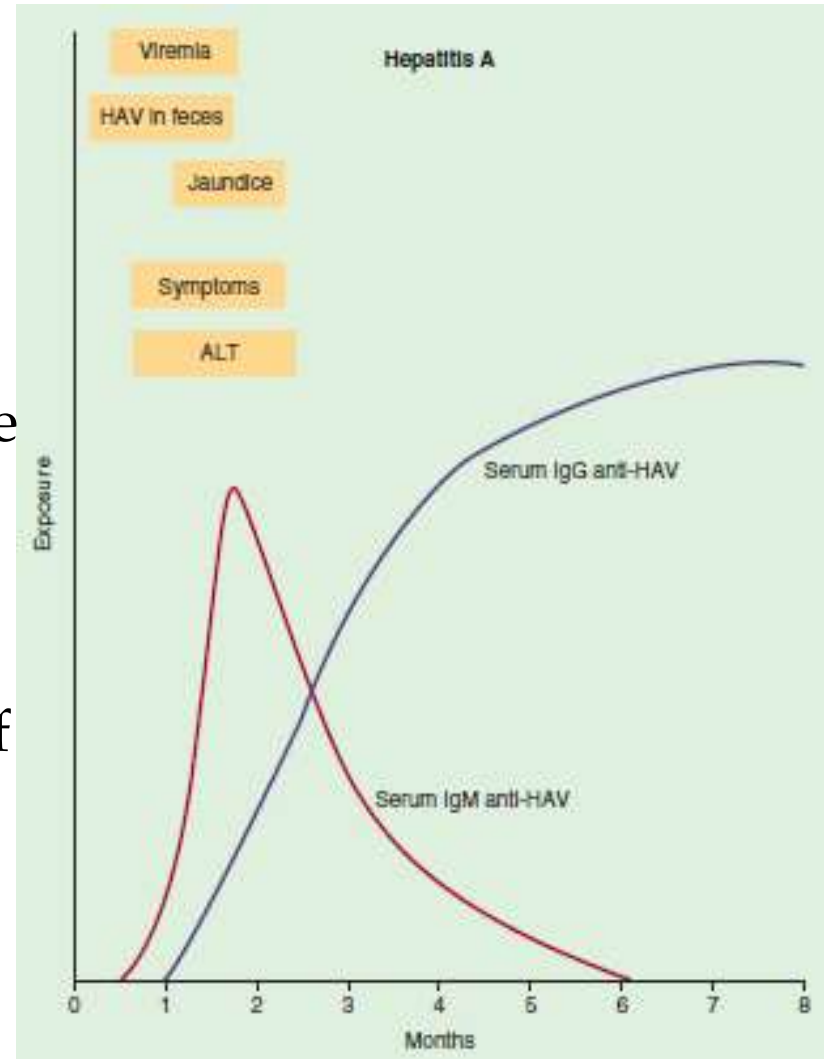
- clinical manifestations -

- Incubation period that lasts 15 to 45 days
- Followed by fever, anorexia, loss of appetite, nausea, pain in the upper right quadrant of the abdomen and jaundice
- Dark urine and pale stool
- The liver is enlarged and palpably sensitive, serum transaminases and bilirubin levels are increased
- The incidence of clinically manifest disease depends on age (20:1 in children and 1:1 in adults)



- diagnosis, treatment, prevention-

- Specific IgM antibodies are sufficient for diagnosis
- There is no specific treatment
- **Passive immunization:** hyperimmune globulins administered before and during incubation
- **Active immunization:** inactivated vaccine that induces the production of antibodies, provides protection in 100% of cases and today is recommended for all children aged one year, and in adults only for those at high risk



Hepatitis B virus (HBV)

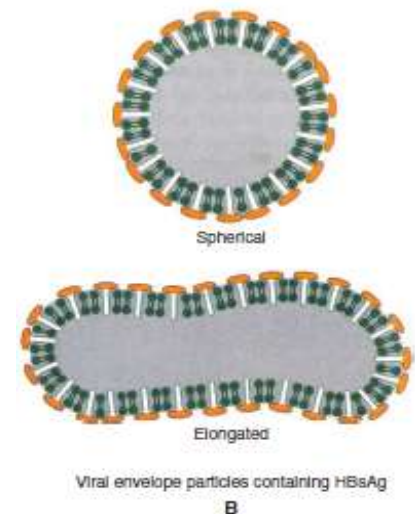
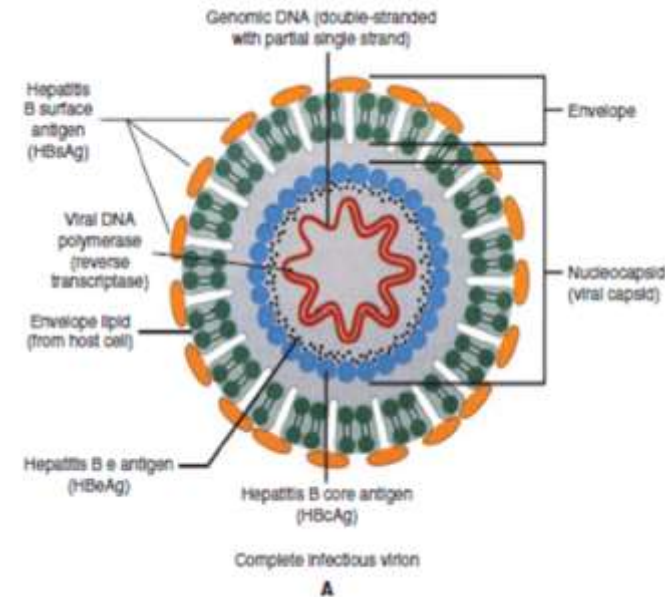
- Belongs to the family *Hepadnaviridae*, the cause of “serum” hepatitis

Complete infectious virion, *Dane particle*, is spherical and consists of:

Core:

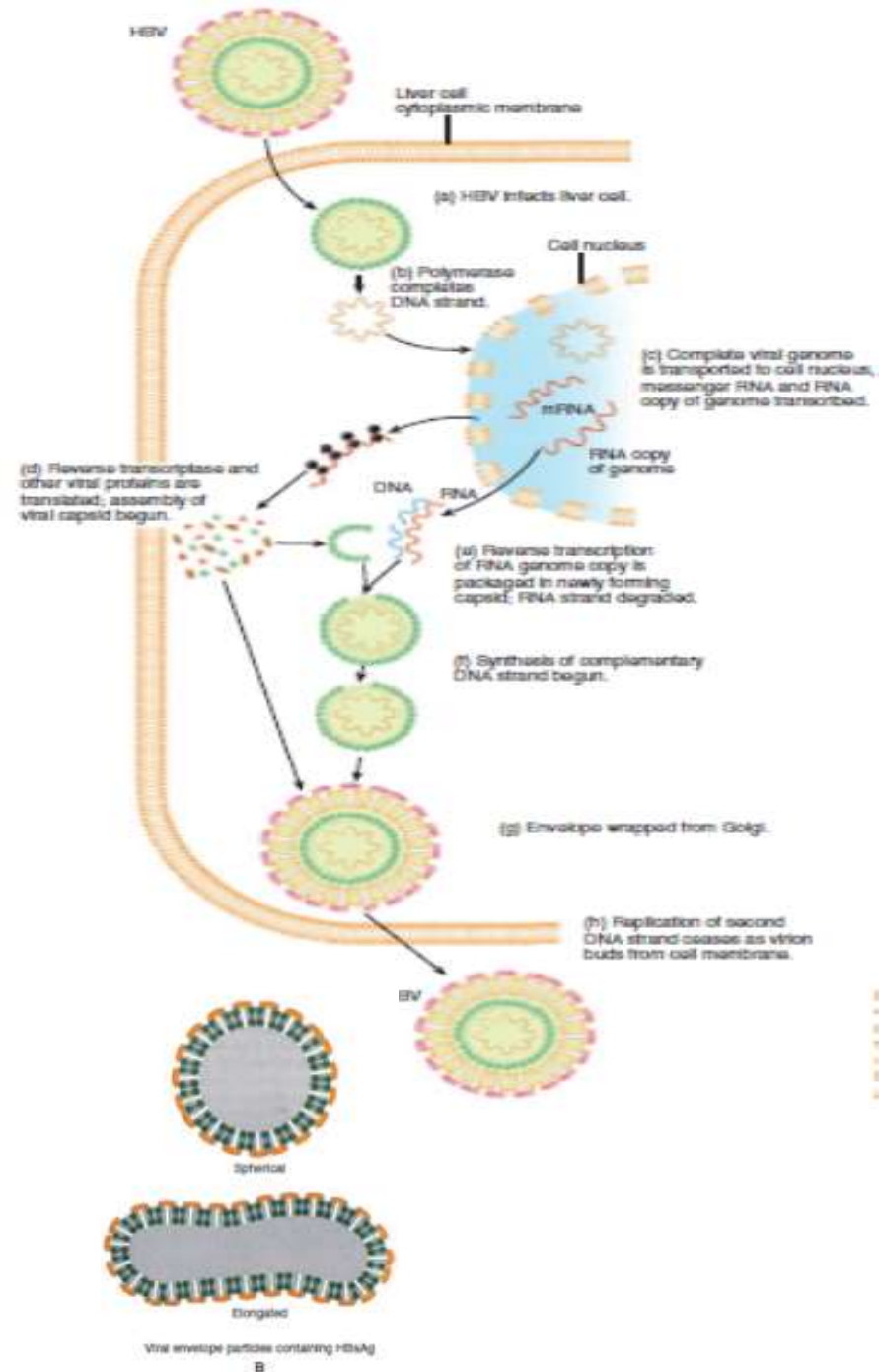
1. Nucleocapsid (partly double-stranded DNA). **viral DNA codes envelope proteins:** hepatitis B surface antigen (**HBsAg**); *core*, nucleocapsid protein (**HBcAg**); DNA polymerase (**reverse transcriptase, RNA-ase H**) and **HBx** protein, a transcriptional activator
2. Hepatitis B antigen or **HBsAg**, a low-molecular-weight glycoprotein secreted by infected cells

Lipid bilayer containing HBsAg



Hepatitis B virus (HBV) -replication-

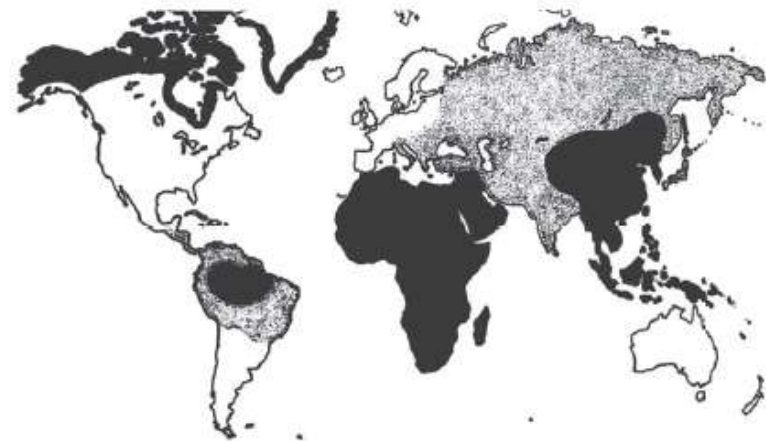
- HBV replication involves a step of **reverse transcription** (unique among all DNA viruses)
- **HBsAg aggregates** (spherical and filamentous forms) **and HBV DNA are detected in the serum**, indicating the presence of an infectious virus
- In infected liver tissue, HBcAg, HBeAg, and HBV DNA can be found in the nuclei of infected hepatocytes, while HBsAg is found in the cytoplasm



HBV -epidemiology-

- **Chronic infection carriers** are the major source of infection
- HBV transmission occurs through **the exchange of blood and body fluids** with the infected people
- In some countries, especially in the Far East, 5 to 15% of people carry this virus and most are asymptomatic

areas with high prevalence are marked in black

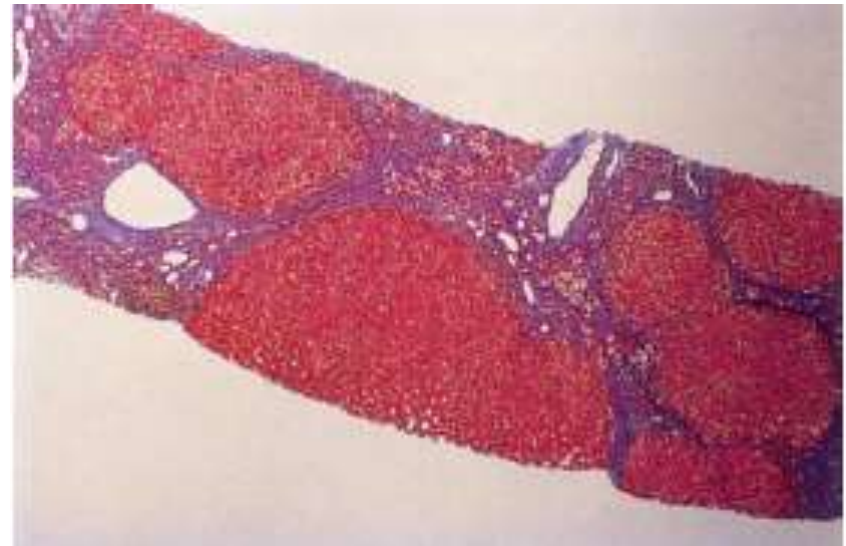


- **Neonatal infection** is not a consequence of transplacental transmission but **occurs intrapartum** and is usually asymptomatic - lifelong chronic carriers of the infection due to the inability to produce anti-HBsAg antibodies
- **Persistent HBV infections** are associated with the development of **hepatocellular carcinoma**

