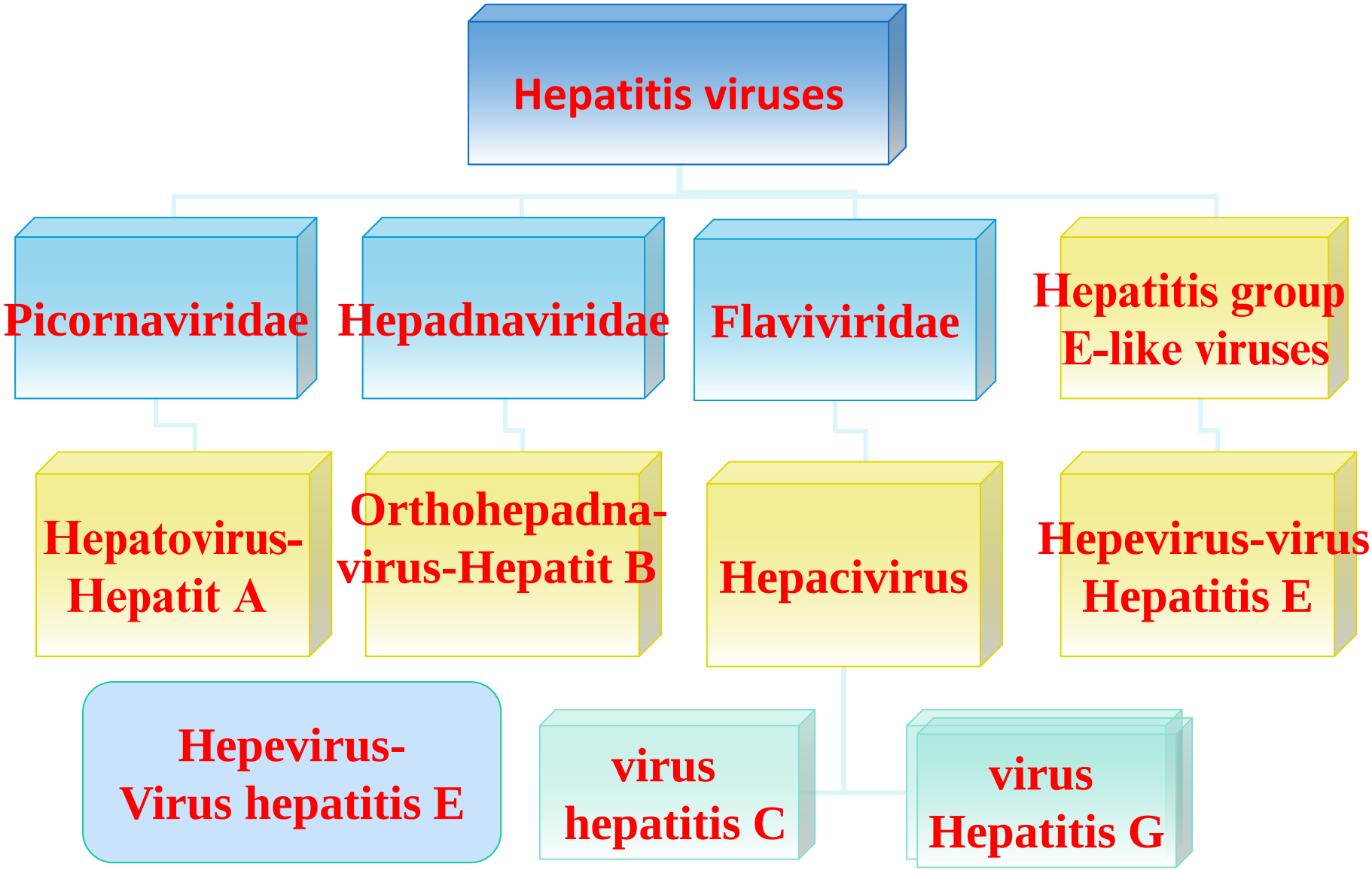
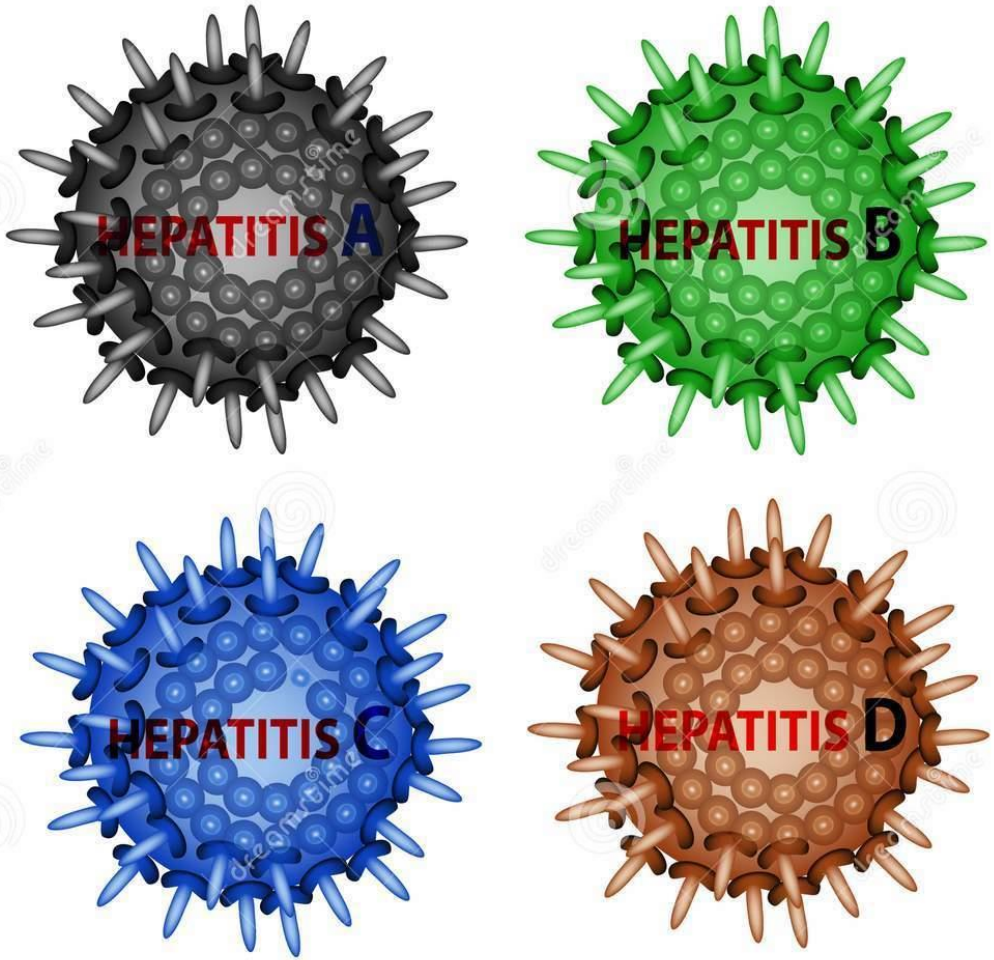
Lesson 25

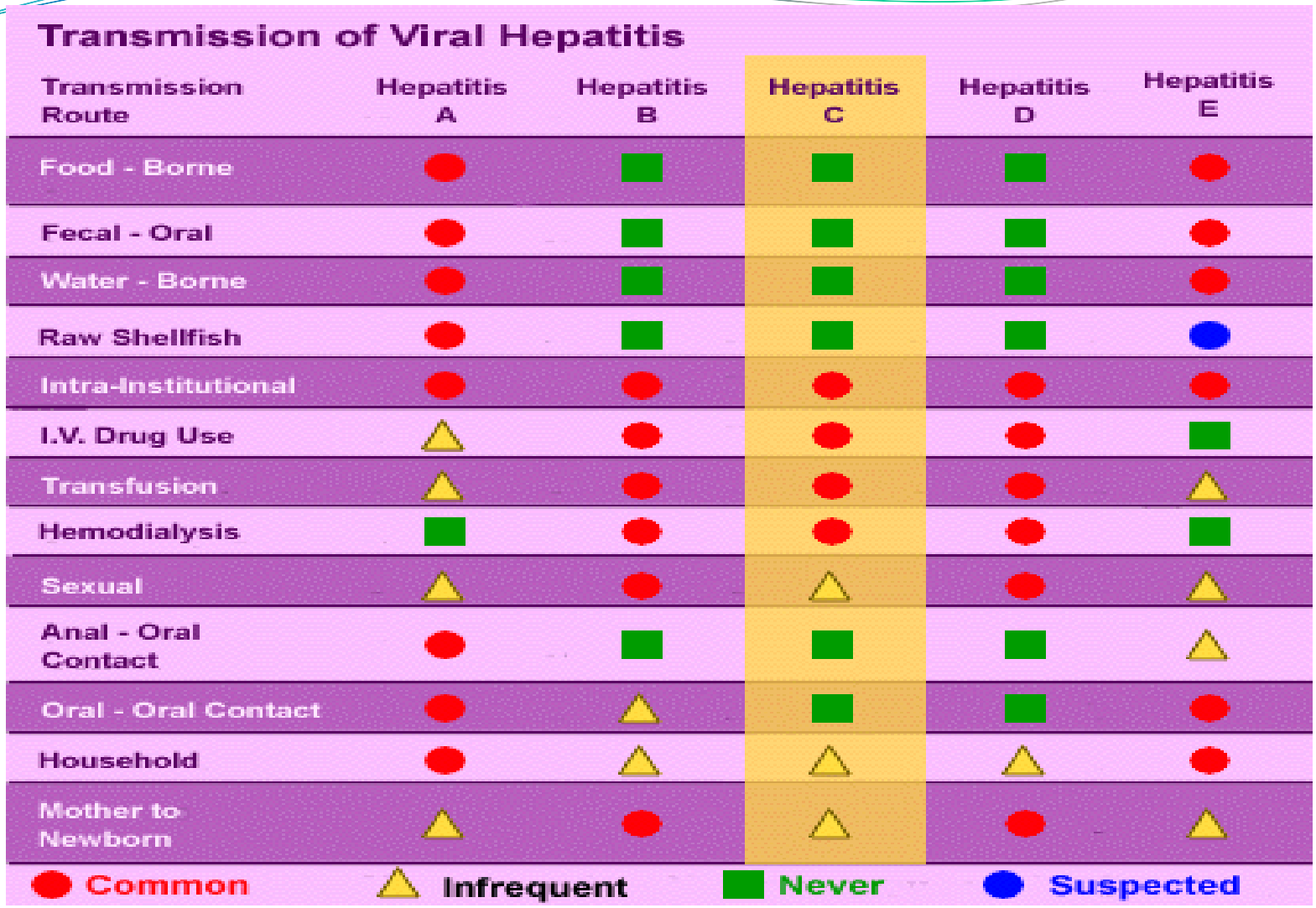
Microbiological diagnosis of viral hepatitis and HIV infections


Hepatitis viruses
Picornaviridae
Hepadnaviridae
Flaviviridae
Hepatitis group E-like viruses
Hepatovirus-Hepatit A
Orthohepadna-virus-Hepatit B
Hepacivirus
Hepevirus-virus Hepatitis E
Hepevirus-Virus hepatitis E
virus hepatitis C
virus Hepatitis G

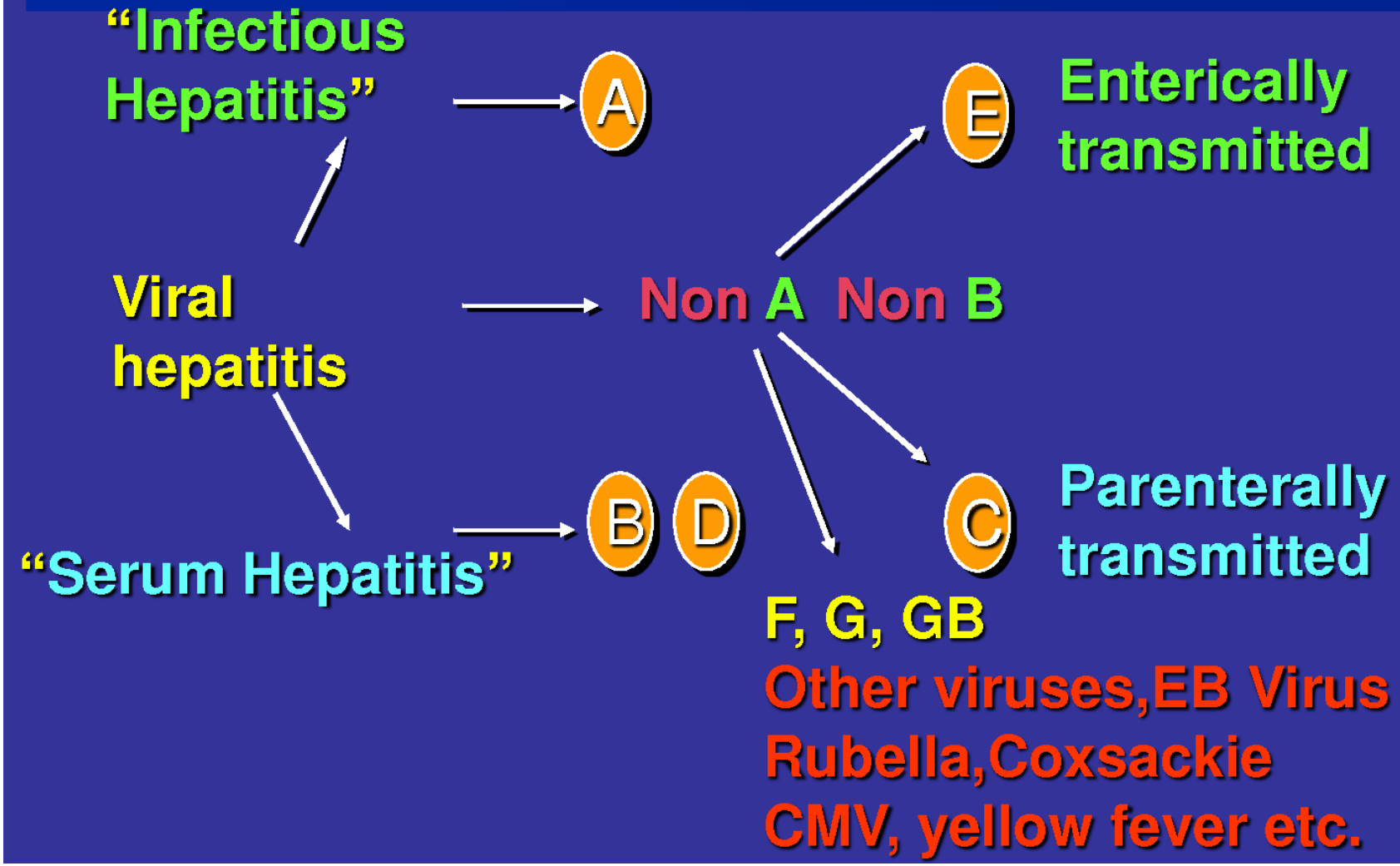
TYPES OF HEPATITIS

- Hepatitis is an inflammation of the liver that is caused by a variety of infectious viruses and noninfectious agents leading to a range of health problems, some of which can be fatal. There are five main strains of the hepatitis virus, referred to as **types A, B, C, D and E**.