HBV

-pathogenesis-

- Tissue damage is probably a consequence of immune reactions
- Cellular immunity (cytotoxic lymphocytes) is crucial for virus control, but also contributes to liver damage
- Antibodies to HBcAg, which are present in chronic carriers of the disease that show persistent production of hepatitis B virion, are not important in protection against the virus
- Antibodies to HBsAg are protective and are associated with disease resolution !!!
- Inflammation – Necrosis – Fibrosis

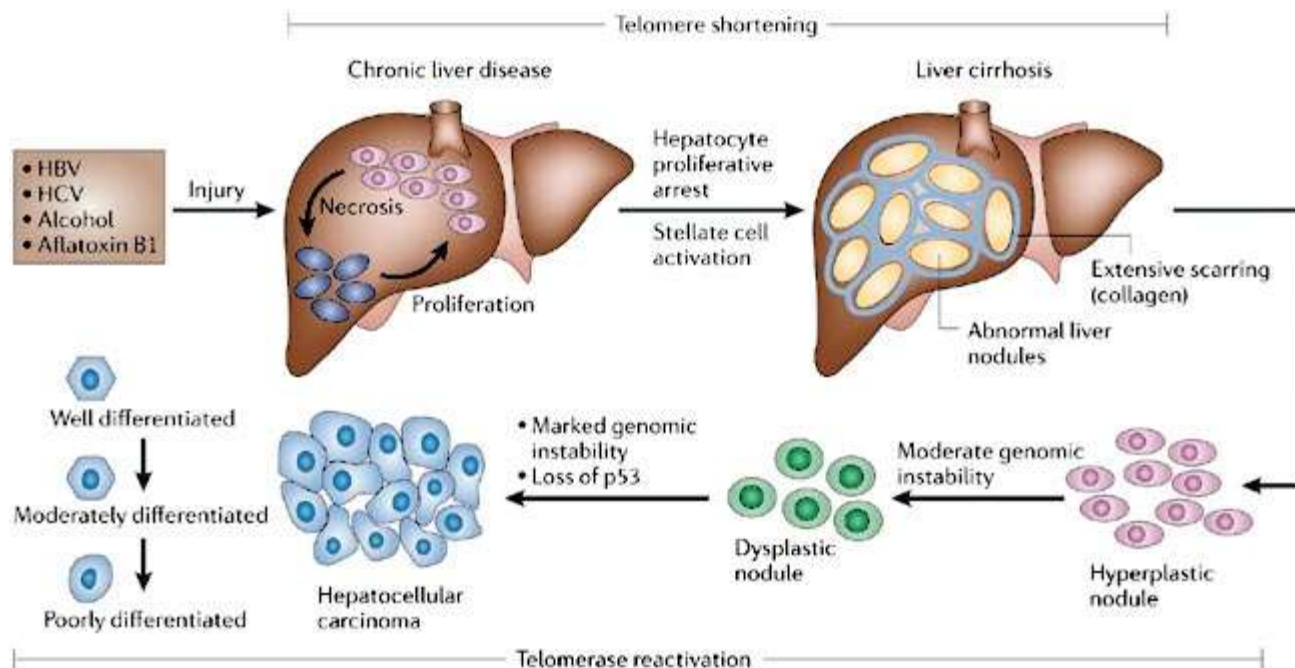


HBV

- pathogenesis -

Integrated HBV DNA can be found **in the cells of almost all hepatocellular carcinomas**

- HBV transcriptional transactivator protein HBx activates Src kinases that may affect carcinogenesis
- HBx protein interacts with the tumor suppressor gene p53, which may play a role in the development of this cancer



HBV

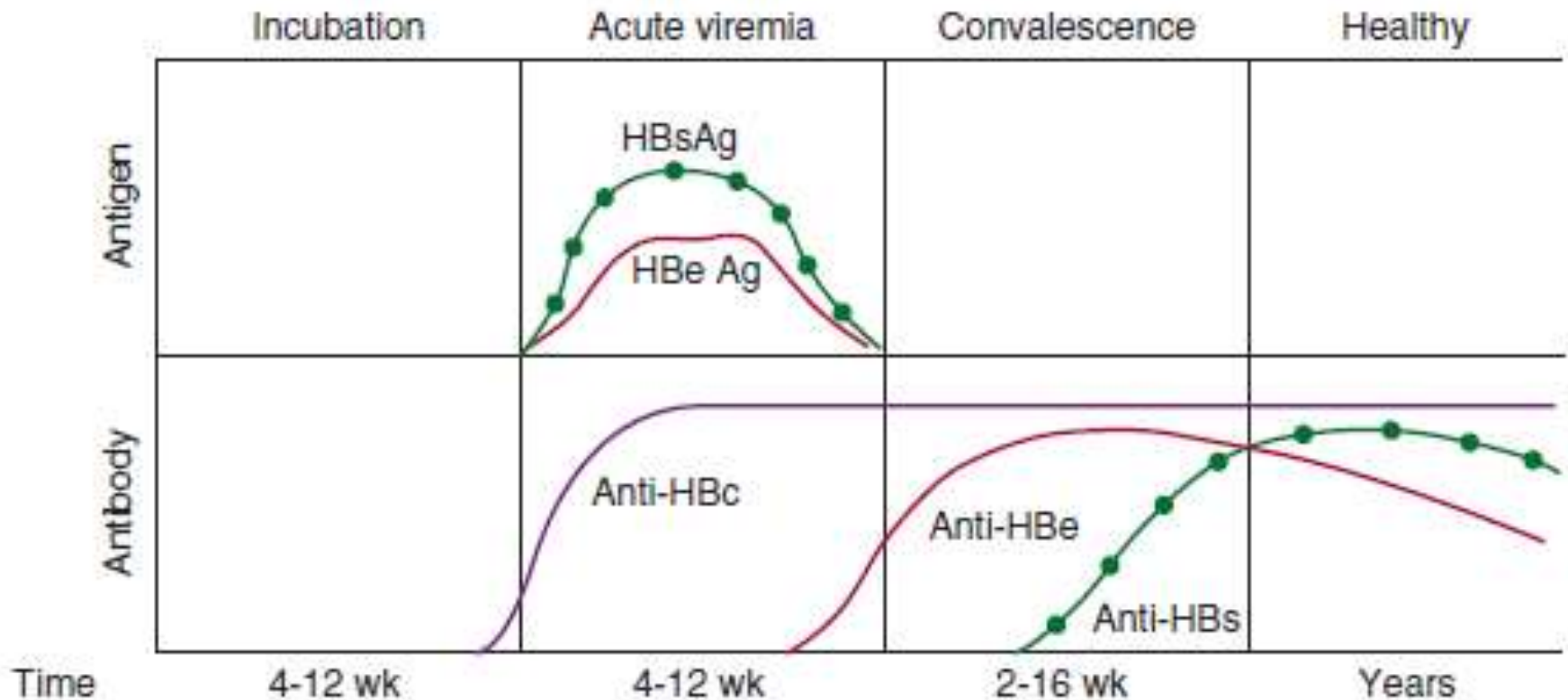
-clinical manifestations-

- Incubation period may be short, up to 30 days, but may last up to 180 days
- Possible clinical forms:
 - **Subclinical**
 - **Acute** (fatigue, loss of appetite, nausea, pain and a feeling of fullness in the upper right quadrant of the abdomen, swelling and pain in the joints, skin rash. With further enlargement of the liver, cholestasis develops and poor stool discoloration, darker urine and jaundice occur)
 - **Fulminant** (extensive hepatocyte necrosis), 1% of cases
 - **Chronic** (constant replication of the virus in the liver and the presence of serum HBsAg), 10% of cases

HBV

-diagnosis-

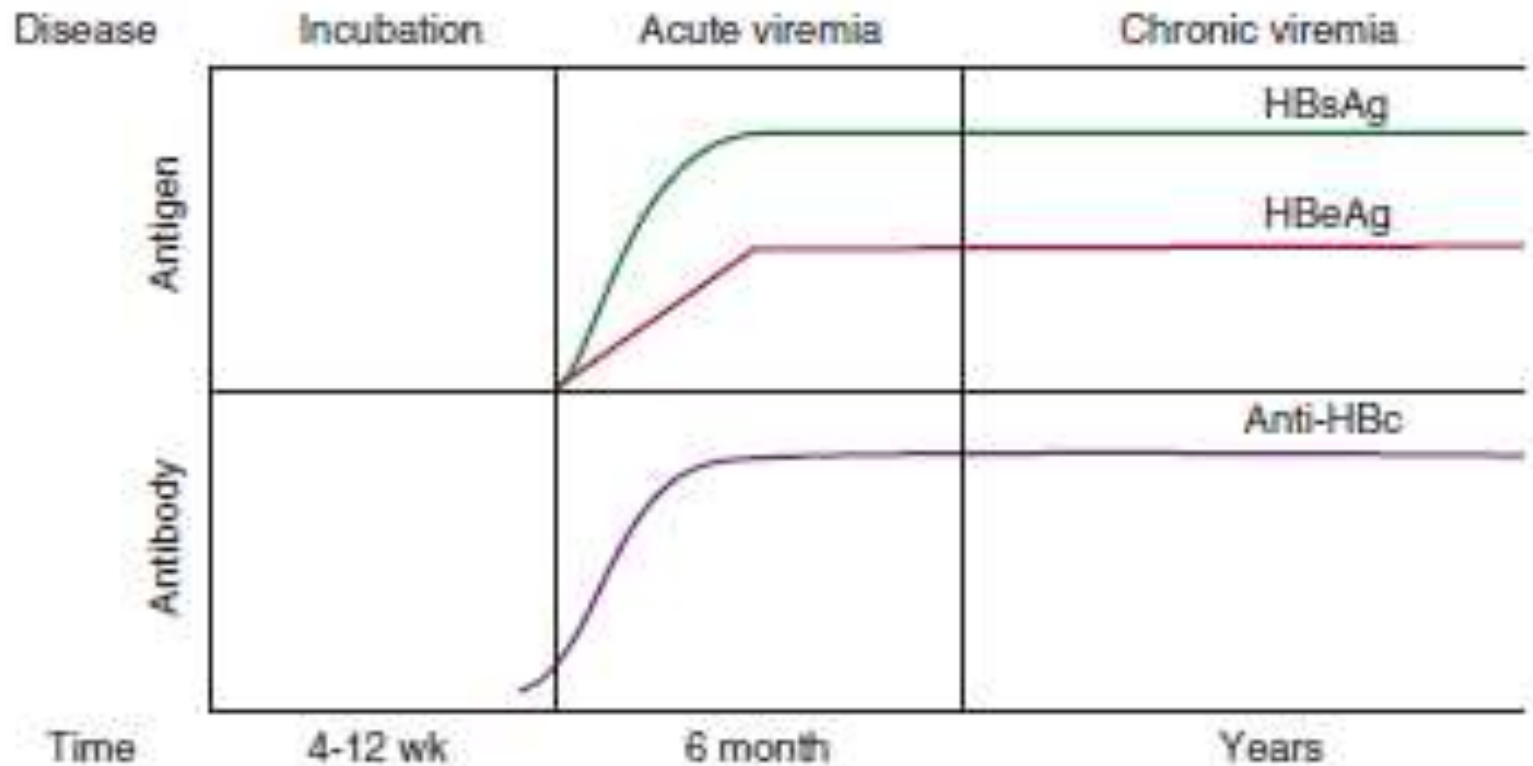
- **Acute infection:** large amounts of HBsAg and HBV DNA in the serum, and **anti-HBc antibodies IgM** (these antibodies disappear 6-12 months from the onset of acute disease)
- The appearance of anti-HBsAg antibodies indicates the elimination of the infection



HBV

-diagnosis-

- **Chronic infection:** detection of serum HBsAg in the absence of anti-HBsAg antibodies



The time of onset of serum antibodies and antigens in chronic hepatitis

HBV

-treatment and prevention-

Treatment:

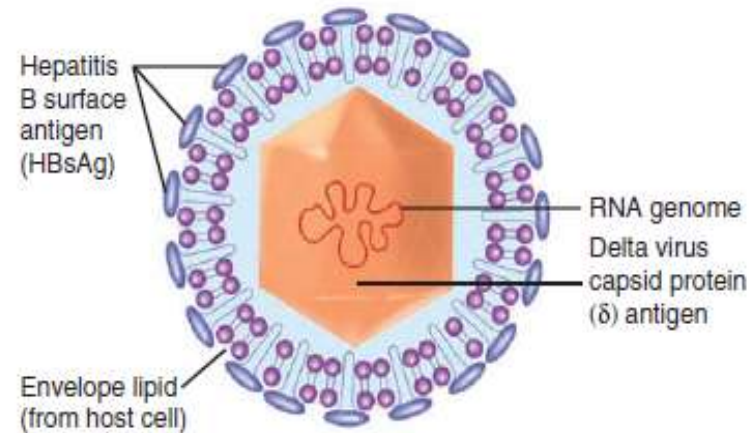
- PEG-IFN- α , lamivudine (HIV reverse transcriptase inhibitor) and nucleoside analogs (entecavir, telbivudine, adefovir) inhibit viral replication and can reduce viral load, but do not play a role in curing HBV infection

Prevention:

- Screening of donor blood and plasma products for the presence of HBsAg and anti-HBcAg significantly reduced the incidence of hepatitis B
- Hiperimmune hepatitis B immunoglobulins, HBIG for passive prophylaxis
- Purified inactivated HBsAg subunit vaccine for active immunization
- The combination of active and passive immunization is a more effective method for the prevention of neonatal infection and chronic carrier state, which is frequent in this case
- Routine testing of pregnant women for the presence of HBsAg is recommended, and in case of a positive finding, newborns should receive HBIG immediately after birth and three doses of vaccine

Hepatitis D virus (HDV)

- A small virus containing a single-stranded circular negative RNA,
- **It requires the presence of HBsAg to be transmitted from person to person and is only found in people with acute or chronic HBV infection**



- Proteins associated with circular RNA form HDV capsid antigen surrounded by HBsAg
- Because HDV does not have its own RNA polymerase, it uses cellular RNA polymerase to synthesize mRNA and genomic RNA.
- Delta capsid antigens are synthesized, associated with HDV circular RNA as it obtains the envelope of the endoplasmic reticulum and Golgi apparatus containing HBsAg

Hepatitis D virus (HDV)

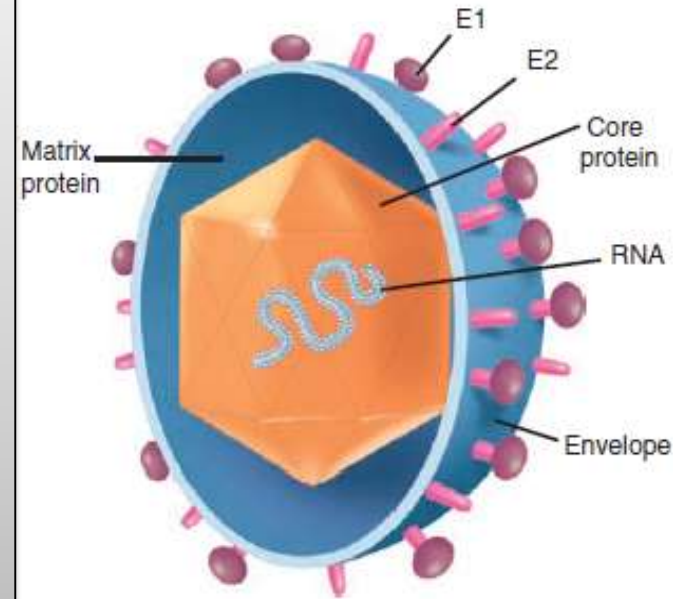
Countries where 10% of people infected with HBV also have HDV infection



- Simultaneous infection with HDV and HBV results in the development of clinical hepatitis that is not different from acute hepatitis A and E, but may manifest as a secondary increase in AST, ALT
- HDV superinfection in people with chronic hepatitis B is characterized by relapse of jaundice and a much higher chance of developing chronic cirrhosis
- Diagnosis of infection is made by detecting IgM or IgG antibodies, or both, to serum delta capsid antigen
- Treatment and prevention are the same as for HBV hepatitis

Hepatitis C virus (HCV)

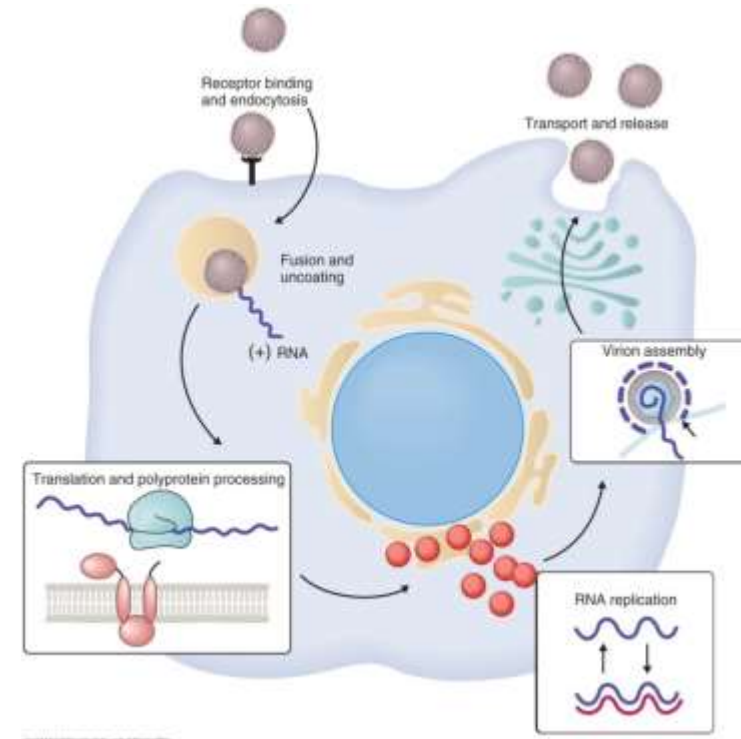
- RNA virus, in the family *Flaviviridae*, genus *Hepacivirus*
- Icosahedral capsid or core (C) protein
- Lipid bilayer envelope with two typical viral glycoproteins E1 (gp31) and E2 (gp70) that interact with receptors and coreceptors on host cells (Antibodies to these glycoproteins are involved in virus neutralization)



- **The HCV genome is very prone to mutations** (E2 glycoprotein) that allow the virus to evade the host immune system and cause chronic persistent infections
- There are at least 11 genotypes and many subtypes of HCV

HCV -replication-

- In the human body, HCV forms a complex with lipoproteins – lipoviroparticle (LVP)
- LVPs bind to hepatocyte proteoglycan heparan sulfate and further to low molecular weight lipoprotein (LDLR) receptors resulting in unproductive infection
- In productive infection, the E2 glycoprotein interacts with the scavenger receptor B and the CD81 molecule; the virus enters hepatocytes by receptor-mediated endocytosis
- Like other positive RNA viruses, HCV replicates in the cytoplasm of infected cells
- RNA-dependent RNA polymerases, structural (C, E1 and E2) and non-structural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) viral proteins are synthesized in the form of polyproteins which are then cleaved to mature proteins by viral and cellular proteases in the cytoplasm



HCV

-epidemiology and the mode of transmission-

- Worldwide, about 150 million people have chronic HCV infection, and 3 to 4 million are infected annually
- The highest prevalence is in the Middle East, especially in Egypt

Mode of transmission:

- HCV is, as HBV, spread **parenterally, through blood** (prior to the introduction of blood screening, transfusion was the main route of transmission for hepatitis C.)
- **Sexually** transmitted disease (less frequently than HBV)
- Transmission **by contaminated needles** (40% of cases)
- **Vertical transmission** during childbirth

HCV

-pathogenesis-

- HCV infects B and T lymphocytes and peripheral blood monocytes and is transferred to the liver
- The replication rate in hepatocytes is very high
- **Liver damage** is partially a consequence of **direct cytopathic effect of the virus** and mainly **the immune response to the virus**
- **Immune complex formation:** arthritis, vasculitis and glomerulonephritis

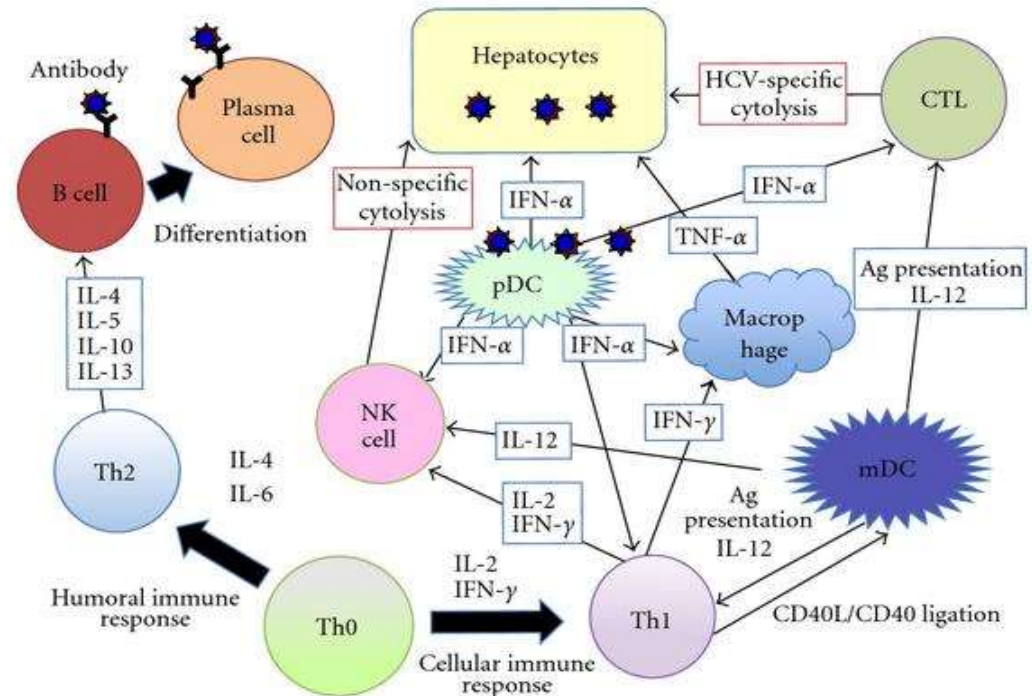
Impaired cellular immune response significantly increases the risk of developing a chronic form of the disease

Chronic HCV disease bears a risk for developing **liver cirrhosis** and **hepatocellular carcinoma**

HCV

-immune response-

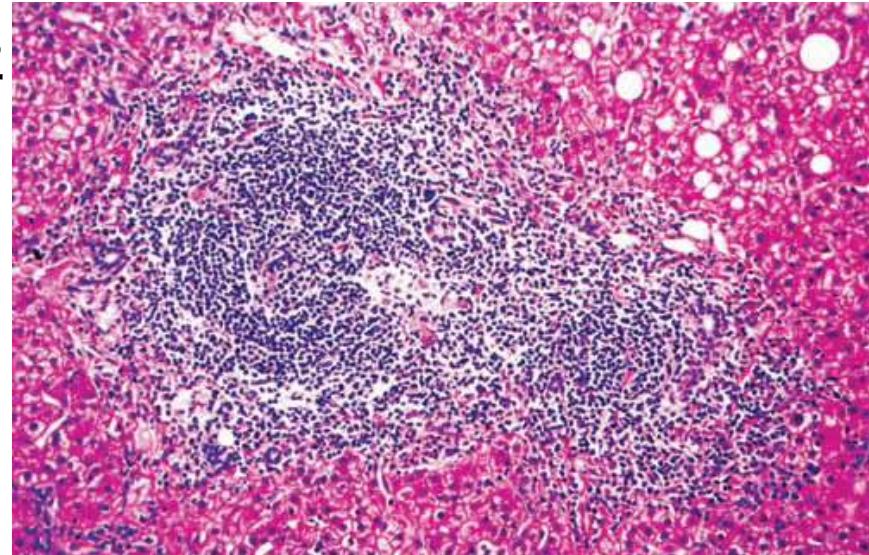
- **Mutations** of E1 and E2 proteins enable the virus to **evade humoral immune response** and establish a persistent infection
 - **Anti-HCV antibodies** – immune complex formation
 - Any deficiency of cytotoxic lymphocyte responses is associated with the occurrence of chronic infection
 - Chronic infection is probably due to an imbalance between Th1 and Th2 cytokines
-
- **Pronounced production of TNF- α** causes hepatocyte damage and chronicity
 - **Genetic factors** contribute to the development of chronic infections: the DR5 allele is associated with a lower incidence of cirrhosis, and the HLA A2 restricted response of cytotoxic lymphocytes is shown in 97% of people with chronic hepatitis C.



HCV

-clinical manifestations-

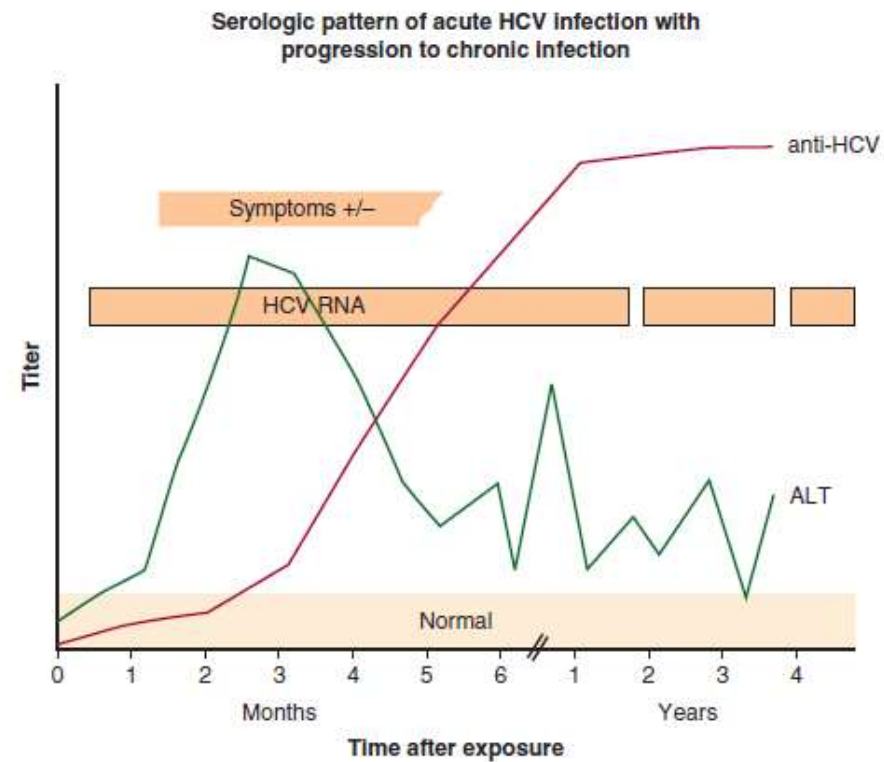
- Incubation period for HCV is 6 to 12 weeks
- HCV **generally does not cause clinically evident acute disease**, mild chronic hepatitis that eventually leads to liver failure develops in about 25% of the infected
- Fulminant HCV hepatitis is quite rare
- The median time from infection to the development of chronic hepatitis is 10 to 18 years
- **Cirrhosis** and **hepatocellular carcinoma** are late sequelae of chronic hepatitis



HCV

-diagnosis, treatment and prevention-

- The humoral immune response to HCV does not develop in acute disease for the first three weeks after the onset of clinical symptoms, so RT-PCR is the method of choice for HCV detection
- Combination therapy with IFN- α and ribavirin is the treatment of choice for chronic forms
- Blood product screening is a very important prevention measure
- Prophylactic use of intravenous immunoglobulins does not provide protection against hepatitis C



Hepatitis E virus (HEV)

- Positive, single-stranded RNA, icosahedral nucleocapsid, nonenveloped virus
- It is transmitted by **fecal-oral route**, usually by contaminated drinking water, but transmission by ingestion of infected animal products is also possible. Transmission from animals to humans, by **transfusion** of infected blood products, as well as **vertical transmission** are also possible.
- The incubation period for hepatitis E is approximately 40 days
- The infection is very often **subclinical**, and symptomatic infection is characterized by an **acute illness that can be fatal**, especially in **pregnant women**
- Diagnosis is made by detecting specific IgM antibodies in serum and by detecting viral RNA by RT-PCR analysis
- There is no specific treatment

Hepatitis G virus (HGV / GBV-C)

- The RNA virus
- belongs to the Flaviviridae family, as does the hepatitis C virus.
- It has no clearly proven role in the development of chronic hepatitis or cirrhosis.
- It is often detected in individuals who are co-infected with HBV, HCV, or HIV.