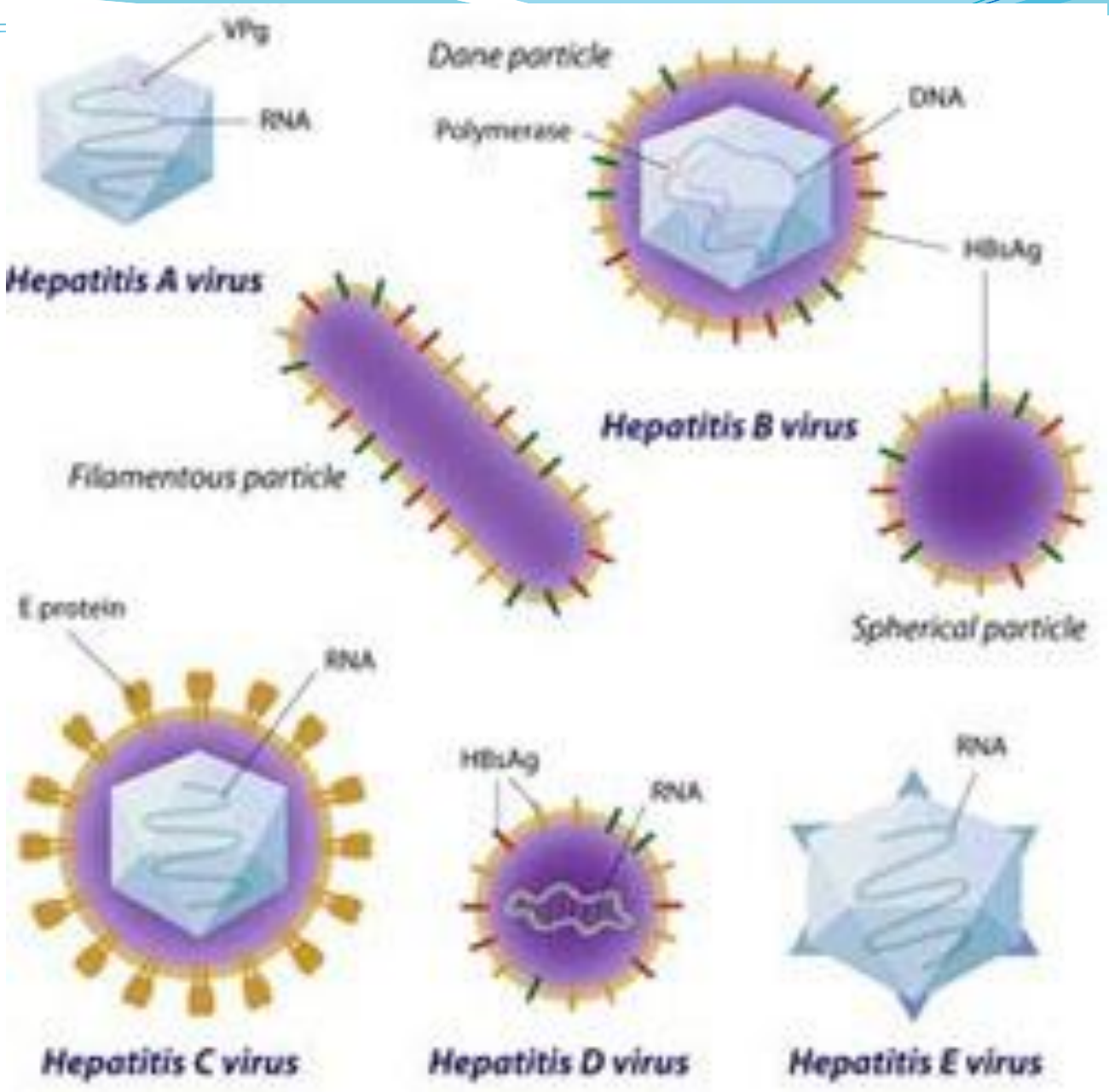



Transmission of Viral Hepatitis
Transmission Route
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D
Hepatitis E
Food - Borne
Fecal - Oral
Water - Borne
Raw Shellfish
Intra-Institutional
I.V. Drug Use
Transfusion
Hemodialysis
Sexual
Anal - Oral Contact
Oral - Oral Contact
Household
Mother to Newborn
Common
Infrequent
Never
Suspected

Viral Hepatitis - Etiology



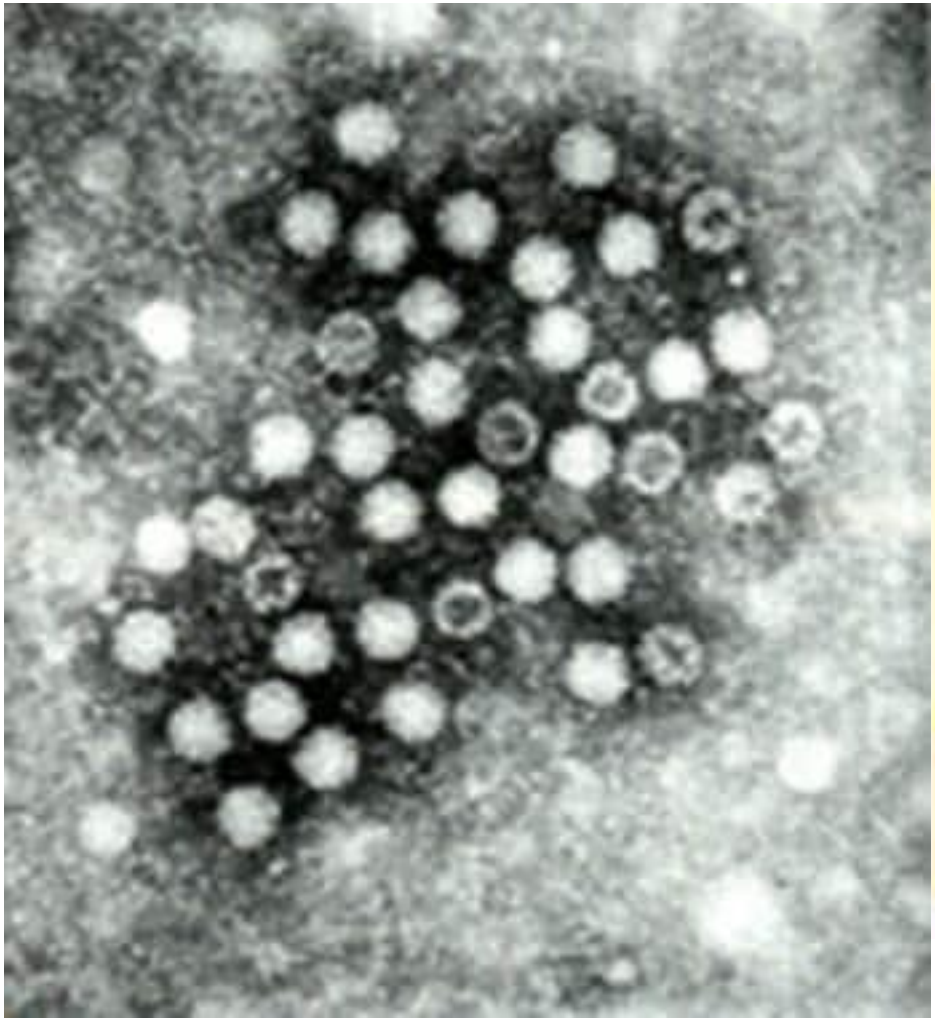
Hepatitis viruses A,B,C,D,E



Hepatitis A virus

- **Opened in 1973 by S. Feston.**
- **Hepatitis A virus (HAV) belongs to the family Picornaviridae, genus Hepatovirus.**
- **The RNA-containing virus, simply organized, has a diameter of 27-28 nm and one virus-specific antigen. 1 serotype of this virus is known, which includes 7 genotypes.**
- **Cultivation. The virus is grown in cell cultures of monkeys, causing a slow persistent infection without cytopathic effect. Biological models are marmoset monkeys and chimpanzees.**

Electron diffraction pattern and diagram of the structure and VGA



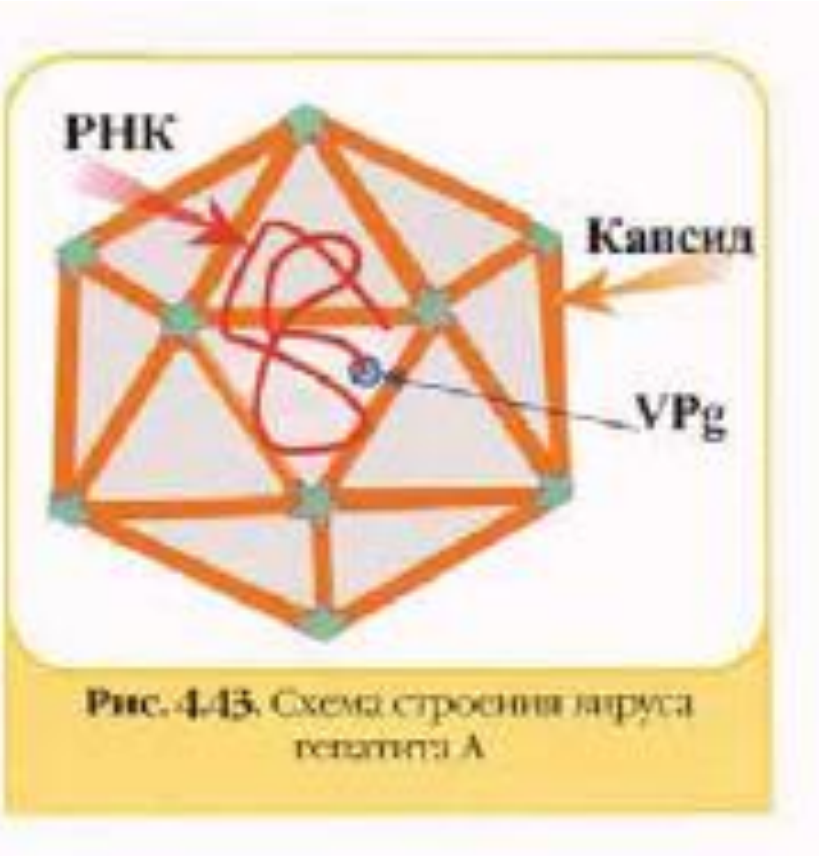
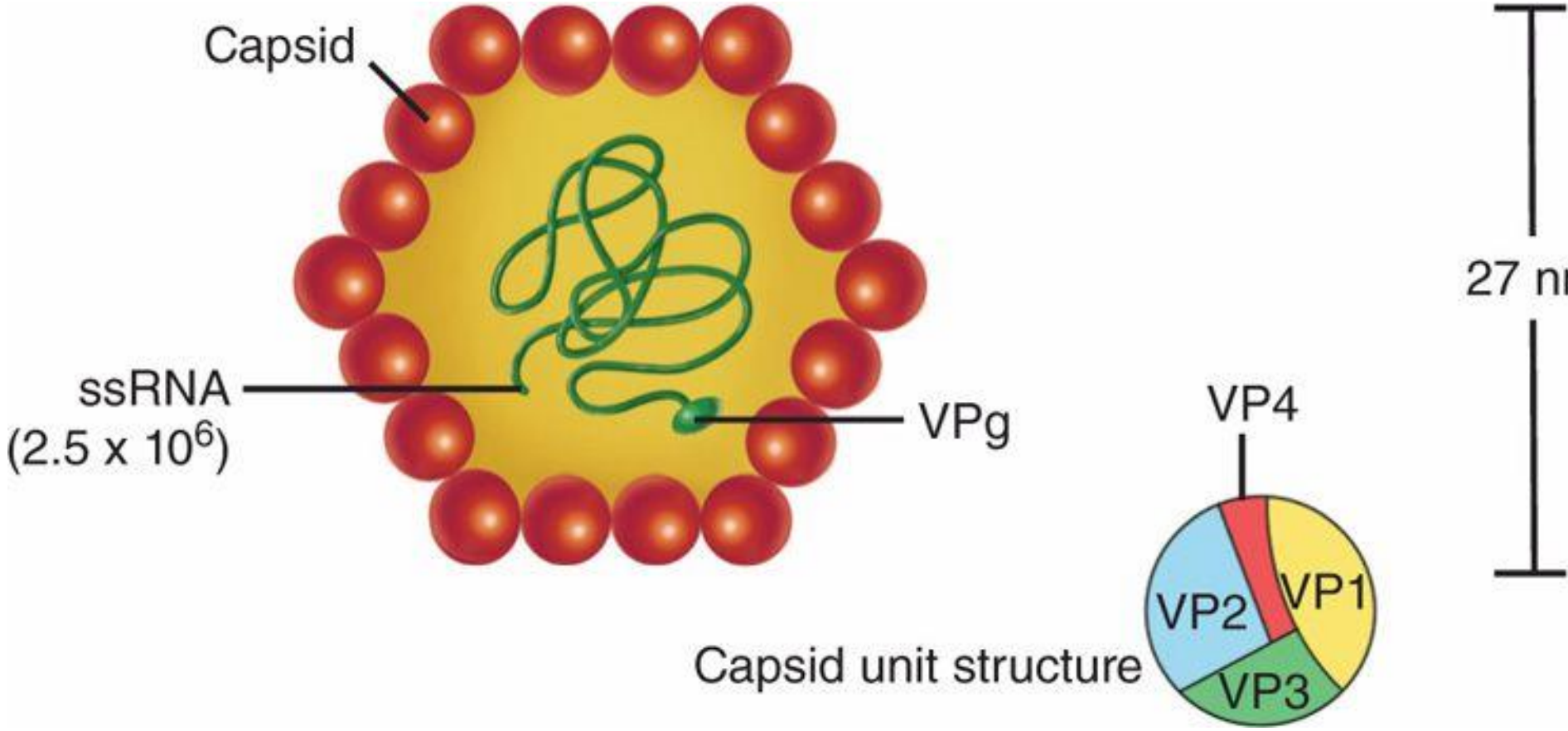


Рис. 4.43. Схема строения вируса гепатита А

STRUCTURE Hepatitis A virus

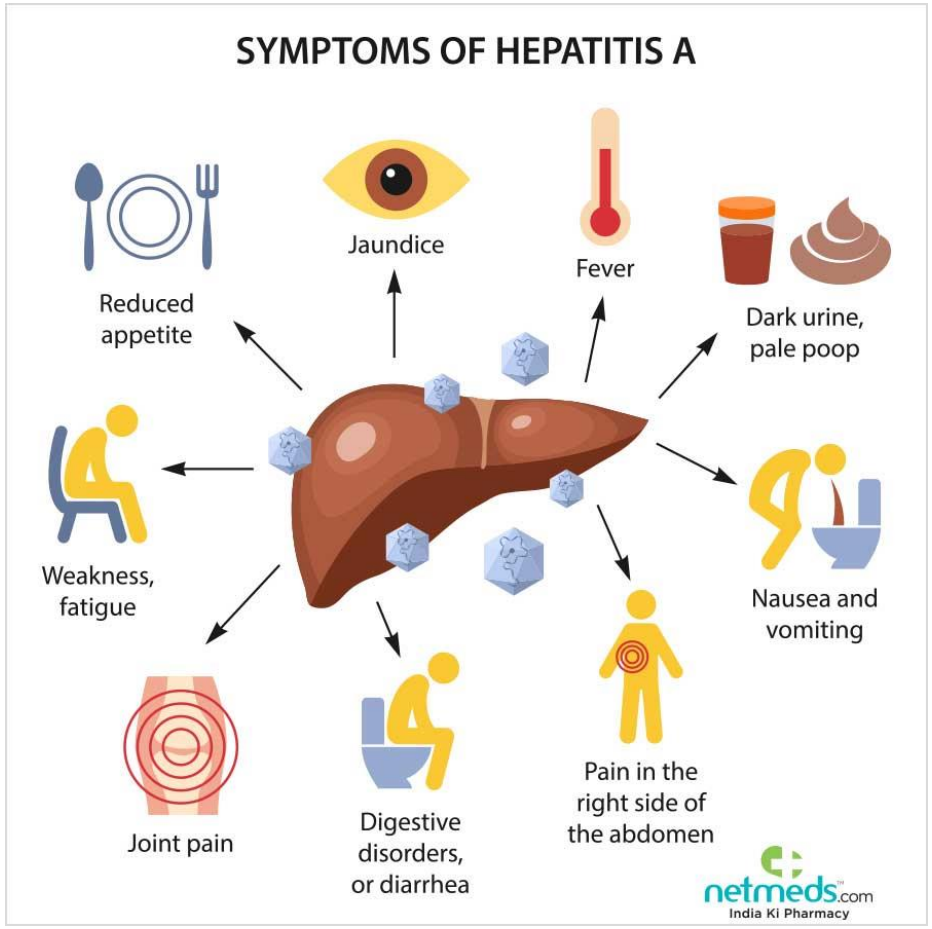


- **Resistant to heat, to low temperatures. Relatively stable in the environment (water, excretions of patients). Retains its pathogenicity in fresh and sea water for 3 months. At a pH of one, the virus remains viable while other picornaviruses are inactivated. Inactivated by boiling for 5 minutes. Sensitive to UV.**
- **The source of infection are patients with both severe and asymptomatic forms of infection. The main ways of transmission are water, alimentary (through water, food, household items, dirty hands; in children's groups - through toys, pots).**