Hepatitis G virus (HGV / GBV-C)

Modes of transmission

- Blood and blood product transfusions
- Intravenous drug use
- Sexual transmission
- Vertical transmission from mother to child
- Infection is most often asymptomatic and in most cases does not lead to significant liver damage

Hepatitis G virus (HGV / GBV-C)

Diagnostics

- Detection of viral RNA by PCR
- Serological tests have limited value
- Often discovered incidentally during testing for other viral hepatitis

HUMAN RETROVIRUSES

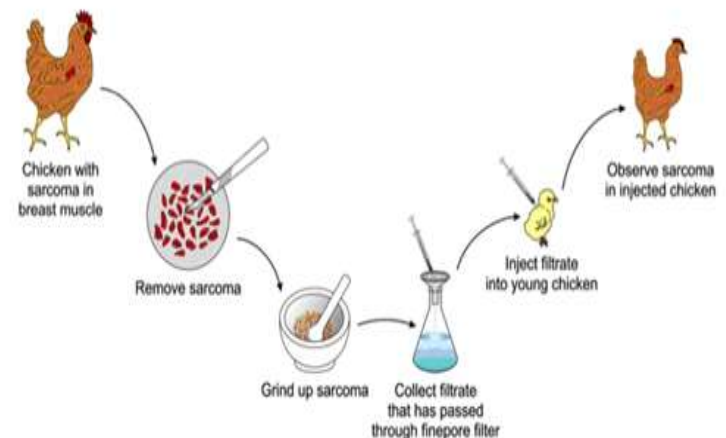
HTLV-1	HTLV-2
HIV-1	HIV-2

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**

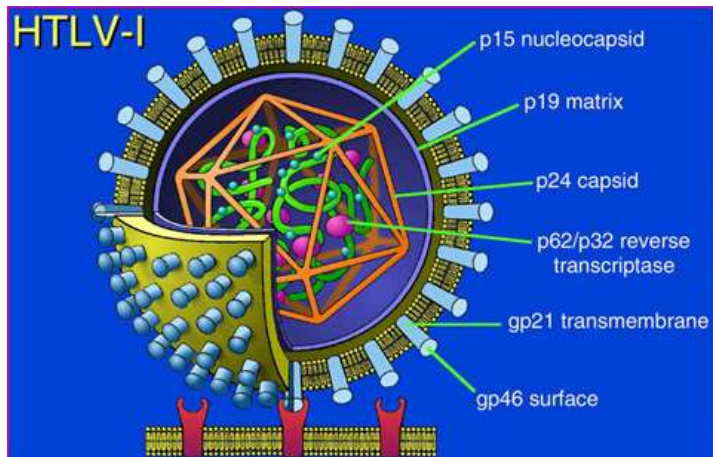


**Synthesis of complementary DNA that eventually
integrates into the genome of the host cell
(provirus), a transitional form in the replicative
cycle of the virus**

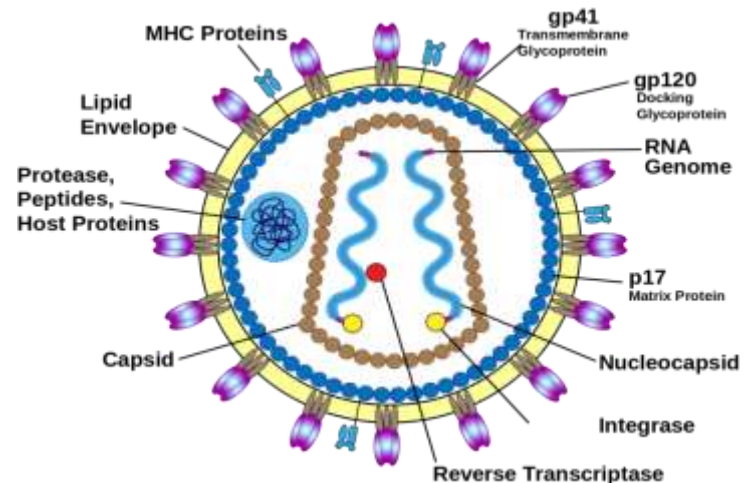
History of retrovirology

- 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

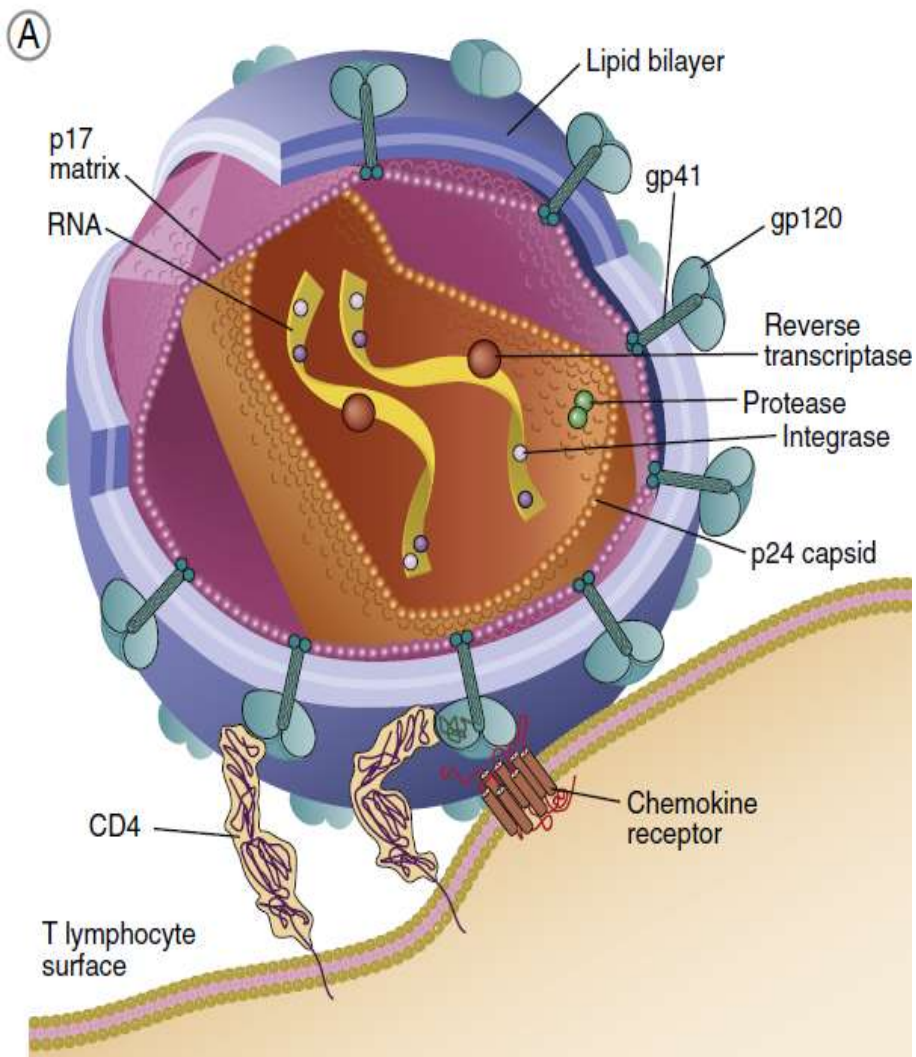


HIV-1 and HIV-2



HIV

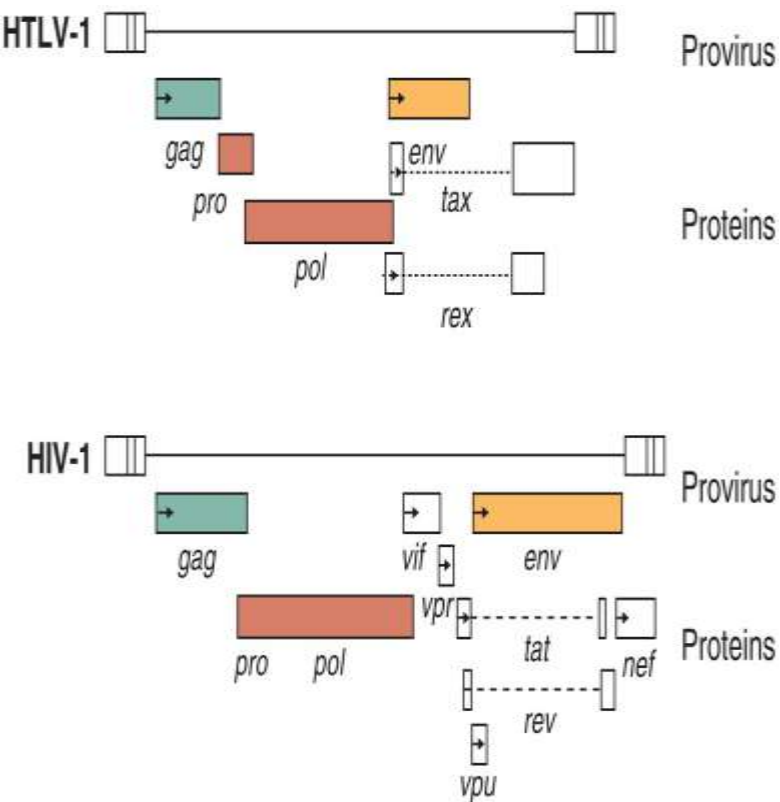
Structure of the virion



- 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



Copyright © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

Four viral genes are essential for retrovirus replication:

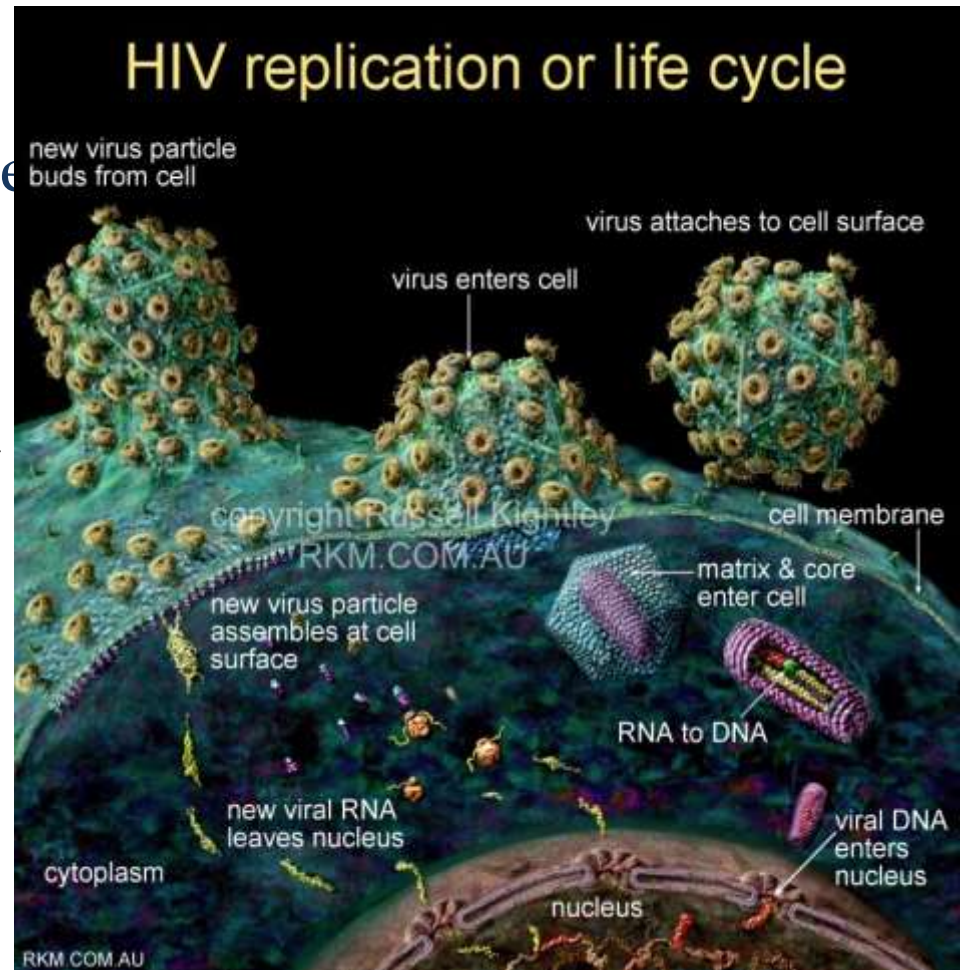
- **Gag gene** encodes several core (Gag) proteins of the viral envelope
- **Pol gene** encodes **reverse transcriptase** or RNA-dependent DNA polymerase (Pol), an enzyme responsible for genome replication, as well as **integrase**, an enzyme required for the integration of viral DNA into the host cell 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

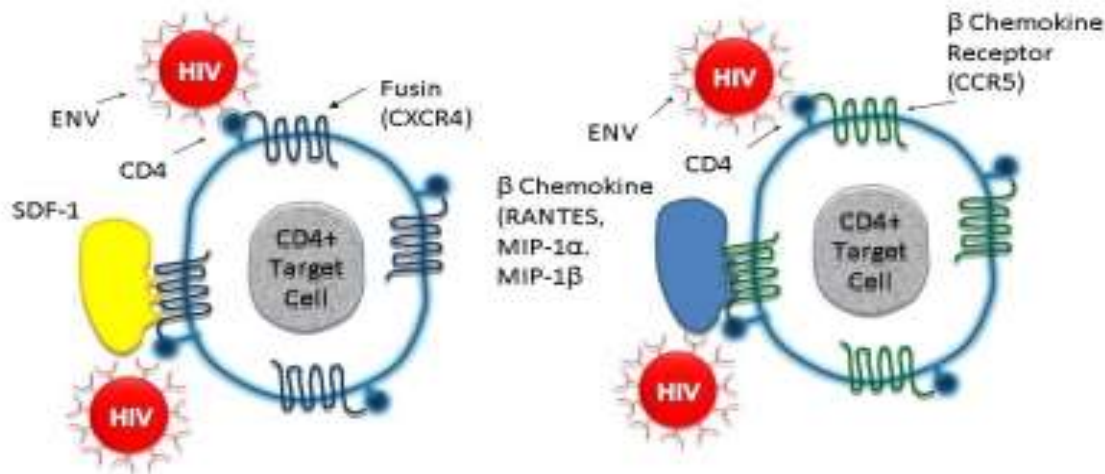


HIV

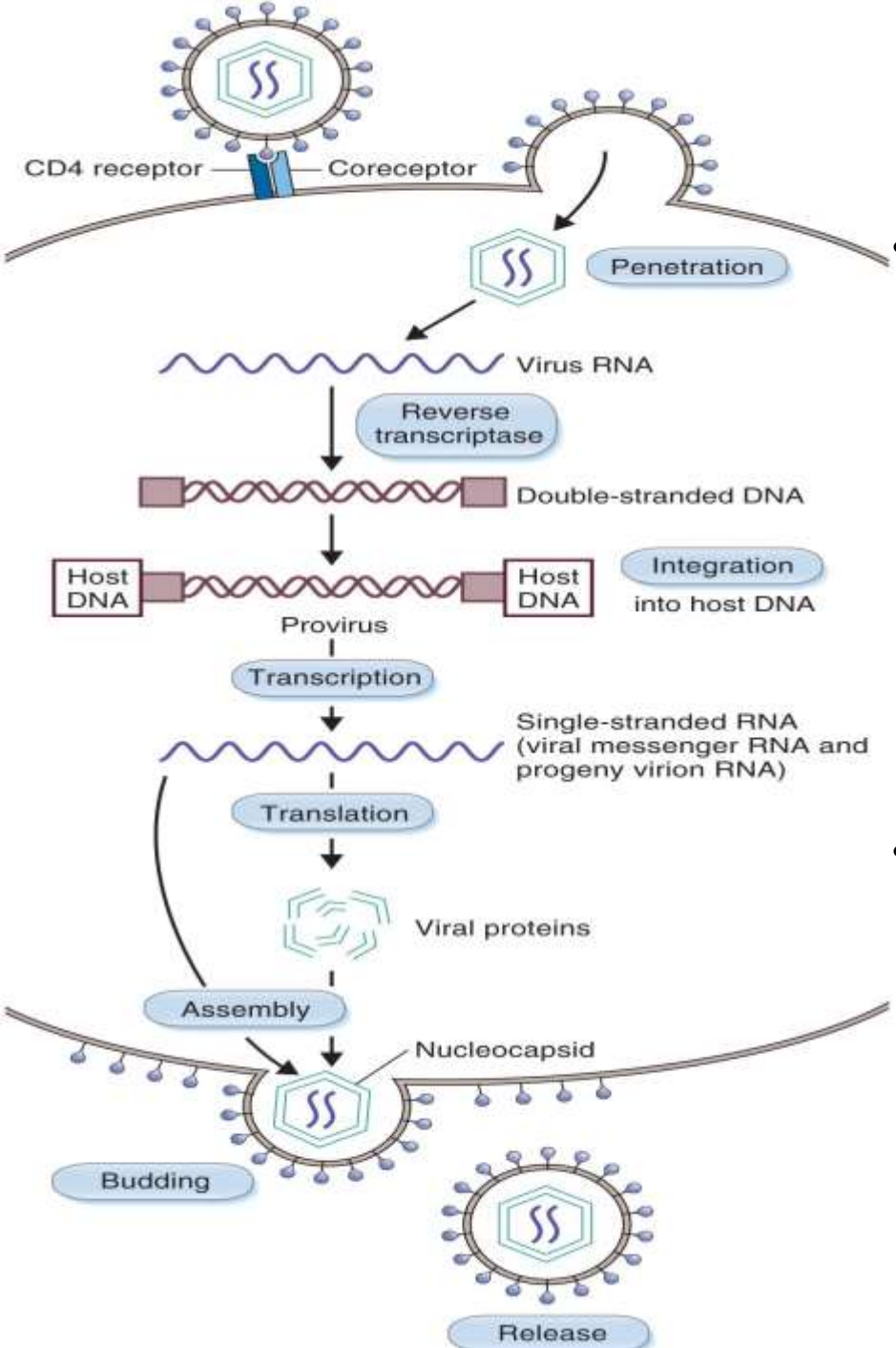
-spread in the host organism-

- 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

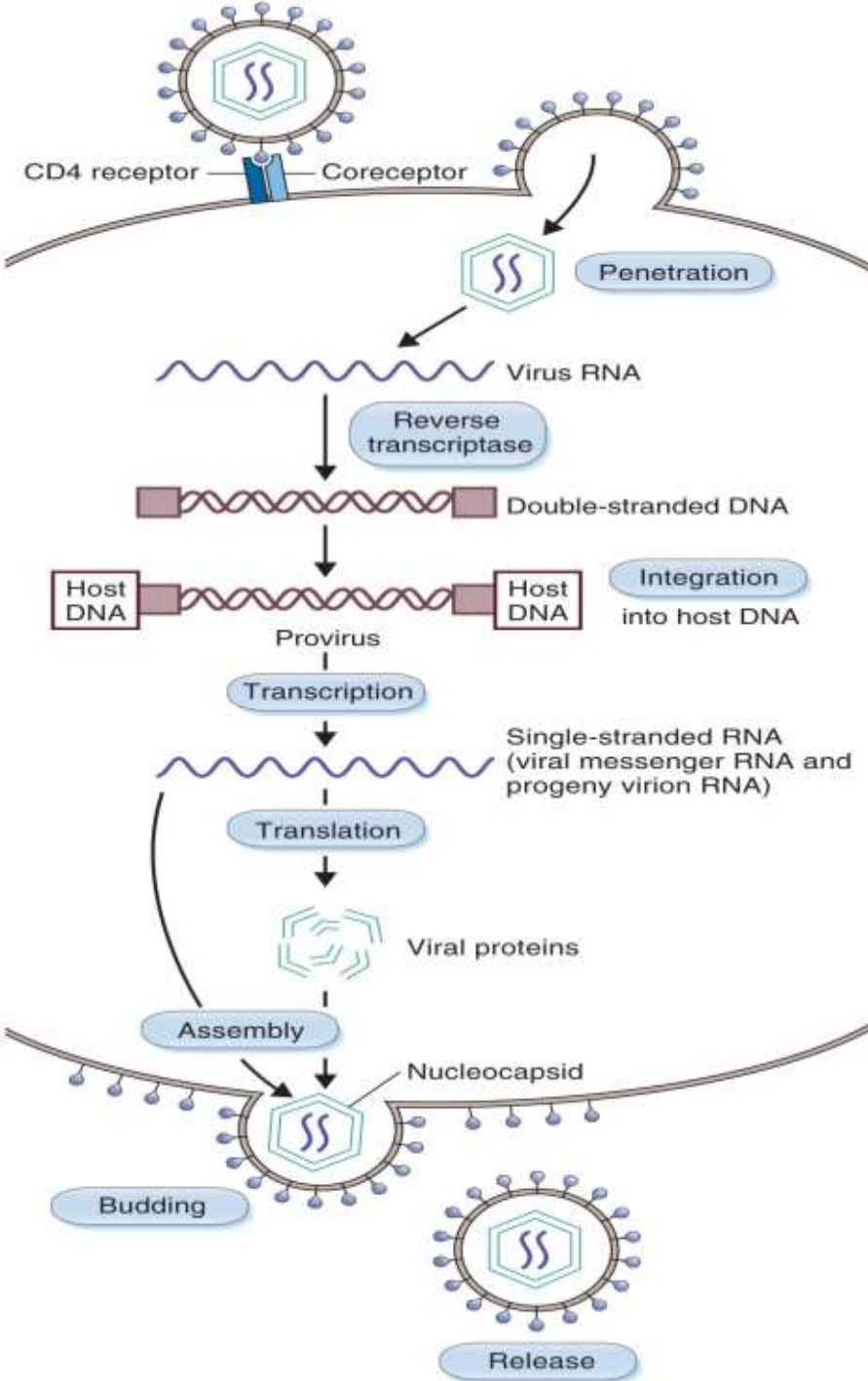


HIV -replication-



- 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-

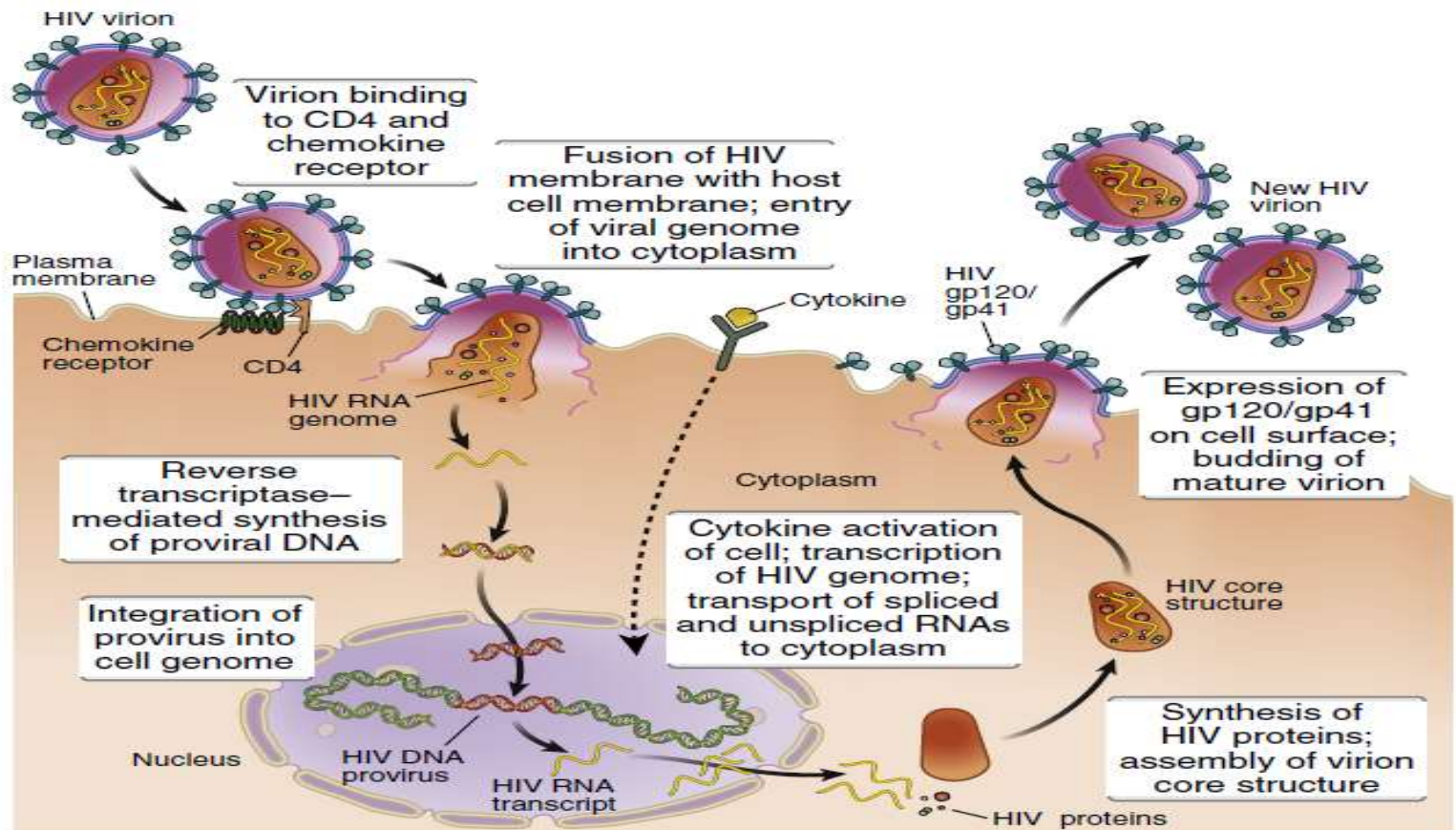


- **DNA synthesis : Reverse transcriptase** is the enzyme responsible for the synthesis of the double DNA strand that is complementary to the RNA molecule of the viral genome. The parts at the ends of the genomic RNA are copied twice, so that at each end of the newly synthesized DNA there are specific 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-