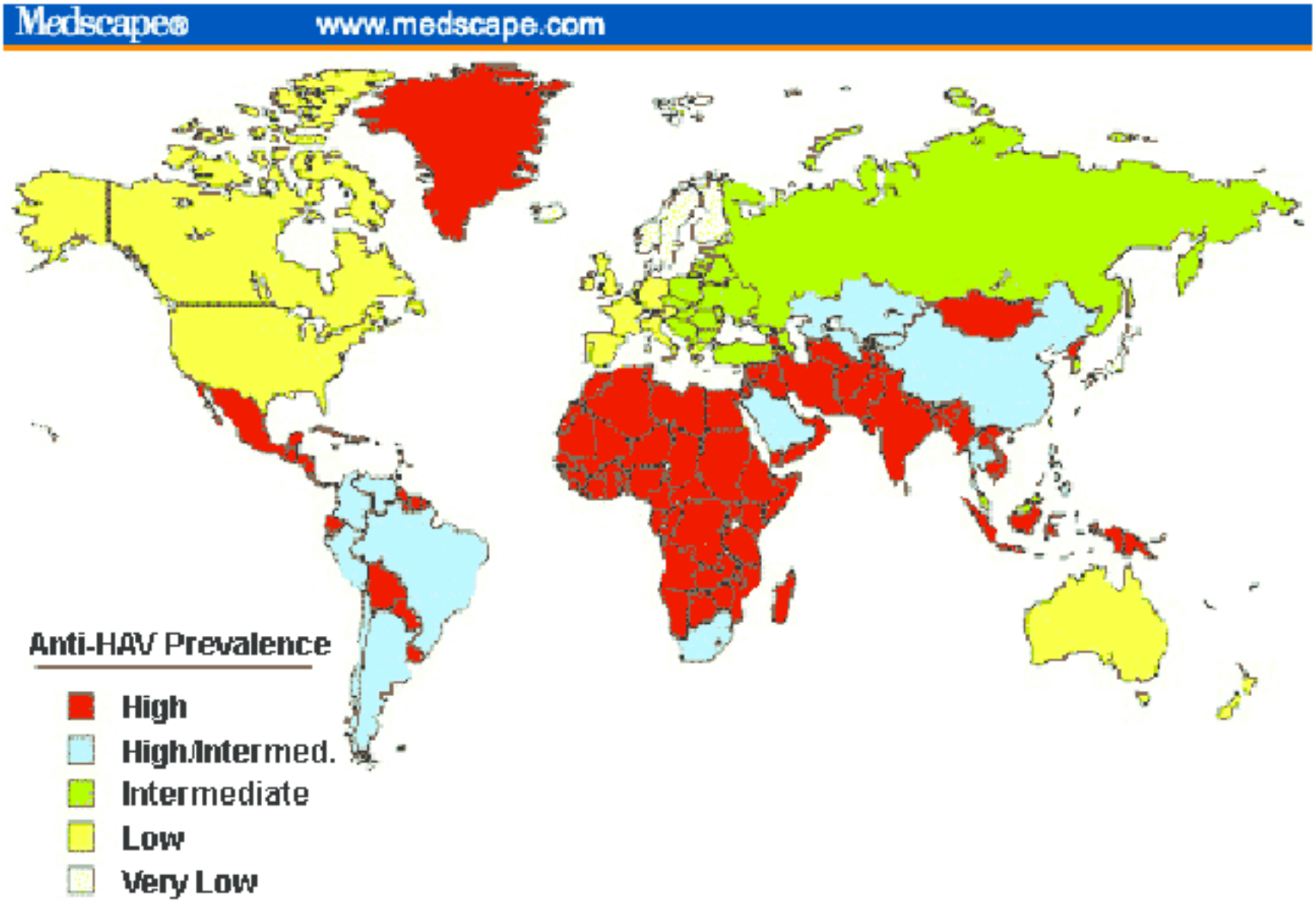
The pathogenesis of hepatitis A

- The incubation period is from 15 to 50 days, usually about a month. The onset is acute, with fever and gastrointestinal symptoms (nausea, vomiting, etc.). Perhaps the appearance of jaundice on the 5th - 7th day. The clinical course of the disease is usually mild, without any special complications; in children under 5 years of age, it is usually asymptomatic. The duration of the disease is 2-3 weeks. Chronic forms do not develop.
- The virus enters the body through the small intestine, in the epitheliocytes and lymphoid cells of which it multiplies.
- From there, blood or lymph enters the liver, where it multiplies in hepatocytes, causing their destruction.
- The development of autoimmune reactions contributes to the destruction of hepatocytes to a greater extent.
- The subsequent development of immune reactions limits the spread of infection, while the virions released from the cells with bile enter the intestinal lumen and are excreted in the feces.

SYPTOMS


SYMPTOMS OF HEPATITIS A
Reduced appetite
Jaundice
Fever
Dark urine, pale poop
Weakness, fatigue
Nausea and vomiting
Joint pain
Digestive disorders, or diarrhea
Pain in the right side of the abdomen
netmeds.com
India Ki Pharmacy

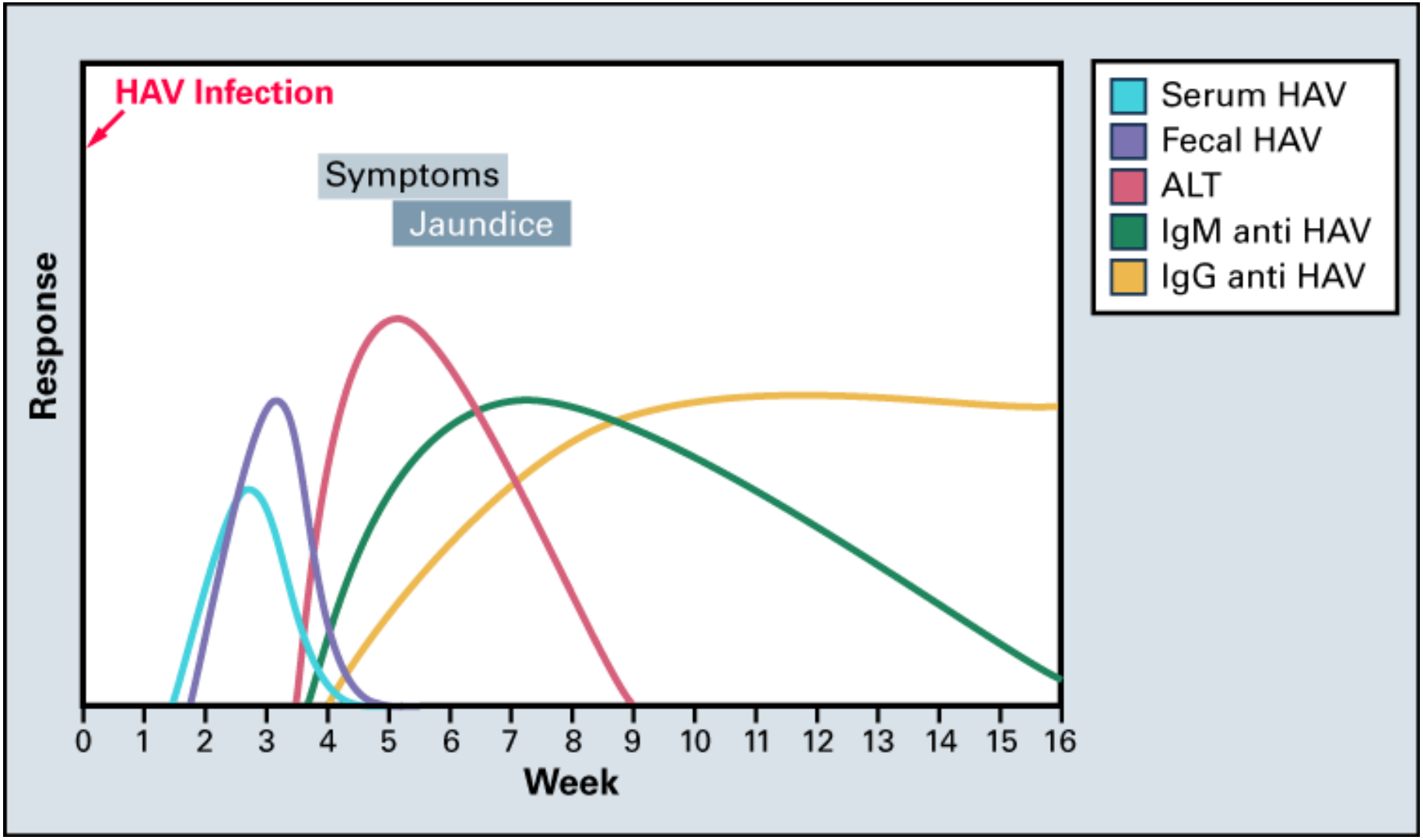
Geographic distribution of hepatitis A



Viral hepatitis A markers

- After infection, persistent lifelong immunity associated with IgG is formed. IgG appear in the serum after the disappearance of the virus from it, their titer persists for life
- At the beginning of the disease, IgM appear in the blood, which remain in the body for 4-6 months and are markers of the acute period of the disease, protecting against re-infection. In children of the first year of life, antibodies obtained from the mother through the placenta are detected. In addition to humoral, local immunity develops in the intestine