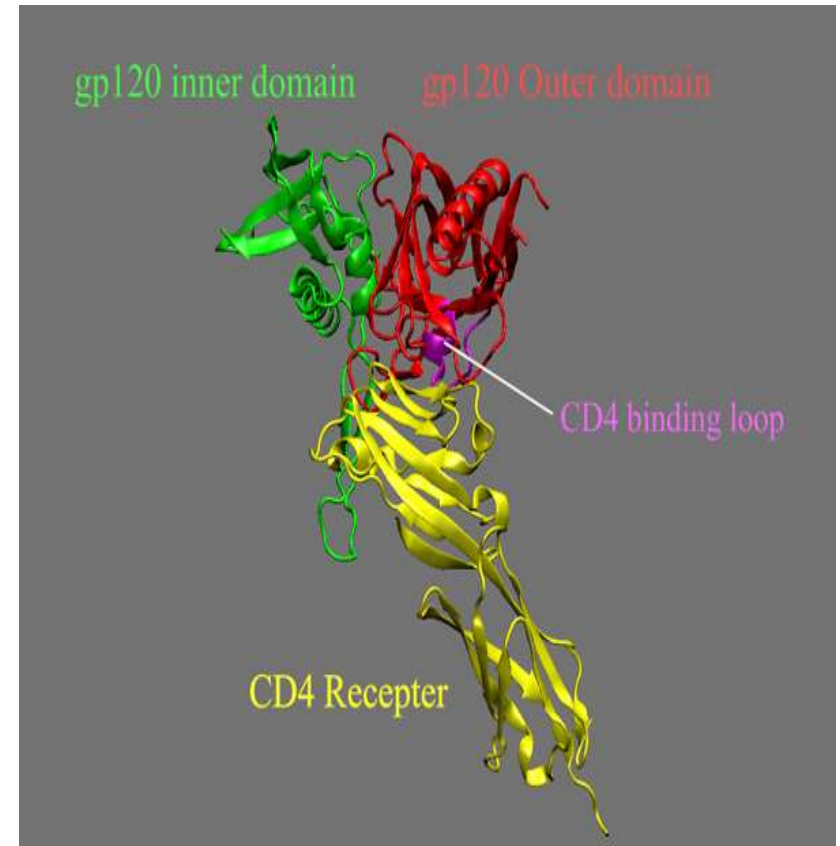
HIV evades the host's immune response by altering large surface antigens

- 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**

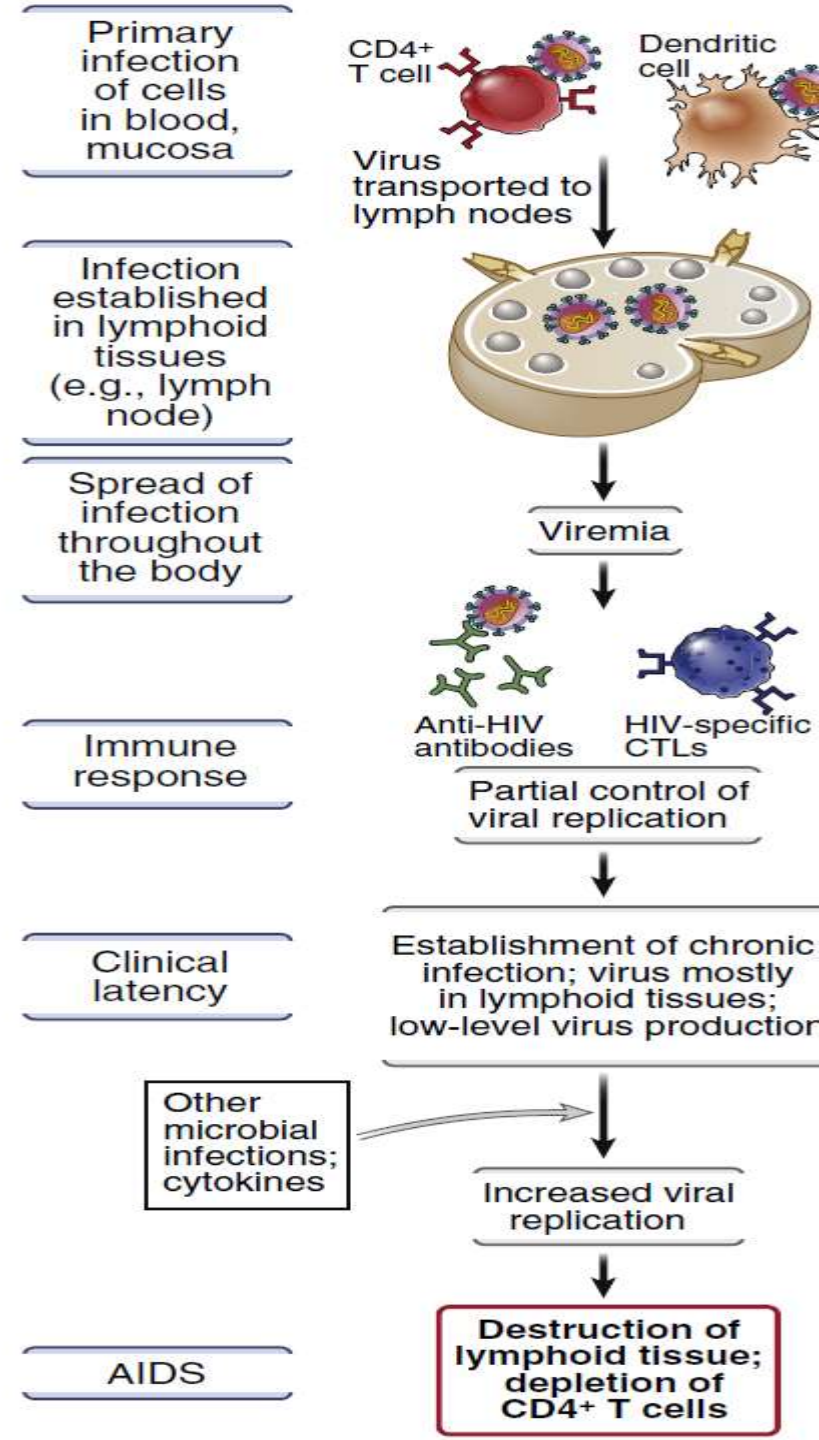


HIV

- disease pathogenesis -

Infection and depletion of helper T lymphocytes

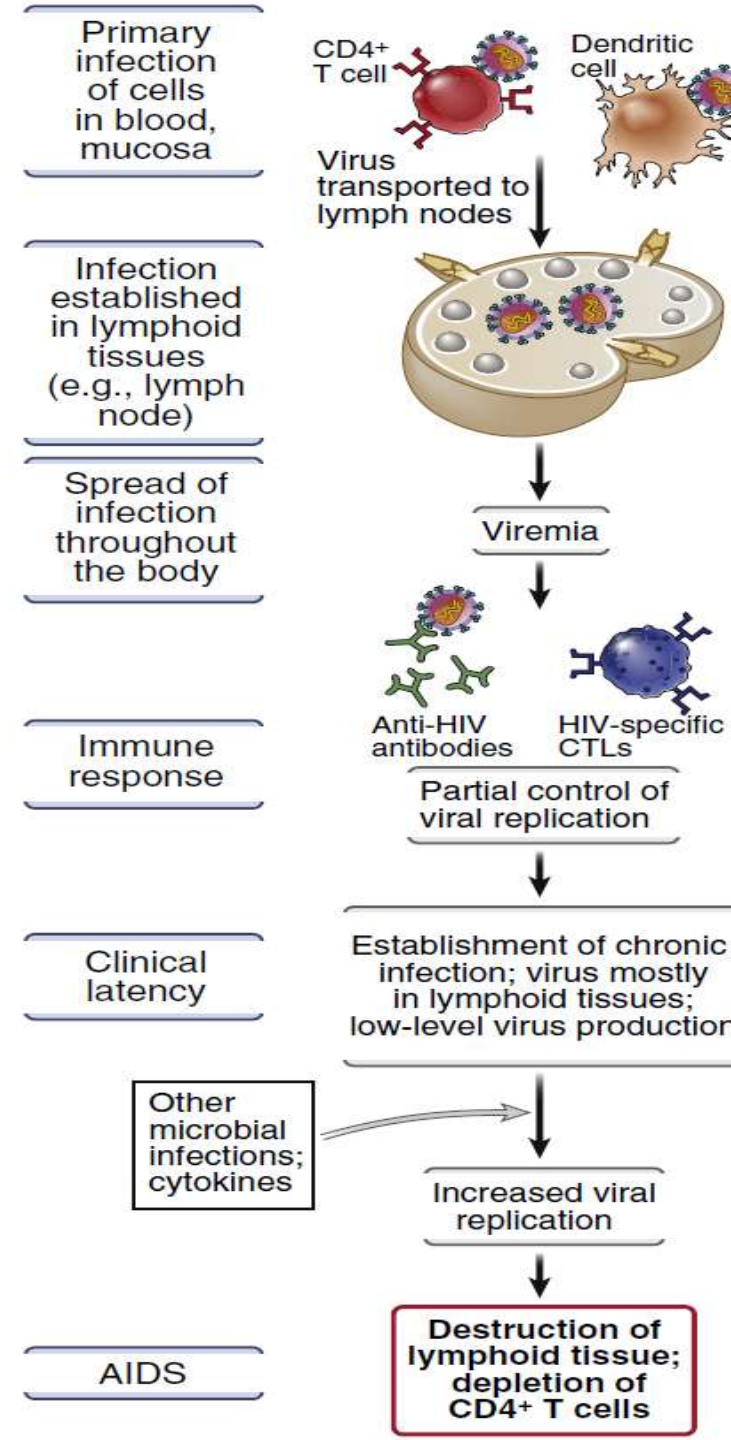
- The CD4 molecule can also be found on the membranes of other cells: monocytes and macrophages (disorders of phagocytosis), NK cells, some B lymphocytes, glia cells and Langerhans cells (important for the establishment of infection)
- These cells can also be infected by the virus and be destroyed in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



Tissue damage

Acute HIV infection

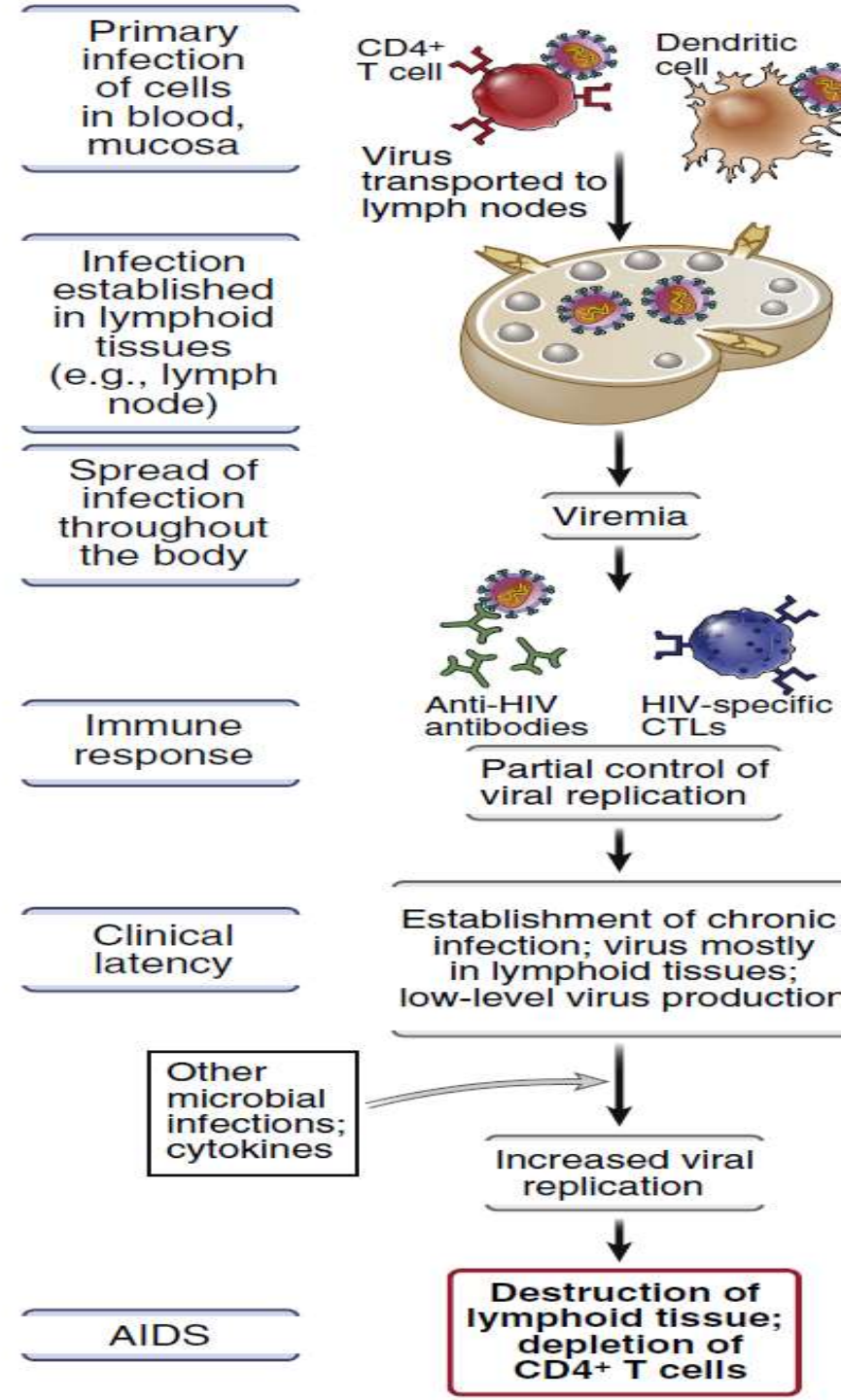
- The virus infects cells that express the CD4 molecule in local mucous membranes, and then rapidly establishes infection in local lymphatic tissues.
- During the next few days, **local replication** is limited to cells present at the site of viral entry. In most cases, the number of local susceptible 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.



...