Dynamics of detection of viral hepatitis A markers

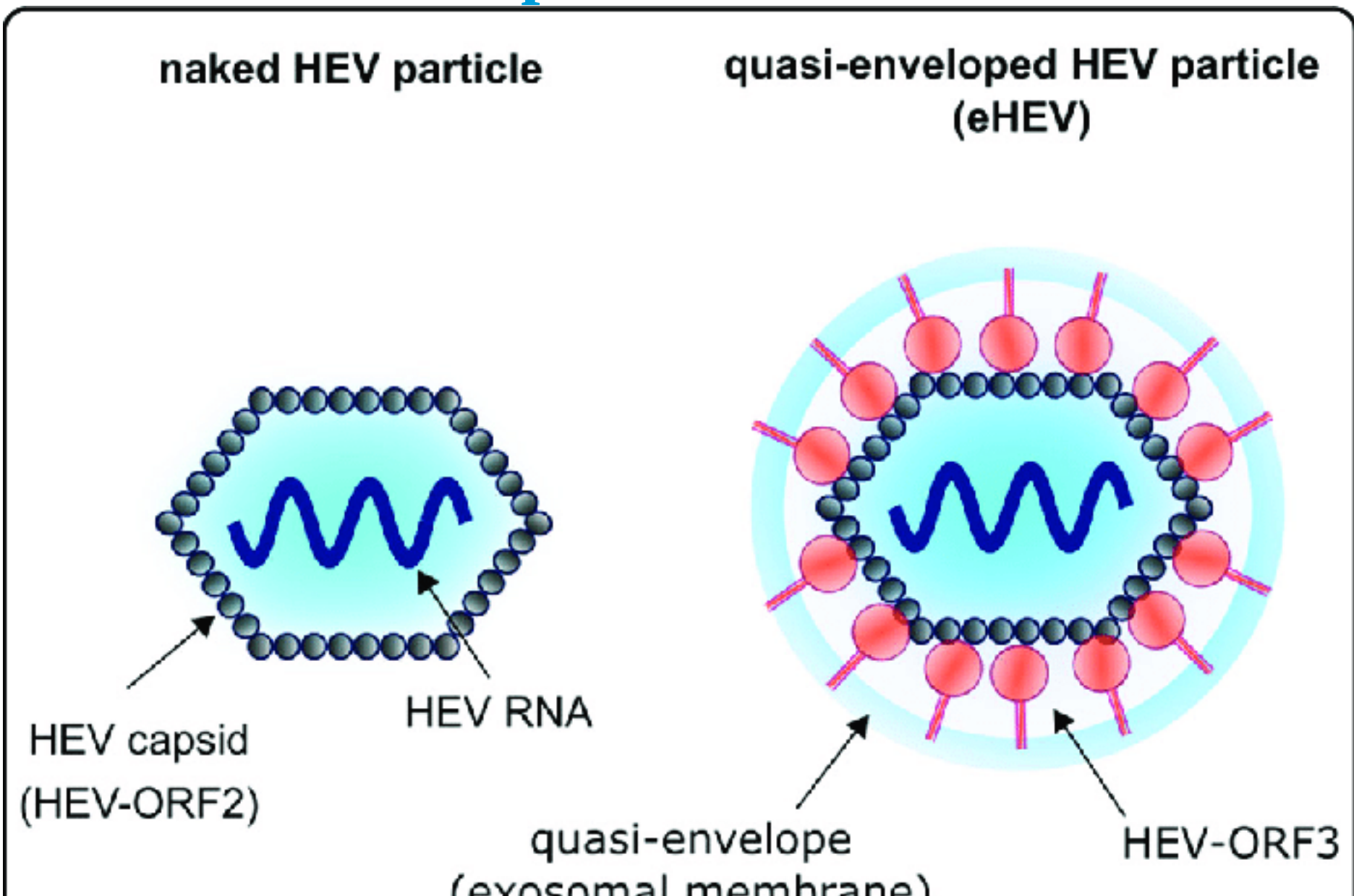


Laboratory diagnostics and specific prevention of hepatitis A

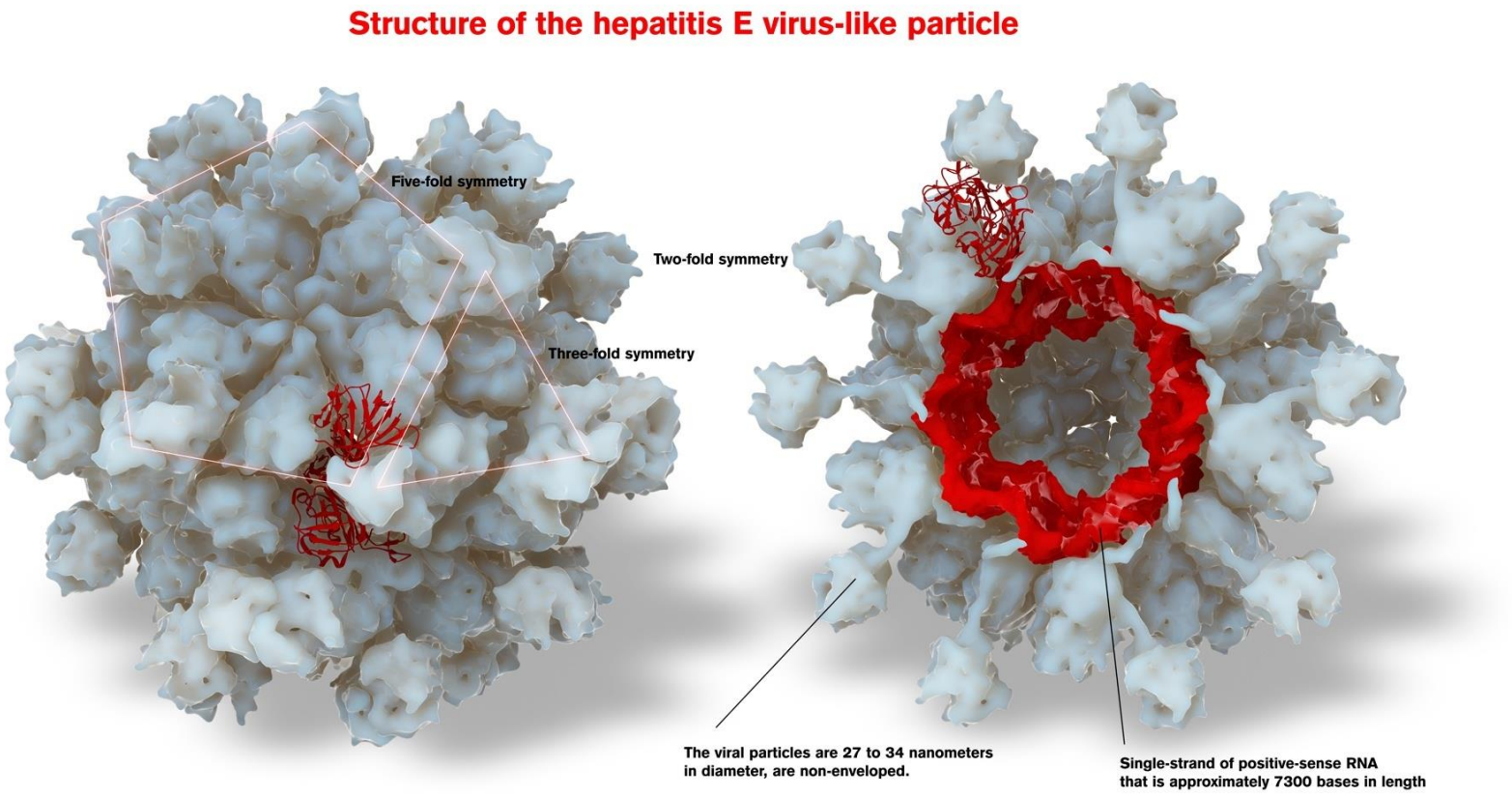
Hepatitis A - Diagnosis

- Three serologic markers available:
  1. Hepatitis A Total (IgG and IgM) antibody
  2. Hepatitis A IgM
  3. Hepatitis A IgG
- First tests available since 1978
- No antigen test
- Antibody response is similar following vaccination or wild type infection
- Incubation time is 7 to 28 days

Hepatitis E virus



Structure of hepatitis E-like virus particles



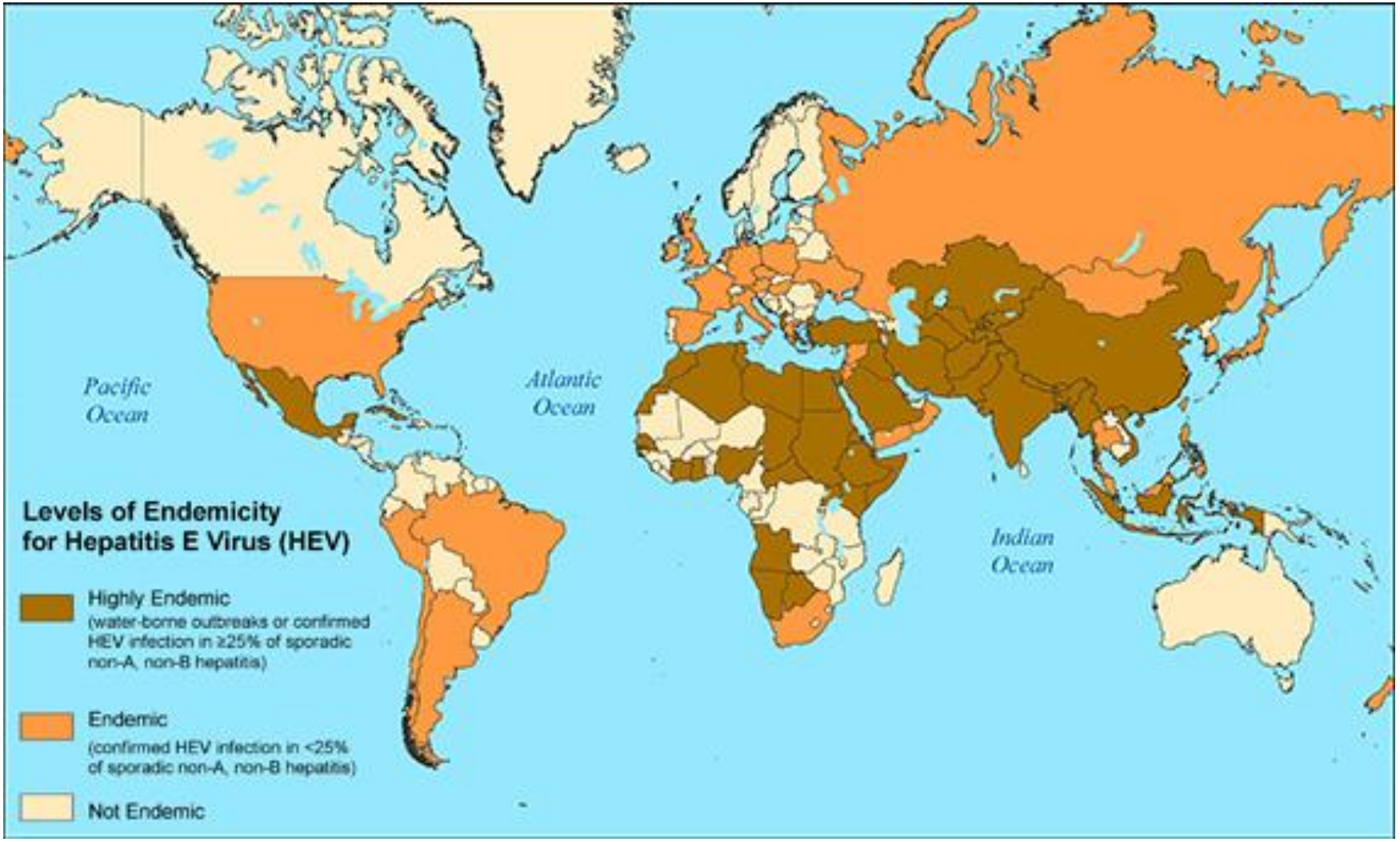
Epidemiology of hepatitis E

- Source - a person with a clinically pronounced or subclinical infection, as well as some wild (rodents) and farm animals (pigs).
- The pathogen transmission mechanism is fecal-oral.
- The main transmission factor is contaminated drinking water and products obtained from infected animals.
- The incubation period is 15-60 days.
- The hepatitis E virus causes acute sporadic and epidemic hepatitis.

Hepatitis E prevalence

- Globally, there are approximately 20 million hepatitis E infections, 3.3 million acute cases and 56,000 deaths each year.
- More than 60% of all hepatitis E infections and 65% of all hepatitis E deaths occur in East and South Asia.
- Differences in epidemiology are determined by different genotypes of the hepatitis E virus.
- Risk factors are associated with poor sanitation in many parts of the world and with the shedding of viruses in faeces.

The hepatitis E virus causes acute sporadic and epidemic hepatitis.



The pathogenesis of hepatitis E

- **The main route of infection transmission is water. The incubation period is from 2 to 6 weeks.**
- **The pathogenesis of hepatitis E is similar to that of hepatitis A.**
- The disease is accompanied by moderate liver damage, intoxication and jaundice. The prognosis is usually favorable, with the exception of pregnant women who develop hemorrhagic syndrome, acute renal failure, while mortality from hepatitis E is 16-20%.

Laboratory diagnostics and specific prophylaxis of hepatitis E

Test	Utility
IgM anti-HEV	First-line diagnostic assay in the immunocompetent
IgG anti-HEV	Marker of past infection
	Seroprevalence estimation
	Vaccine efficacy
HEV RNA	First-line diagnostic assay in the immunocompromise
	Establishing chronicity
	Antiviral treatment response
HEV antigen	Diagnosis of early active infection
	Cost-effective alternative to HEV RNA
Genotyping	Distribution of viral strain

HEV: Hepatitis E virus

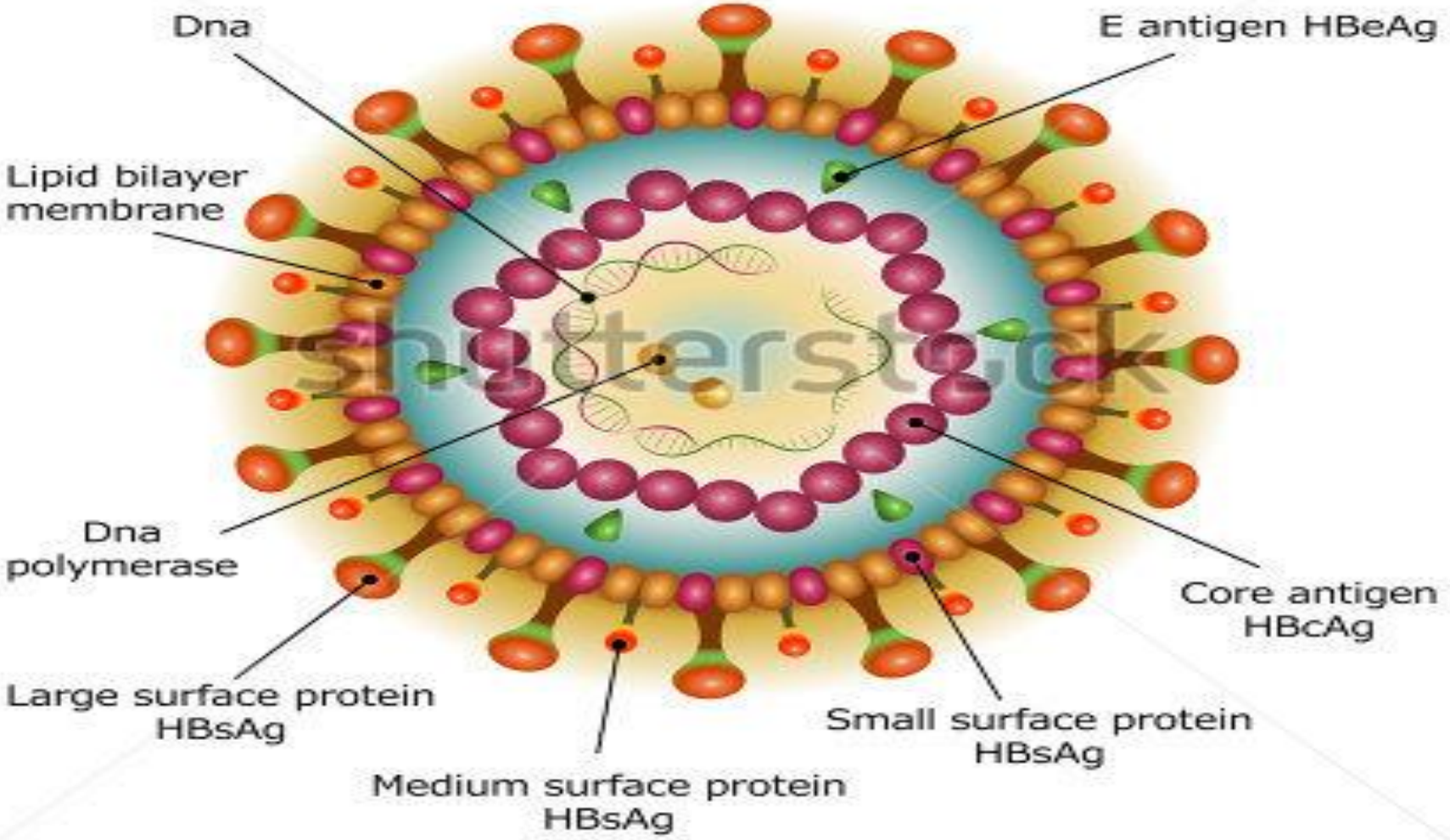
Hepatitis B virus

A complexly organized, DNA-containing virus of a spherical shape, its diameter is 42-47 nm. It consists of a core (core), built according to a cubic symmetry type, consisting of 180 protein particles that make up the core HBc antigen, with a diameter of 28 nm and a lipid shell containing surface HBs - antigen.

Inside the core are DNA polymerase, protein kinase, and the end protein of the HBe antigen.DNA polymerase is a polyfunctional enzyme: it is capable of synthesizing new DNA strands, both on a DNA template and on an RNA template, having both polymerase and reversetase activities. Nuclease activity degrades the RNA strand in the RNA-DNA hybrid

Hepatitis B Virus

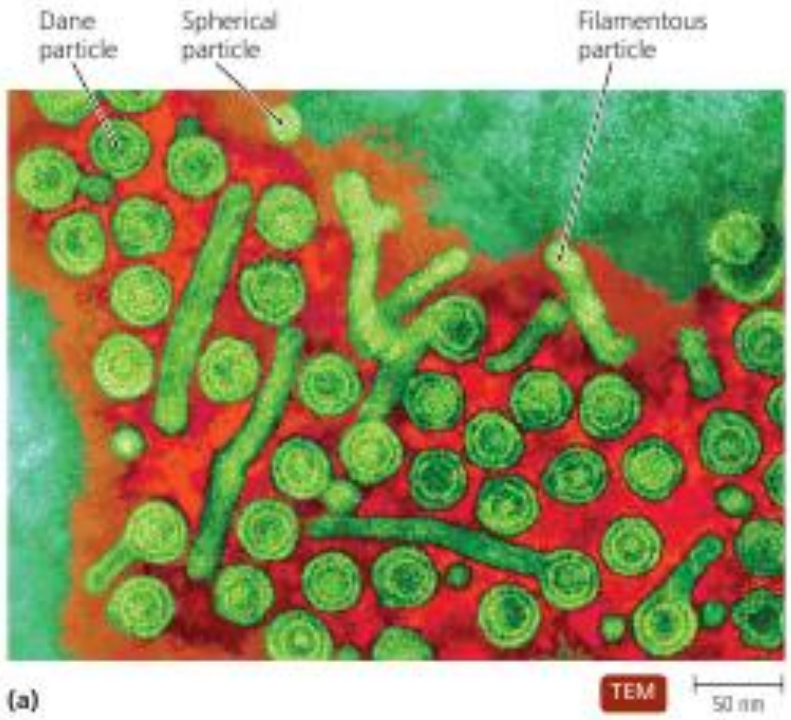
Baltimore Group VII (dsDNA-RT)

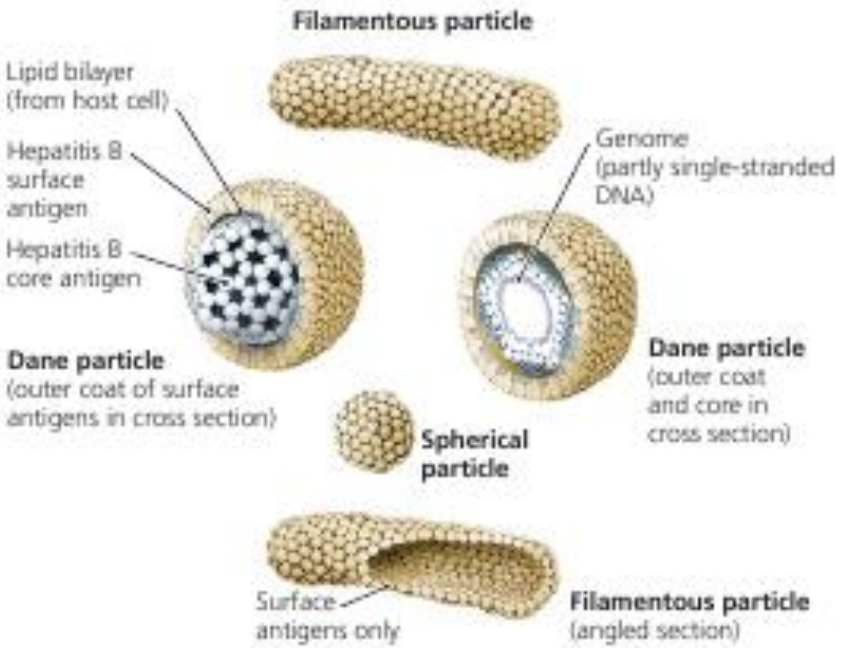


HBV antigens

- ***HBV has a complex antigenic structure. The envelope of the virus contains the HBs antigen, which is formed by 3 polypeptides in the glycosylated form:***
- ***PreS1 - large polypeptide (L - large), PreS2 - medium polypeptide (M-middle), S - small major (small). Antigenic specificity is associated with the S-small major protein, which is included in all 3 envelope proteins.***
- ***The HBs antigen is found in the blood not only as part of the virion, but also in the form of independent "empty" fragments, spherical or filamentous in shape, which are non-infectious, but highly immunogenic and induce anti-HBs neutralizing antibodies.***
- The core HBc antigen is never present in free form in the blood, being an internal component of the viral particle. It can be found in virus-infected hepatocytes.
- ***The HBe antigen is also a core antigen derived from the HBc antigen and is also referred to as a soluble antigen. The appearance of the HBe antigen in the blood is associated with the replication of the virus.***
- ***HBx antigen is a transactivator, the accumulation of which in the blood is associated with the development of primary liver cancer.***

Three types of viral particles produced by the hepatitis B virus





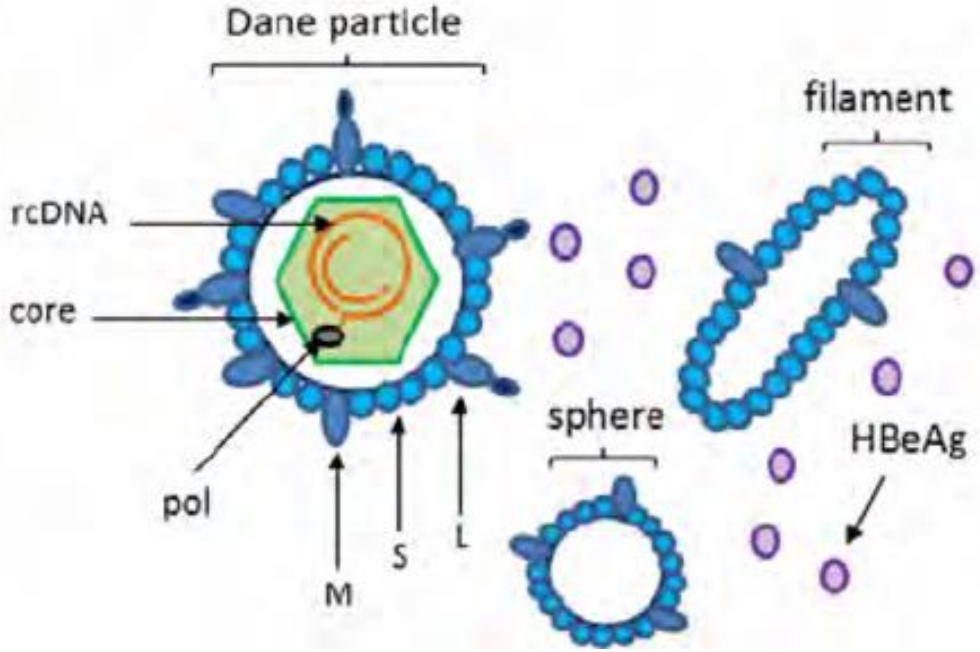
▲ **Figure 23.15 Three types of viral protein particles produced by hepatitis B viruses.** Dane particles are complete virions, whereas filamentous particles and spherical particles are capsomeres that have assembled without genomes. **(a)** Micrograph. **(b)** Artist's rendition.

The structure of the Dane particle

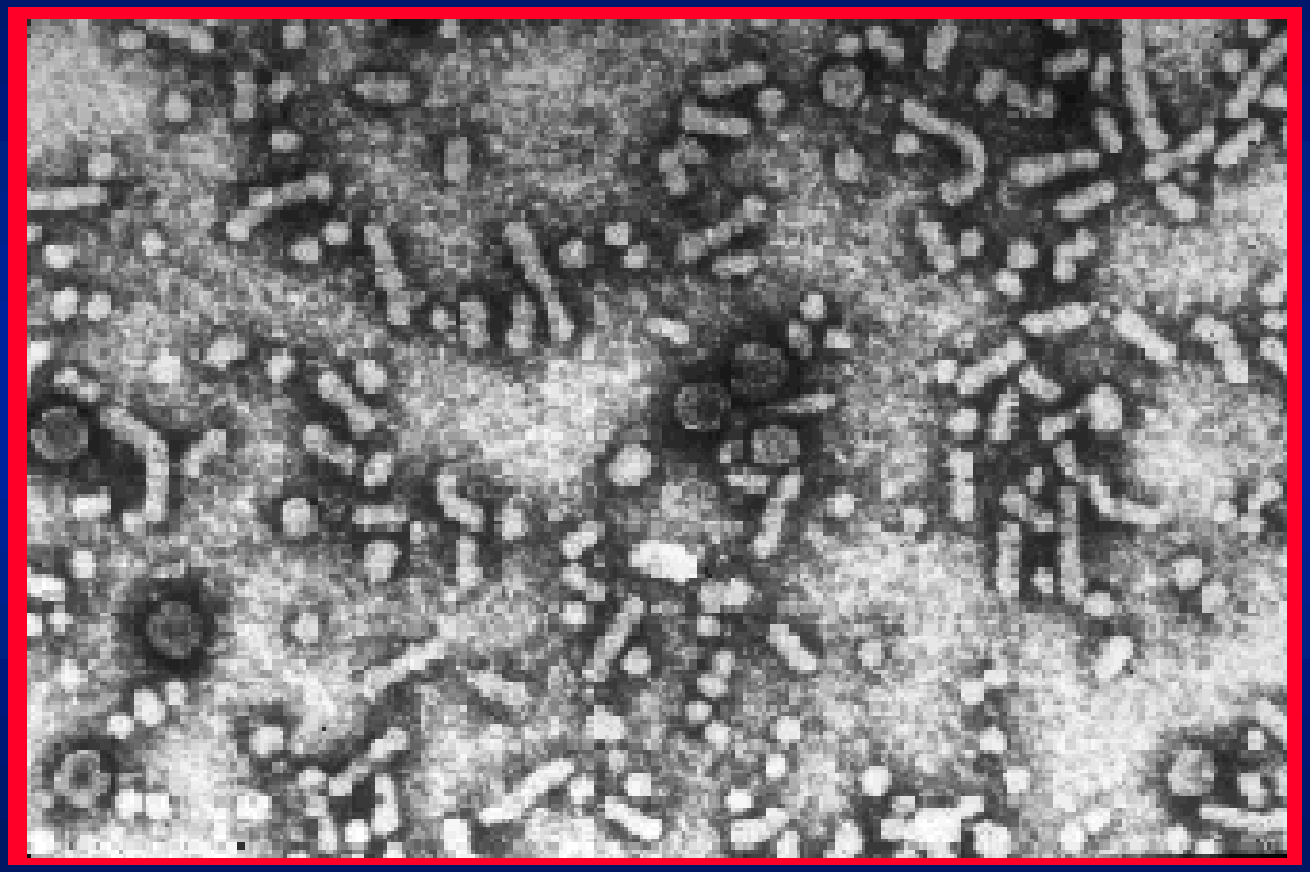
A

HBV proteins	
S	small surface protein
M	middle surface protein
L	large surface protein
core	capsid protein
HBeAg	secreted e antigen
pol	polymerase
HBx	X protein (non-secreted)

B



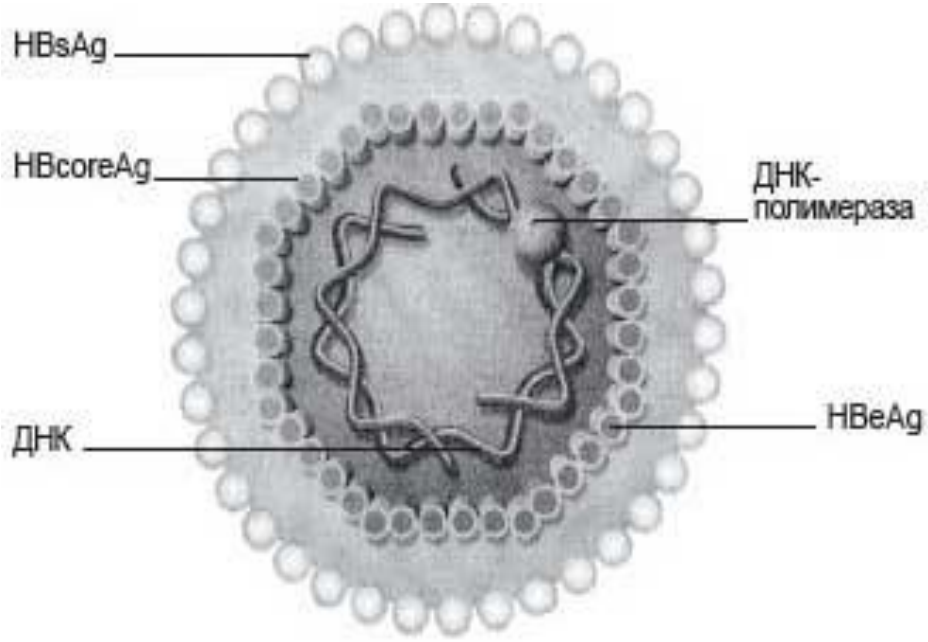
Electronogram of the blood of a patient with hepatitis B

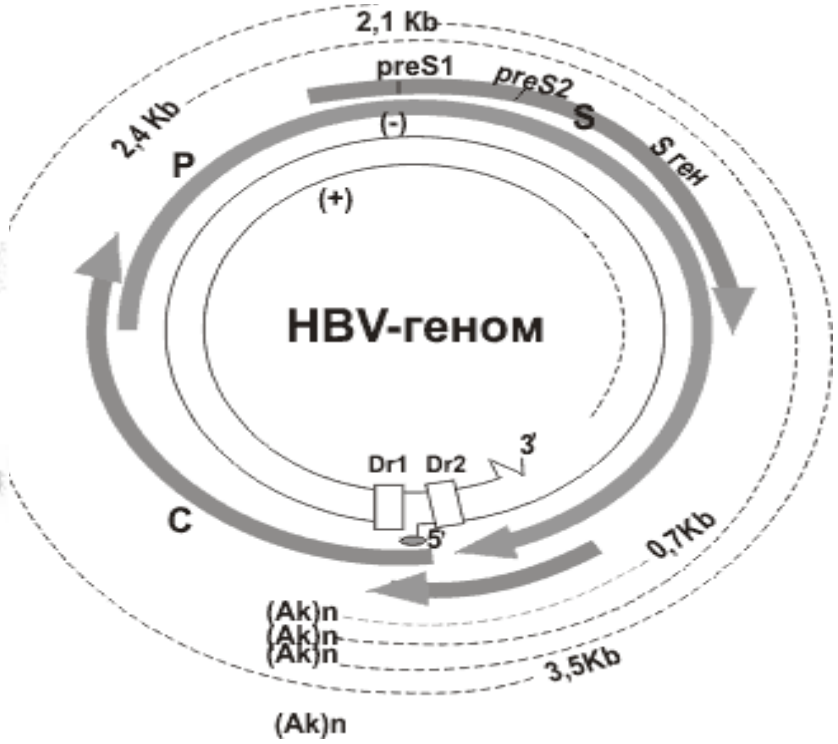


Hepatitis B virus genome

- Double-stranded circular DNA, about 3200 nucleotides, plus strand 1/3 shorter than the other;
- There are 4 genes in the genome: S, C, P, and X, encoding, respectively, HBsAg, HBcAg, a polymerase, and a protein-regulator of gene expression;
- There are 8 genotypes of the virus: A, B, C, D, E, F, G, H.
- A and D are ubiquitous.

DNA structure and HBV genome





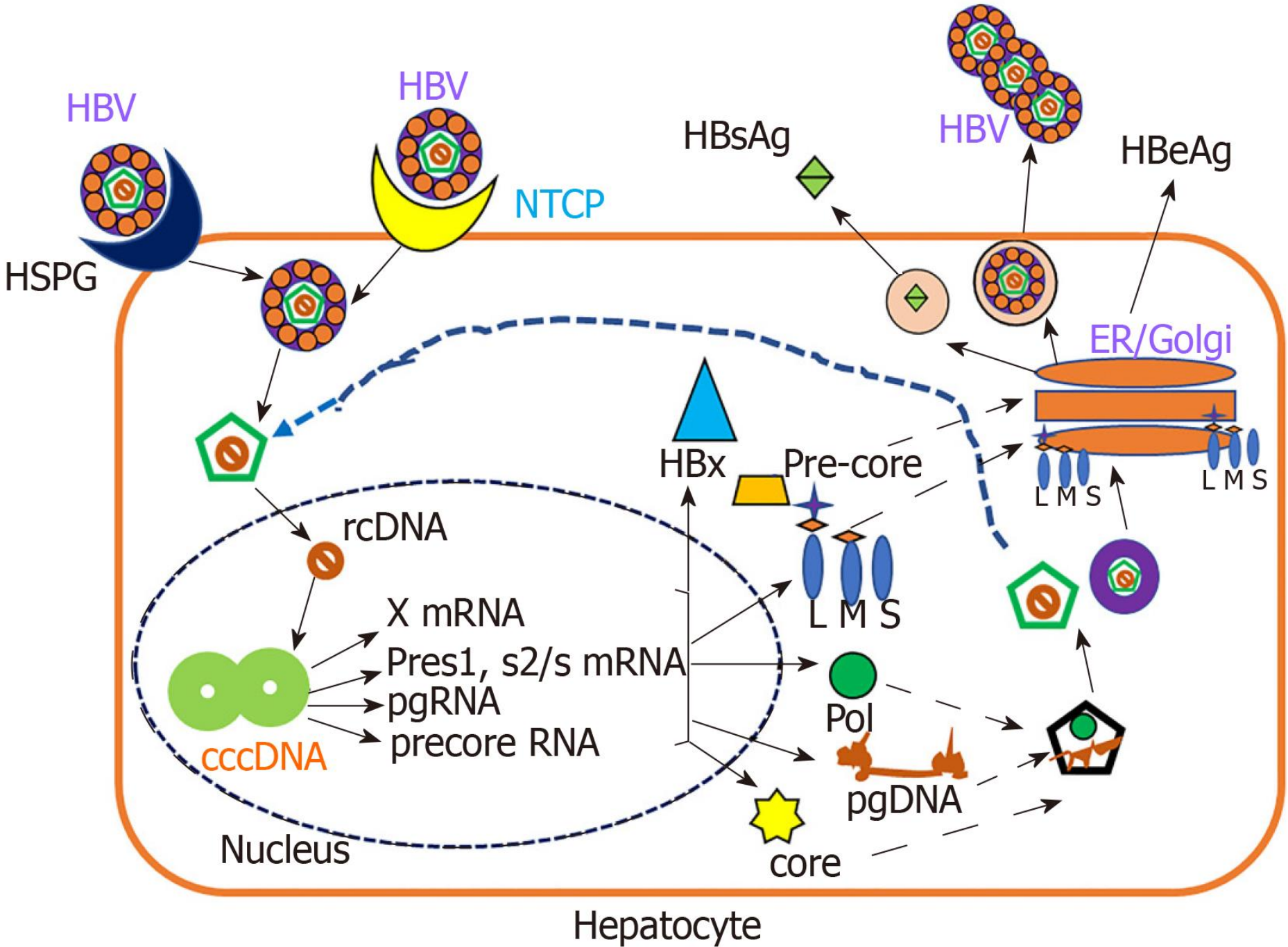
Remains infective at 0-20°C -15 years, at room temperature - 1 hour, at 100°C -20 minutes, at dry heat 160°C -1 hour. In dried plasma 25 years. Resistant to phenol, UV, alcohol. Sensitive to formalin, ether. 1-2% chloramine solution lasts 2 hours

- **HBV is not cultured in chick embryos,**
- **does not have hemolytic and hemagglutinating activity**
- **It is cultivated only in cell culture obtained from primary liver cancer tissue without cytopathic and cytolytic effects and with a small accumulation of virions.**
- **Primates are susceptible to the virus: gorillas, chimpanzees, African green monkeys**

Types of interaction between HBV and the cell

There are 2 ways of interaction between HBV and the cell:

1. Productive infection - DNA replication, synthesis of virus-specific proteins, formation of a new generation of viruses.
2. Section - HBV DNA covalently attaches (embeds) to the DNA of an infected cell, which leads to a change in the structure of cellular DNA and a change in the function of nearby genes. Integration can occur in parallel with replicative infection.