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

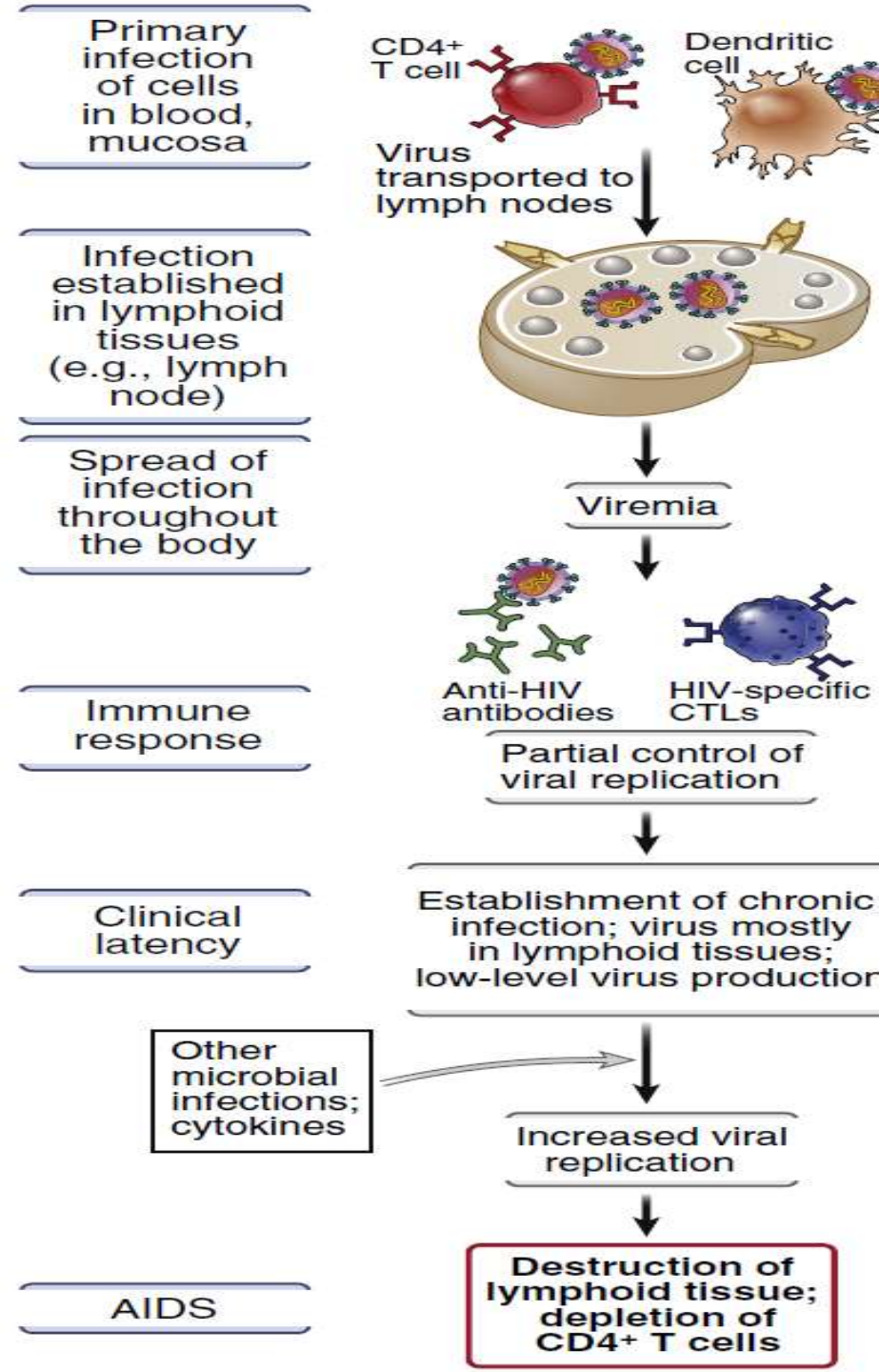
In the first weeks after the onset of infection, specific cytotoxic T lymphocytes appear in the peripheral blood and lymph tissue, and soon after, neutralizing antibodies can be detected in the plasma. During this period of rapid viral replication, the lifelong process of generating viral diversity is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



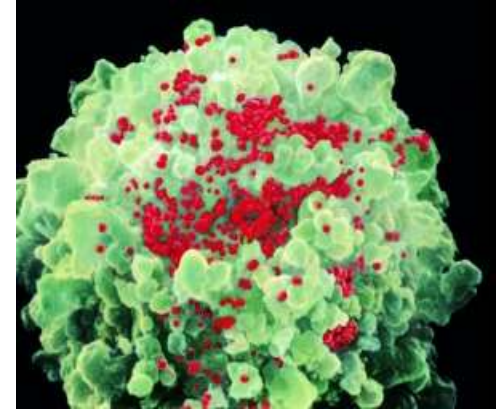
...

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

Here is what your T-cell count can tell you

**More than 500
T-cells/mm³**

Your immune system is
considered normal



**200-500
T-cells/mm³**

Your immune system may
be weakened



**Less than 200
T-cells/mm³**

Your immune system is
severely weakened.
You are at high risk for
getting an opportunistic
infection – an infection that
develops only when the
immune system is weak



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

Acquired Immunodeficiency Syndrome (AIDS)

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

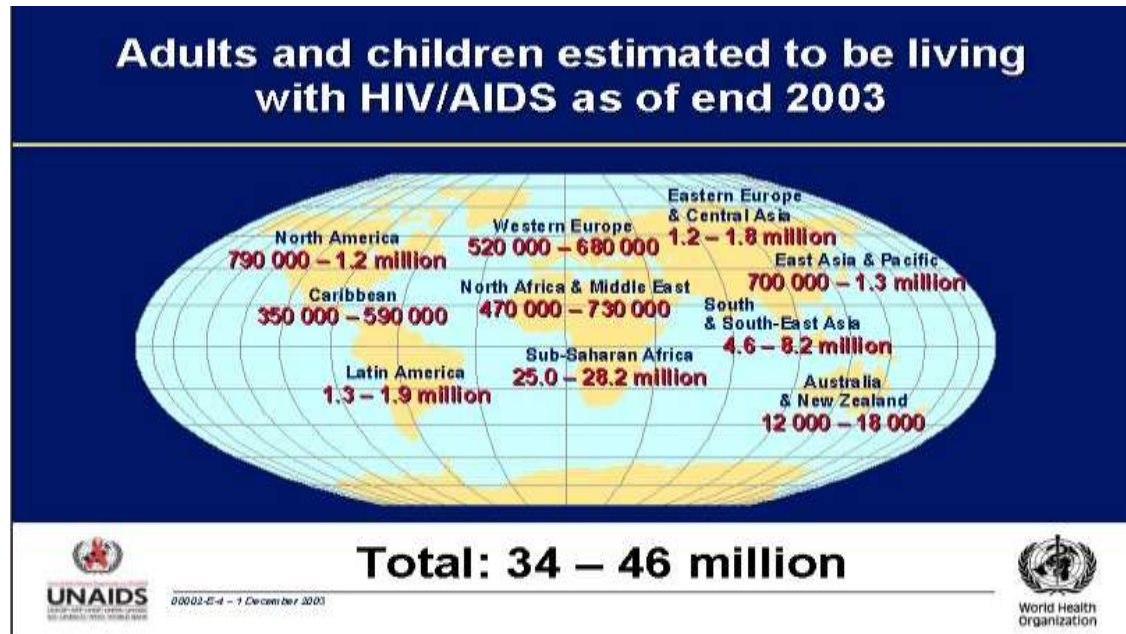
**it is a deadly disease
and most of its devastating symptoms are not the
result of the direct action of the causative agent of
the disease**

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.

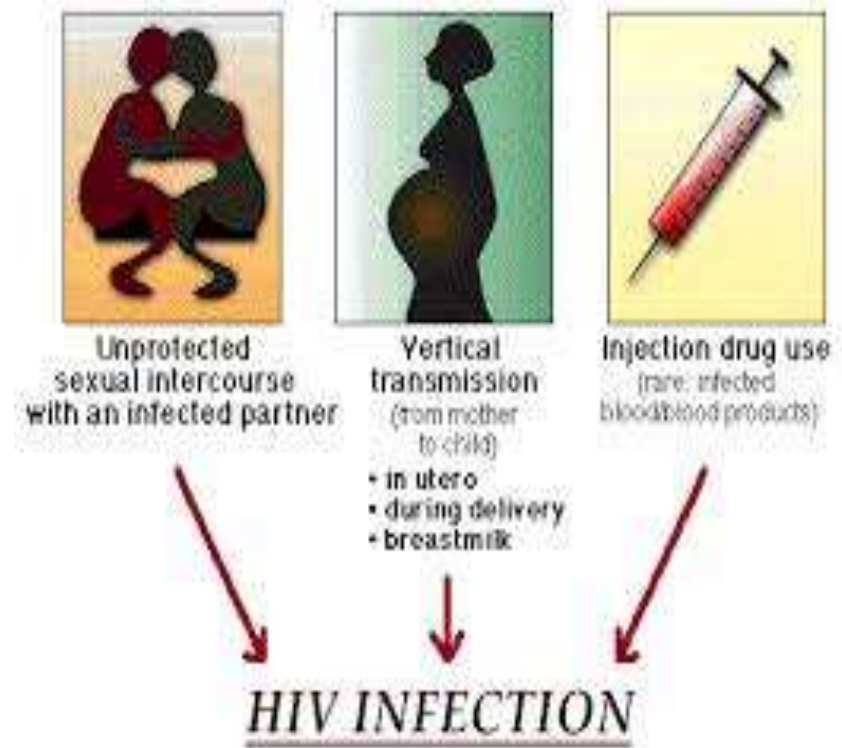


- Unfortunately, only 10% of people living with HIV in the world have access to antiretroviral therapy

HIV transmission

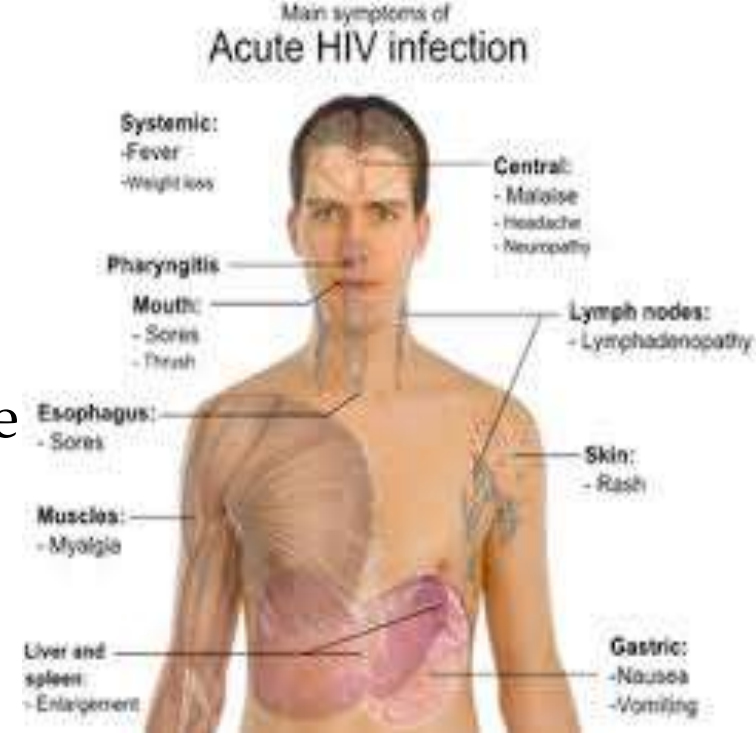
HIV is primarily transmitted by direct inoculation of infected blood or body fluids into the host's body

- 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.