HBV
HBV
HBV
HBsAg
HBeAg
NTCP
HSPG
ER/Golgi
HBx
Pre-core
L M S
L M S
L M S
rcDNA
X mRNA
Pres1, s2/s mRNA
pgRNA
precore RNA
cccDNA
Pol
pgDNA
core
Nucleus
Hepatocyte

Epidemiology of hepatitis B

- Hepatitis B is a severe anthroponosis with a parenteral transmission mechanism.
- The source of infection is patients with various forms of hepatitis and asymptomatic carriers;
- Ways of transmission of the pathogen:

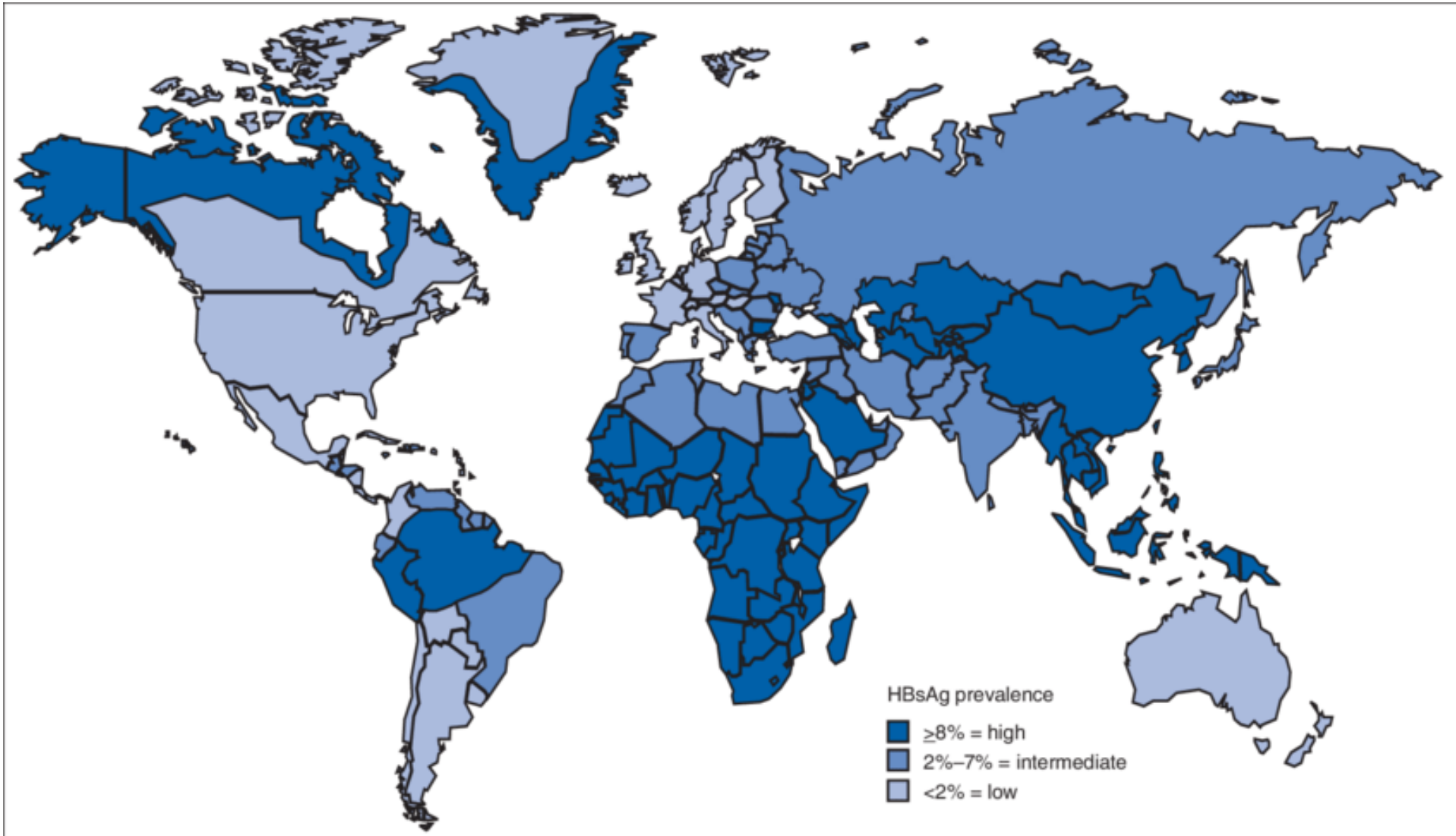
- natural: sexual and intranatal (during childbirth)
- artificial: blood transfusion, organ and tissue transplantation, hemodialysis, use of non-sterile medical and cosmetic instruments.

- The incubation period is 30-180 days.
- Risk groups: recipients of blood and its components, patients with chronic diseases, injecting drug users, people who have promiscuous sex.

Hepatitis B prevalence

- More than 240 million (about 5% of the world's population) have a chronic infection.
- 780 thousand patients die annually.
- Between 2% and 5% of the general population in the Middle East and the Indian subcontinent are chronically infected;
- In North America and Western Europe, less than 1% of the population is infected.

Geographic distribution of hepatitis B virus



Hepatitis B pathogenesis (1)

- After entering the body parenterally, the viruses infect leukocytes, which carry them into the bloodstream.
- Viruses penetrate and multiply in the reticuloendothelial cells (Kupffer and others) of the liver and other organs, causing inflammatory proliferative reactions.
- The virus then enters the hepatocytes, where a reproductive or integrative infection develops.
- During a reproductive infection, virus-specific proteins are formed in hepatocytes, which are introduced into the hepatocyte membrane and change its antigens, causing autoimmune reactions that destroy hepatocytes.

Hepatitis B pathogenesis (2)

- The intensity and nature of damage to hepatocytes depends on the nature of the immune response.
- With a normergic response, hepatocytes are destroyed under the influence of an immune attack, and the released virions are inactivated by immunocytes and antibodies (acute moderate hepatitis).
- With a hyperergic response, massive hepatocellular necrosis occurs (severe forms of acute hepatitis, up to fulminant).
- With a hypoergic response, only a part of the infected hepatocytes undergoes destruction, therefore, the further development of the infectious process follows two options.

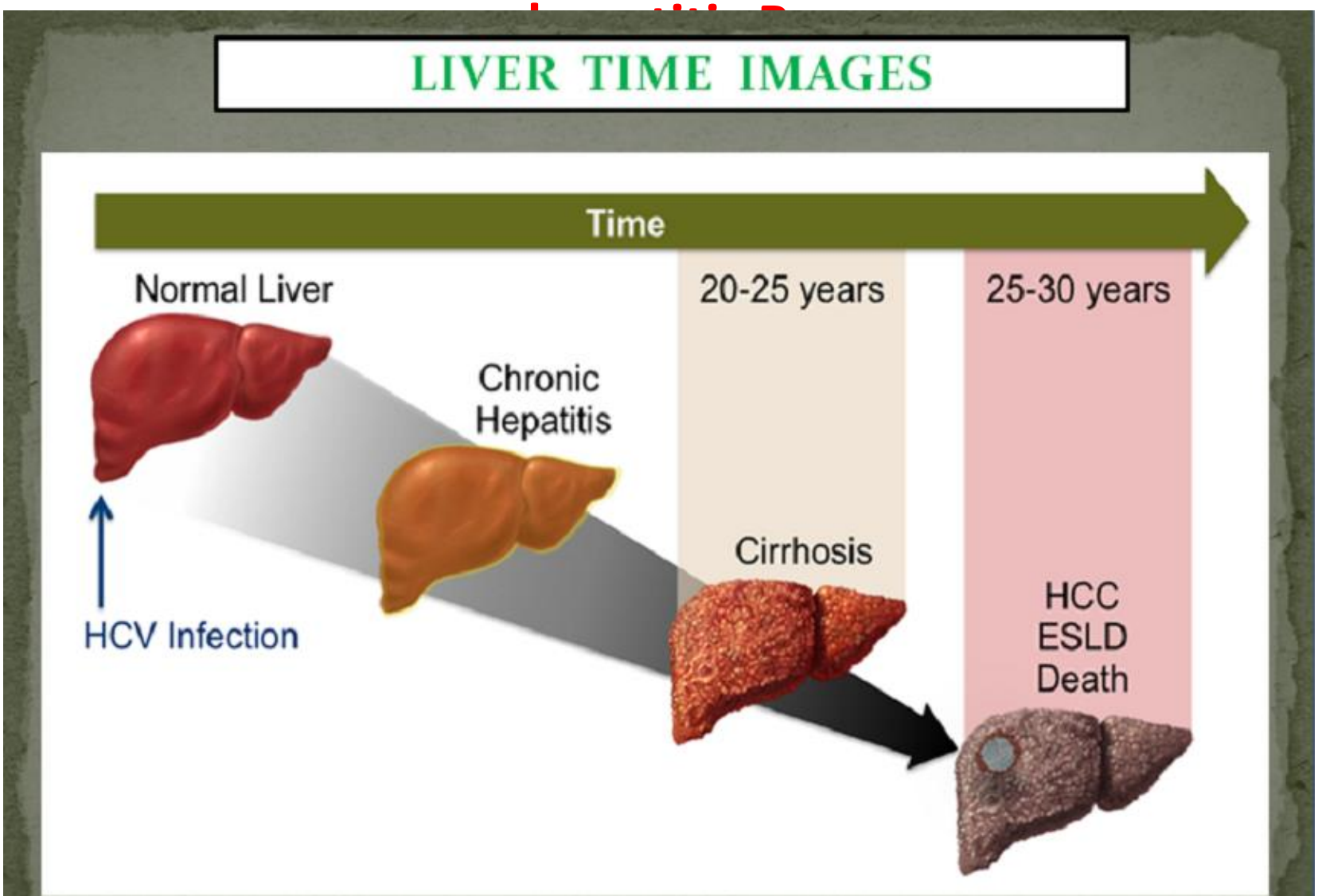
Hepatitis B pathogenesis (3)

- If necrosis is localized, and the immune response is modulated, even with a delay, then an acute subclinical form of hepatitis B develops, which ultimately ends with the elimination of the virus and recovery.
- If necrosis is intense, and the strength of the immune response does not increase, then a chronic infection develops in the form of 2 options: 1. subclinical infection (carriage of the hepatitis B virus) and 2. clinically manifest infection (chronic hepatitis B).

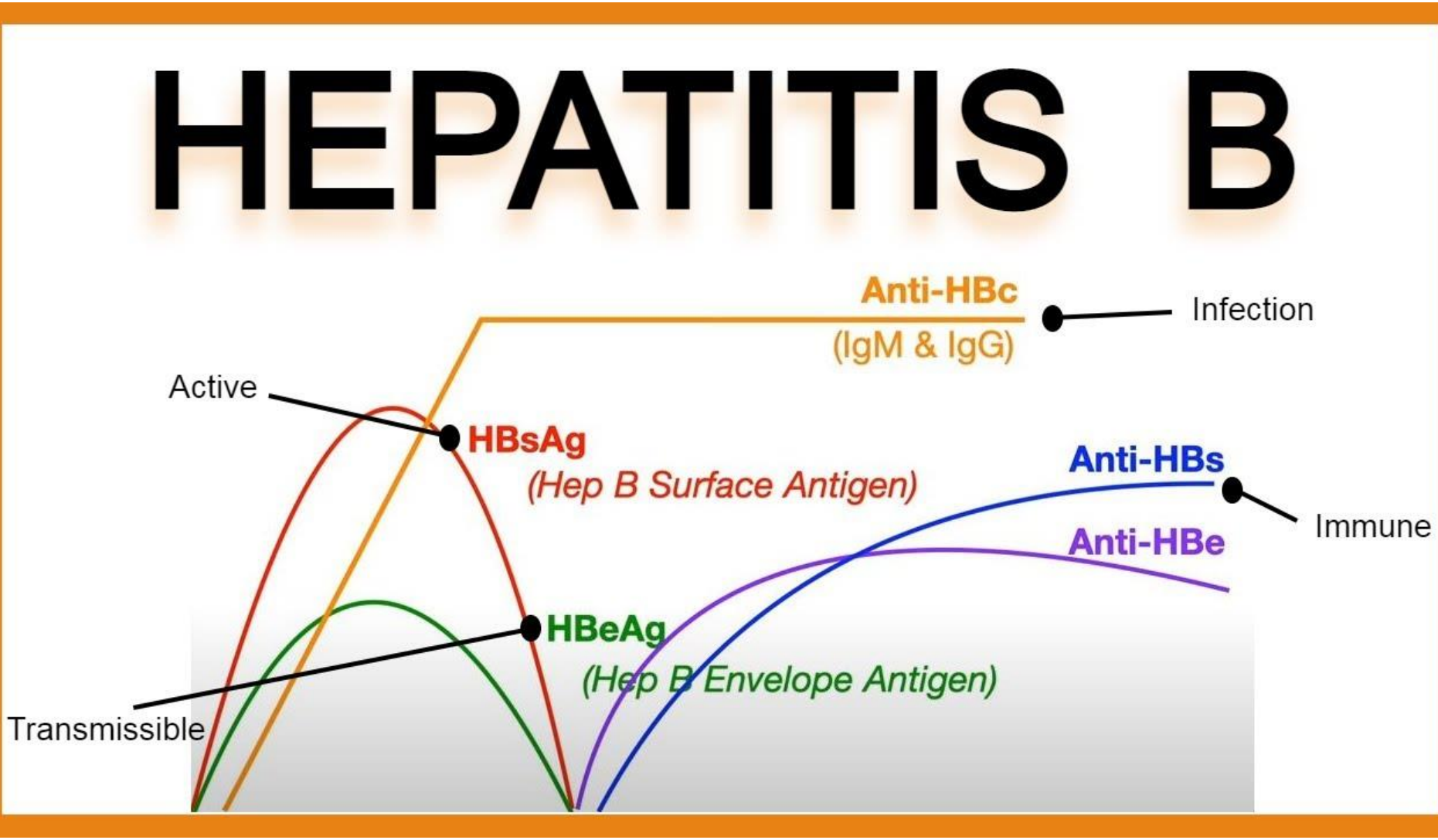
Hepatitis B pathogenesis (4)

- Chronic infections develop in 80-90% of children infected during the first year of life, and in 30-50% of children infected before 6 years of age.
- Chronic infections develop in 5% of infected adults.
- 15-25% of adults who become chronically infected in childhood die from hepatitis B-related cancer or liver cirrhosis.

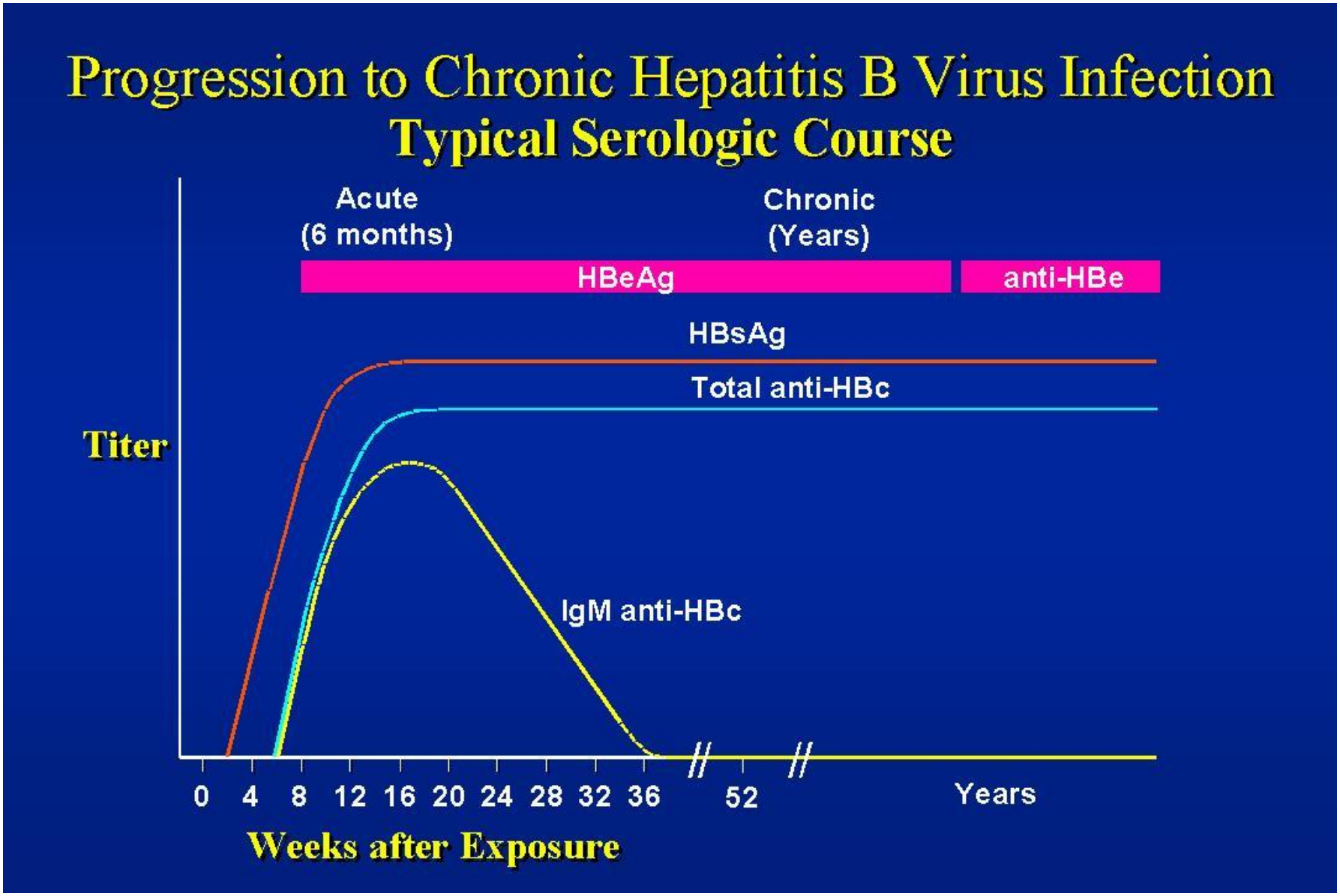
The nature of the changes occurring in the liver in viral



Serological markers of acute HBV infection



Serological markers of chronic HBV infection



Laboratory diagnostics and specific prophylaxis of hepatitis B

- Serology
  - HBsAg
  - Anti-HBs
  - HbeAg
  - Anti-Hbe
  - HBc IgM
  - HBcIgG
- Cultivation
- Molecular

HEPATITIS D VIRUS

- The virion (HDV) has a spherical shape (d. 36nm), which consists of a single-stranded negative strand of ring-shaped RNA and a nucleocapsid HD antigen (delta antigen).
- The delta antigen is present in the nucleocapsid in the form of 60 copies and is the only protein whose synthesis is encoded by viral RNA.
- It uses the HBs-antigen of the outer shell of the hepatitis B virus as an outer shell to protect the genome (HDD). Replication of the viral genome is performed by cellular RNA polymerase-II without the help of the hepatitis B virus. There are 3 genotypes of the virus. In Russia, 1 genotype prevails. All genotypes belong to the same serotype.

Electron diffraction pattern and diagram of the IOP structure

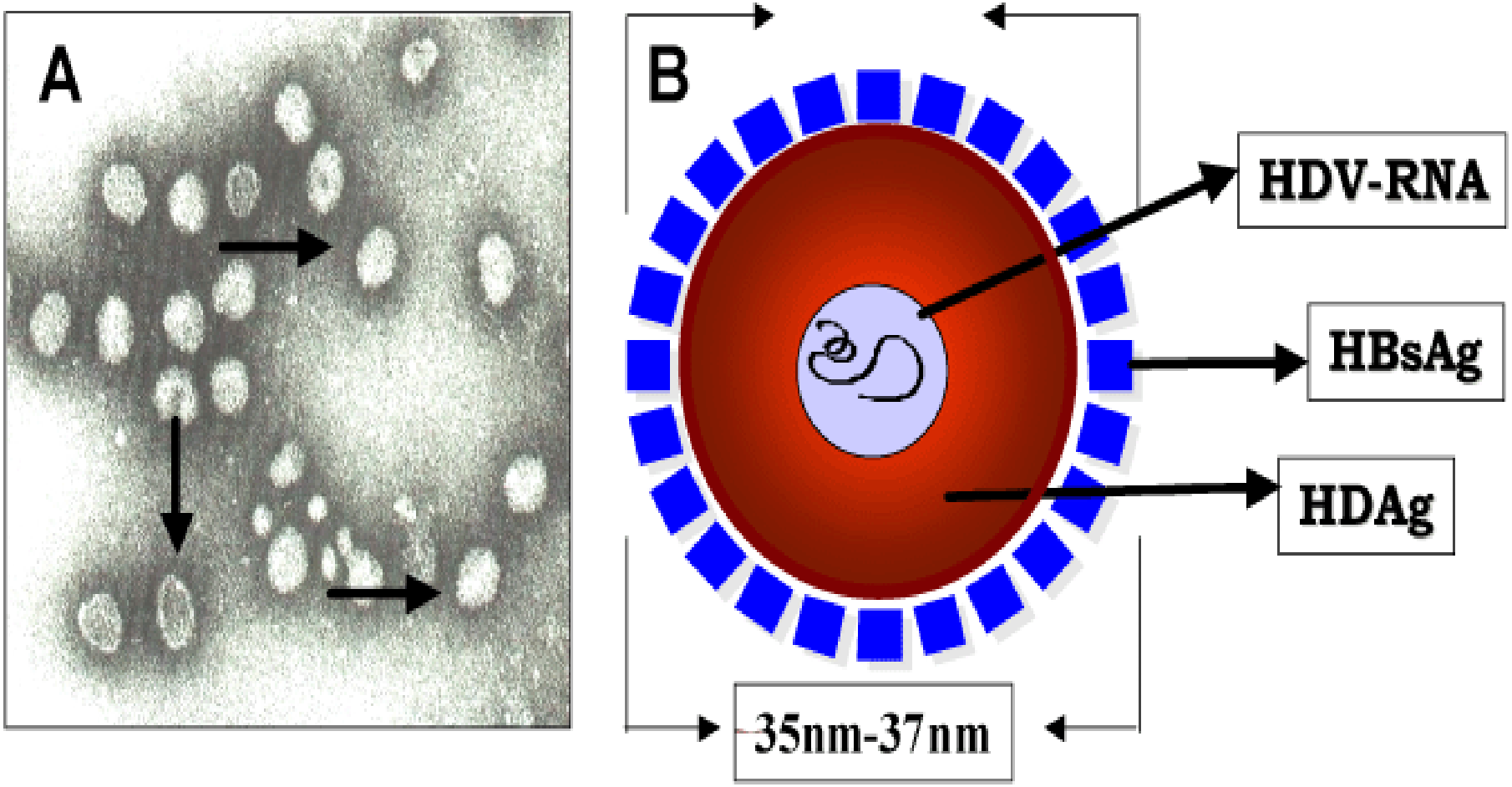
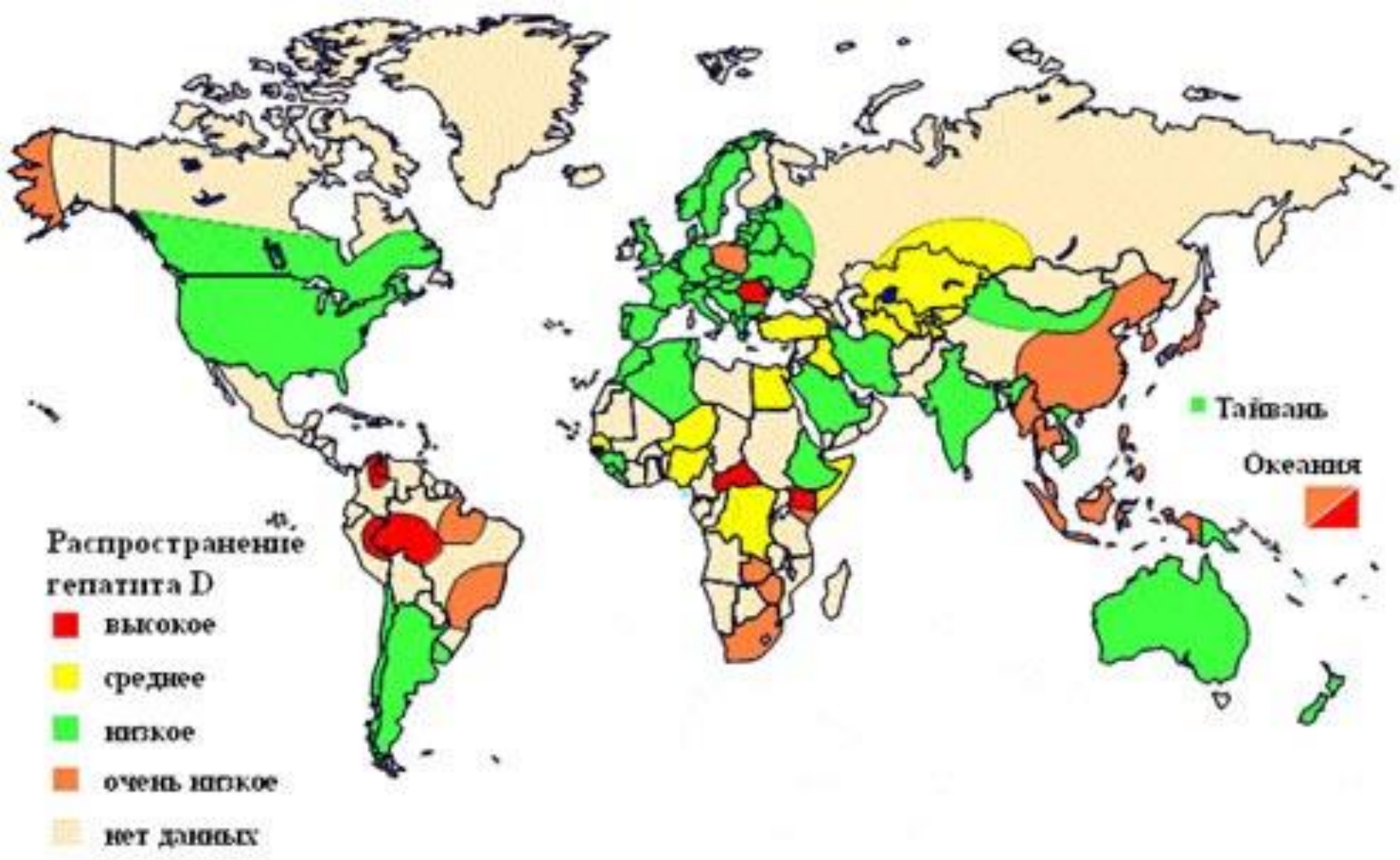


Figura 1 - A) Microscopia eletrônica do VHD, setas (Cortesia do Dr.Mario Rizzetto, Turim, Itália). B) Representação esquemática da partícula do VHD com envoltório do VHB (HBsAg).

Epidemiology of hepatitis D

- The reservoir of the hepatitis D virus is persons with chronic HBV infection who are simultaneously infected with HDV (they make up approximately 5% of chronic HBV carriers).
- The mechanism of transmission of the hepatitis D virus is identical to that of hepatitis B.
- Hepatitis D infection rates range from 0.15% to 25%. It is highest in the countries of South America and Central Africa.
- The hepatitis D virus has three genotypes, the 1st is considered European, the 2nd was found in patients from Japan and Taiwan, the 3rd genotype was found in patients in the Peruvian part of the Amazon.