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

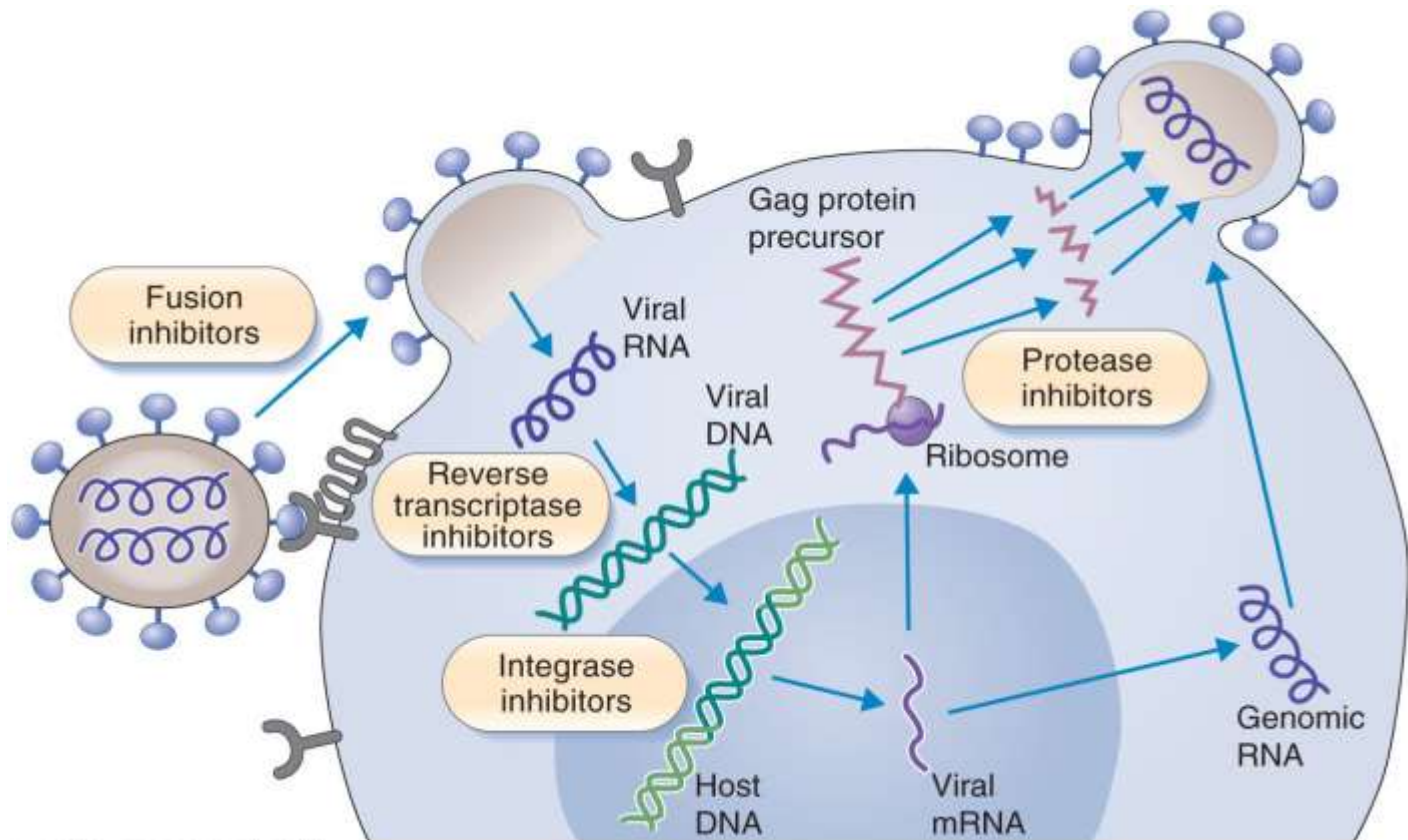
Progression of infection to AIDS

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

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

Prions

Subacute spongiform encephalopathy

Prions

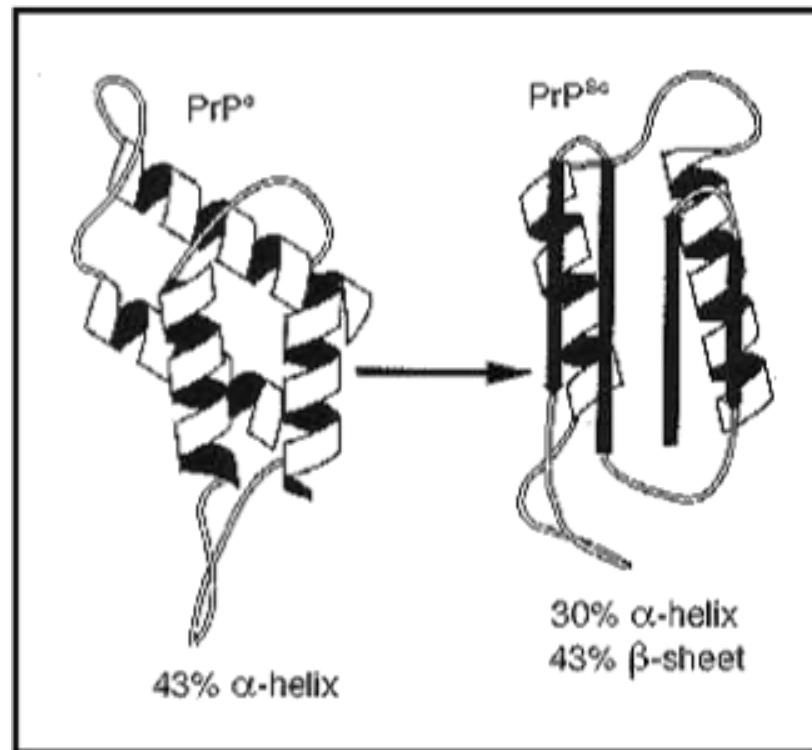
- *Stanley Prusiner* received the Nobel Prize in 1997 for his work on the identification and role of prions in disease

A prion is a small infectious particle of protein structure,
diameter 5-100 nm or less

- It cannot be inactivated by procedures that destroy nucleic acids
- It is resistant to ionizing radiation, cooking and most disinfectants
- It can remain viable in formalin-fixed brains for many years
- It cannot grow in cell culture

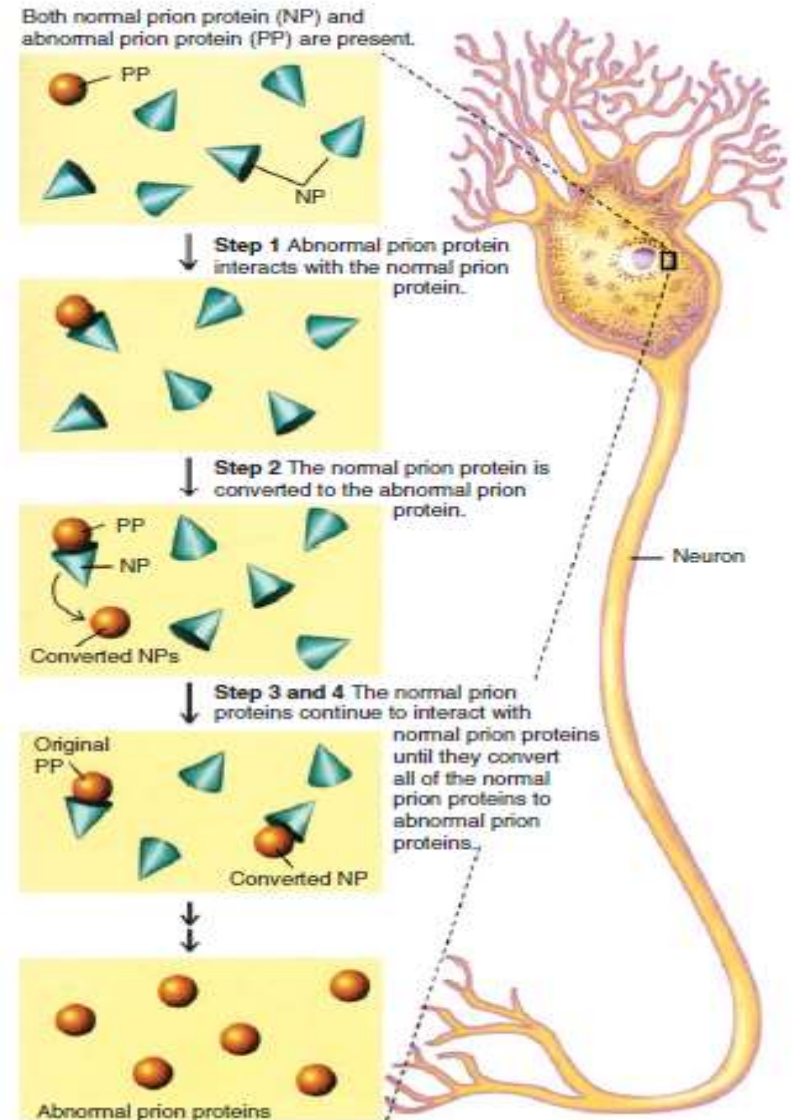
Prions

- A prion consists only of the protein encoded by the normal cellular gene, PrP, in the brain (the gene is located on chromosome 20). The protein designated PrP^c is a **protein converted to a disease-causing form by post-translational modifications that change its conformation.**
- The altered protein is called PrP^{sc}



Prions

- Changing the protein conformation also affects the formation of aggregates that form amyloid-like structures
- In extracts of the brains of animals suffering from these diseases, there is an abnormal form of protein that is not found in normal animals
- PrP^{sc} is responsible for transmission of infection



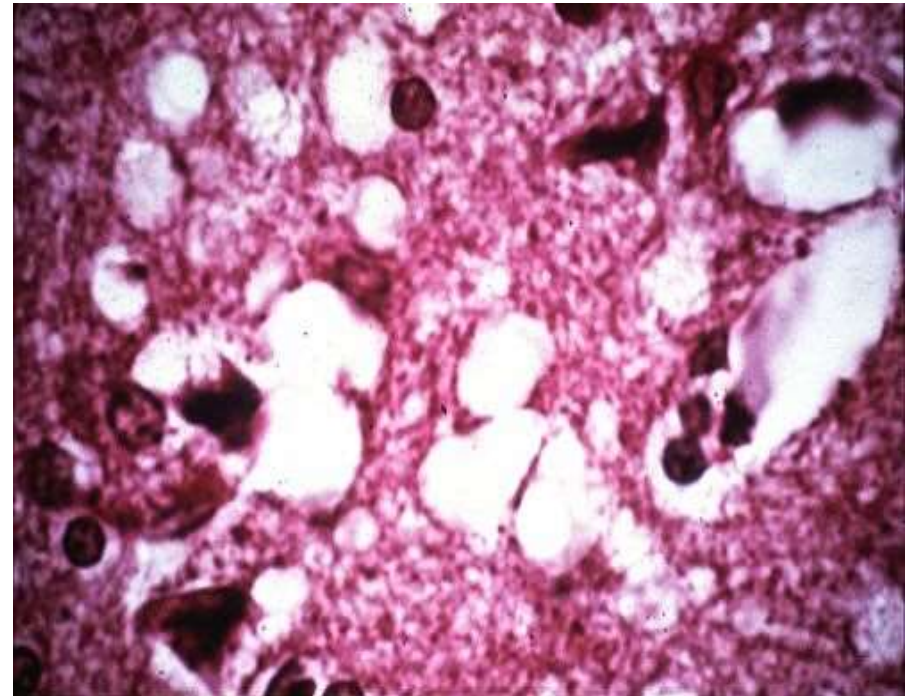
Prion diseases

- Prions are etiological agents that can be **inherited**, **infectious** or occur **sporadically**
- The pathogenesis of this disease is not well understood
- Pathological and clinical features are similar (variable neuronal damage and astrocyte proliferation)
- The disease is designated as **transmissible spongiform encephalopathy** due to **vacuolar changes occurring in the cortex and cerebellum**
- Incubation lasts for months or years, and the disease ends fatally

Prion diseases	
People	Animals
<i>Creutzfeldt-Jakob</i> disease	ШАП (ОВЦЕ)
Variant of <i>Creutzfeldt-Jakob</i> disease	Transmissible Mink Encephalopathy
Kuru	Bovine spongiform encephalopathy
Fatal familial insomnia	

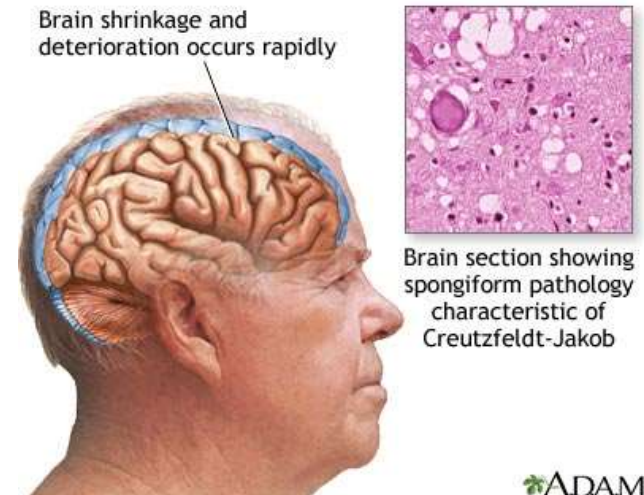
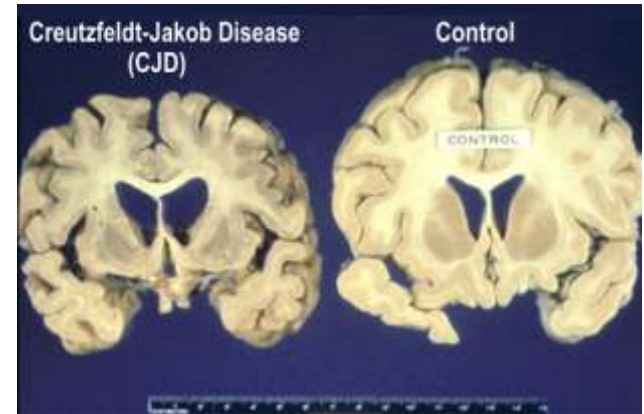
Kuru

- A progressive neurological disease observed in New Guinea
- Symptoms and signs include ataxia, hyperreflexia, spasticity, progressive dementia, and death
- Changes occur only in the CNS in the form of diffuse degeneration of neurons and spongy changes in the cortex of the cerebrum and basal ganglia, without an inflammatory response
- Inoculation of infected brain tissue in primates produced disease that had similar neurological symptoms and pathological changes after an incubation period of approximately 40 months
- Clinically, the disease developed 4 to 20 years after exposure
- Since cannibalism has been eradicated in New Guinea, so has the Kuru



Creutzfeldt-Jakob disease

- It occurs worldwide with an incidence of 1 per million people per year
- **The mode of transmission is unknown**, it occurs sporadically in 85% of cases, and familial in 15% of cases
- Infection can be transmitted through dura mater and corneal **grafts**, **contact with contaminated electrodes and instruments** used in neurosurgical procedures, and **growth hormones** derived from pituitary glands.
- It is most often seen in the 6th and 7th decades of life
- The initial clinical manifestations are changes in cerebral functions, forgetfulness and disorientation progressing to severe dementia and development over 4-7 months, followed by paralysis, pneumonia and death.



Creutzfeldt-Jakob disease -prevention -

- There is a small risk of hospital infections
- Stereotaxic neurosurgical instruments, especially those used in individuals with undiagnosed dementia, should not be retrieved
- Organs from people with undiagnosed neurological diseases should not be used as transplants
- Growth hormone from human tissue is replaced by recombinant proteins
- Recommendations for disinfection of potentially infectious material

Mad cow disease and variant of *Creutzfeldt-Jakob disease*

- The disease was discovered in 1986 when a huge number of cows in England became ill
- The prion can be transmitted to humans by **ingesting** the brain or bone marrow of infected beef (it is resistant to cooking).
- So far, about 100 people have died from this disease
- It was mainly represented in younger people where the initial symptoms were **psychiatric which progressed to neurological changes and dementia.**
- Death occurred in an average of 14 months



Fatal familial insomnia

- It occurs in adults and ends in death within 1 to 2 years
- Hereditary prion disease, a mutated PrP gene is inherited
- It is manifested by sleep attacks and disorders of the autonomic nervous system (excessive lacrimation, hypertension, episodes of hyperventilation, abnormal basal temperature, dysarthria, diplopia, ataxia...)
- The infectious agent can be transferred to experimental animals