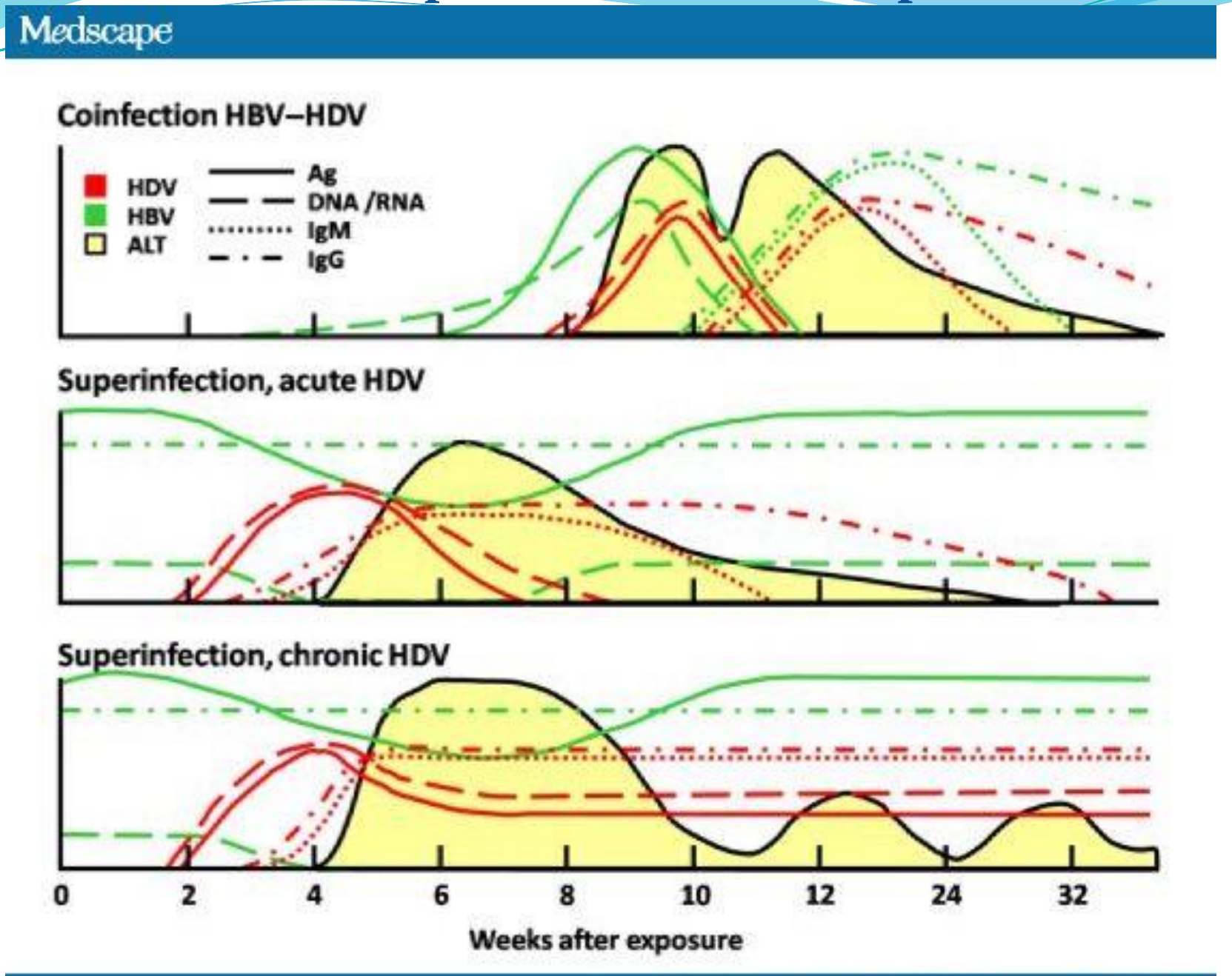
Geographic distribution of hepatitis D



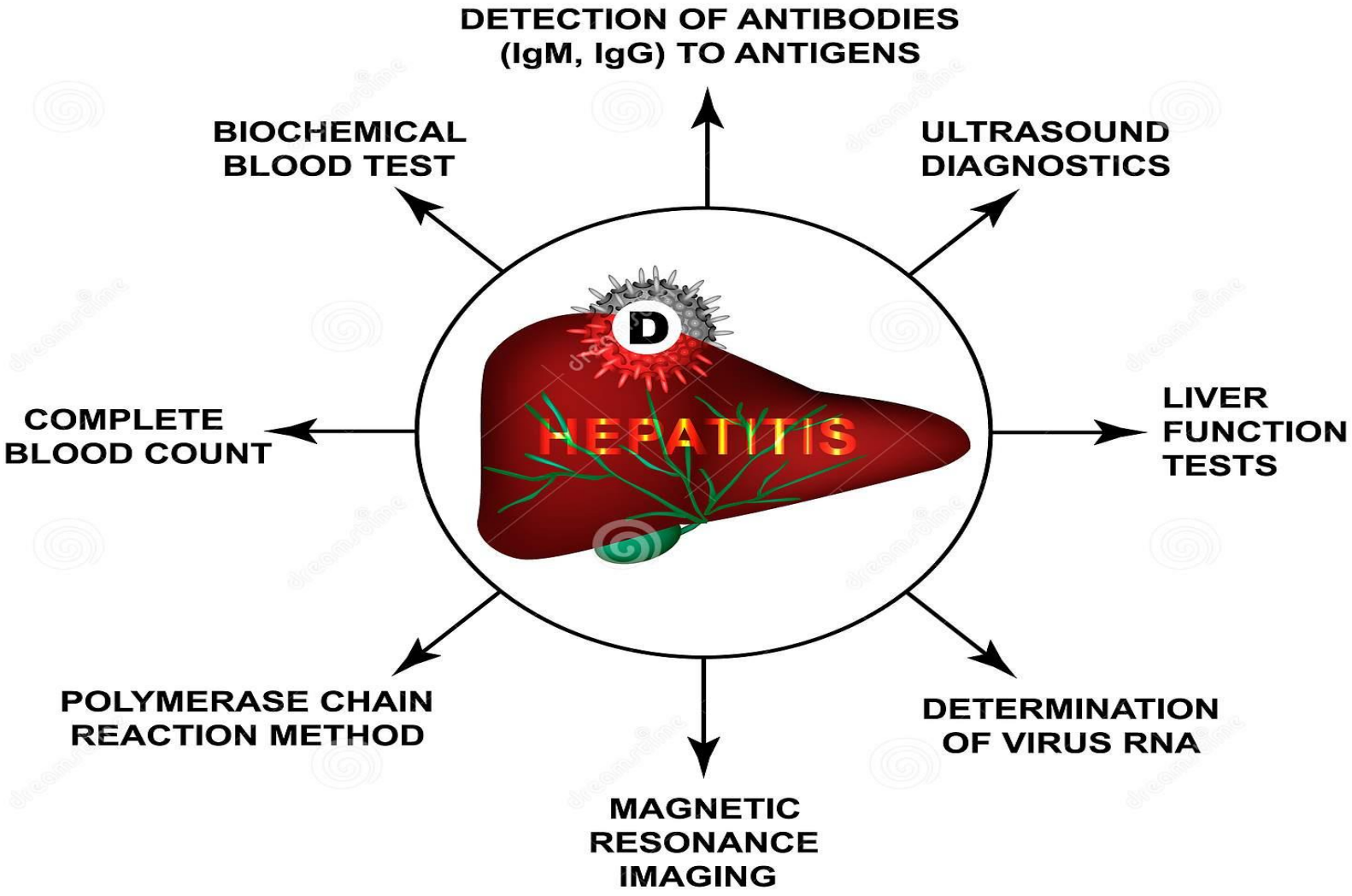
The pathogenesis of hepatitis D

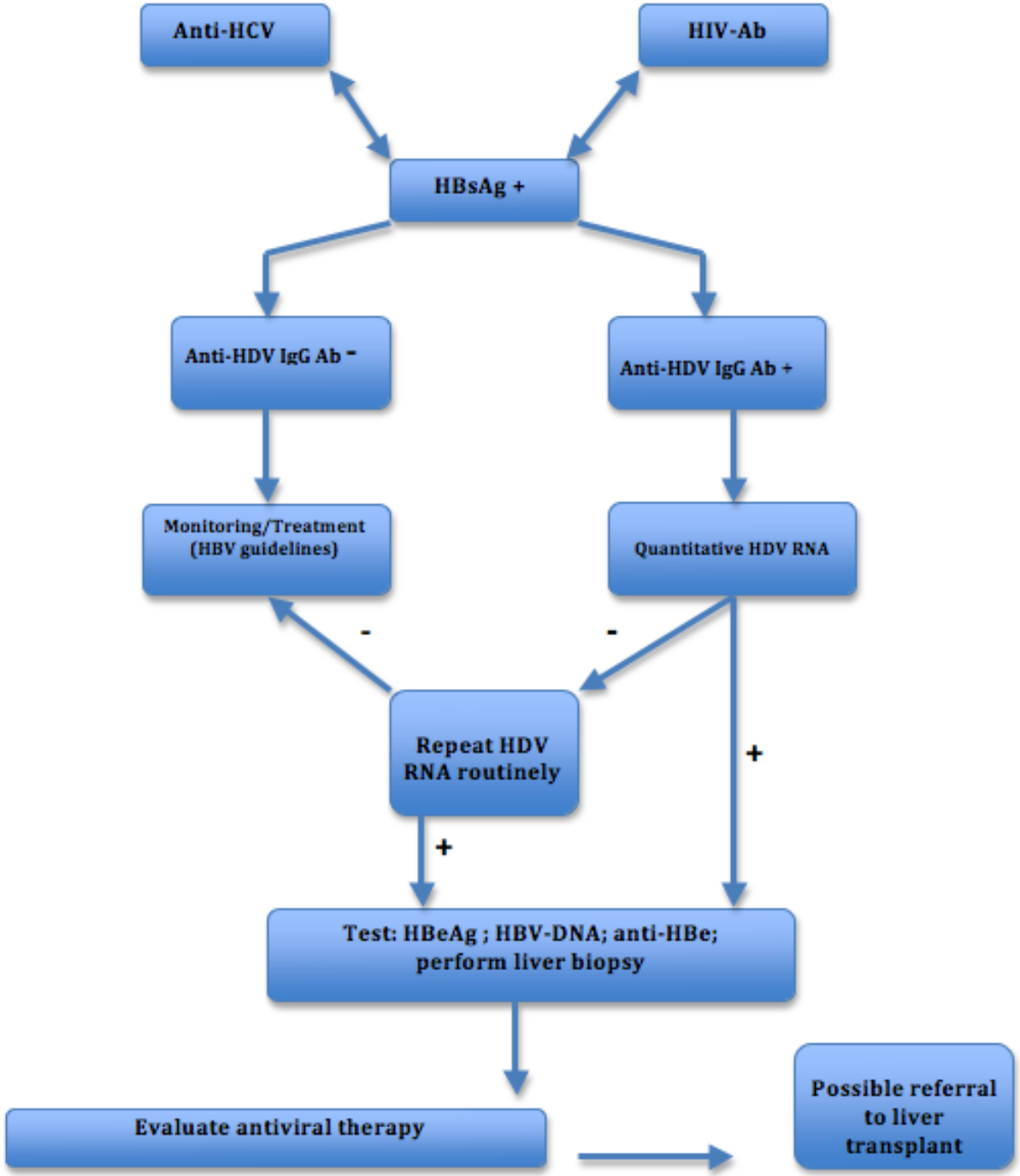
- The pathogenic properties of the hepatitis D virus can only be realized with a mixed infection with hepatitis B.
- The incubation period is 30-60 days.
- Hepatocytes are damaged as a result of the direct cytopathogenic action of the hepatitis D virus and the indirect action of the hepatitis B virus.
- Co-infection is characterized by the development of severe forms of acute hepatitis and a low frequency of chronicity. At the same time, a two-phase course of viral hepatitis is noted.
- Superinfection is characterized by a rarer development of severe and fulminant hepatitis and a higher frequency of chronic HBV infection (up to 80%). Superinfection in chronic hepatitis leads to more frequent transition to liver cirrhosis.

Coinfection and superinfection with hepatitis B and D

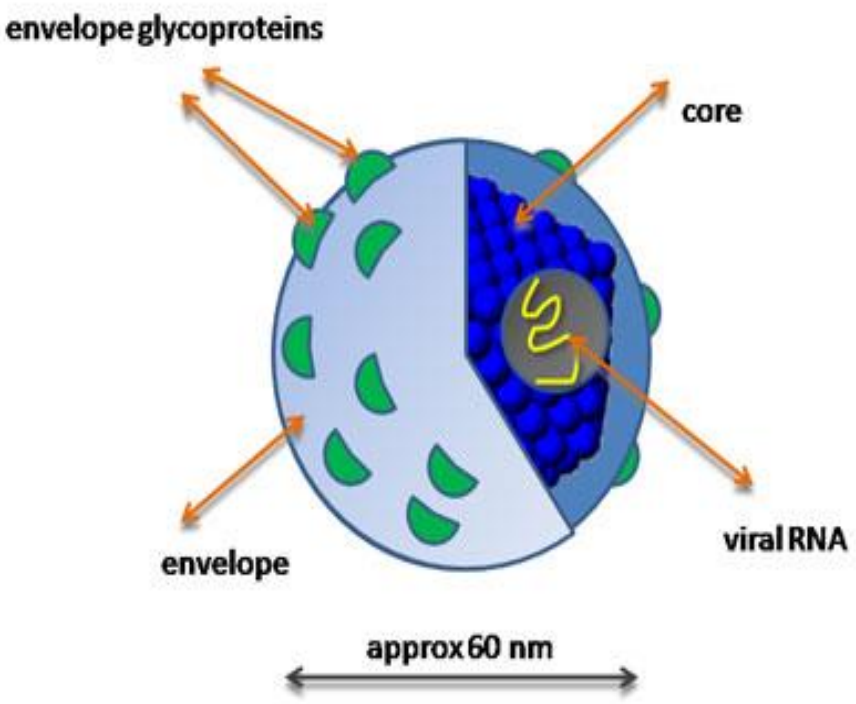


DIAGNOSIS OF HEPATITIS D

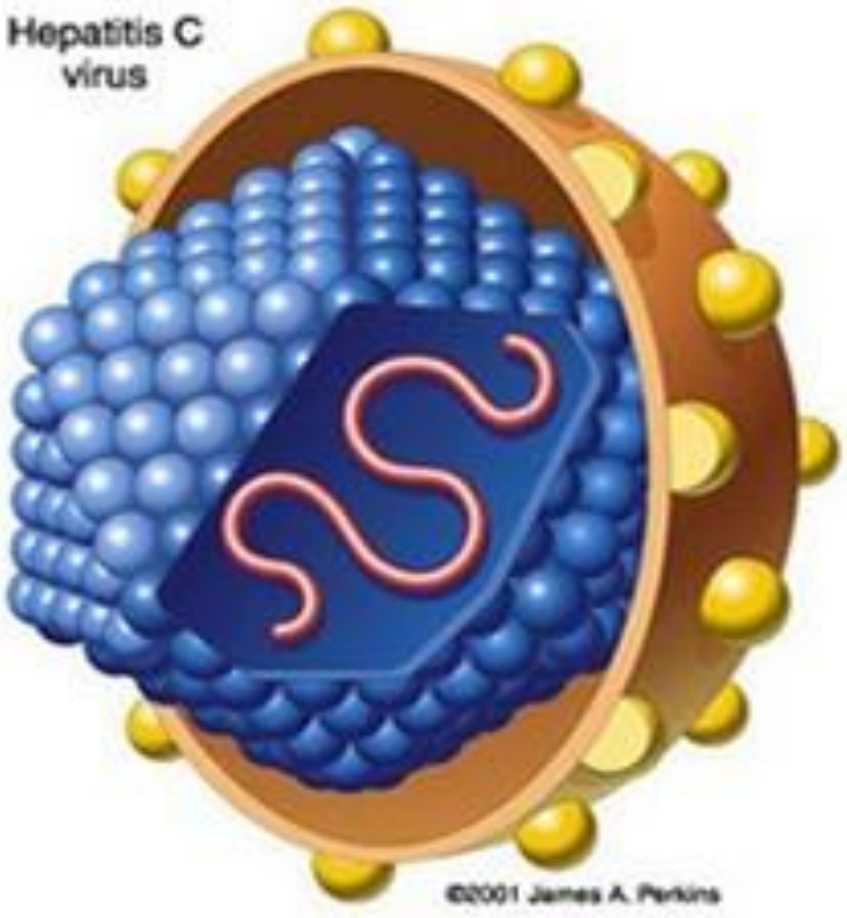



Anti-HCV
HIV-Ab
HBsAg +
Anti-HDV IgG Ab -
Anti-HDV IgG Ab +
Monitoring/Treatment (HBV guidelines)
Quantitative HDV RNA
-
-
Repeat HDV RNA routinely
+
+
Test: HBeAg ; HBV-DNA; anti-HBe; perform liver biopsy
Evaluate antiviral therapy
Possible referral to liver transplant

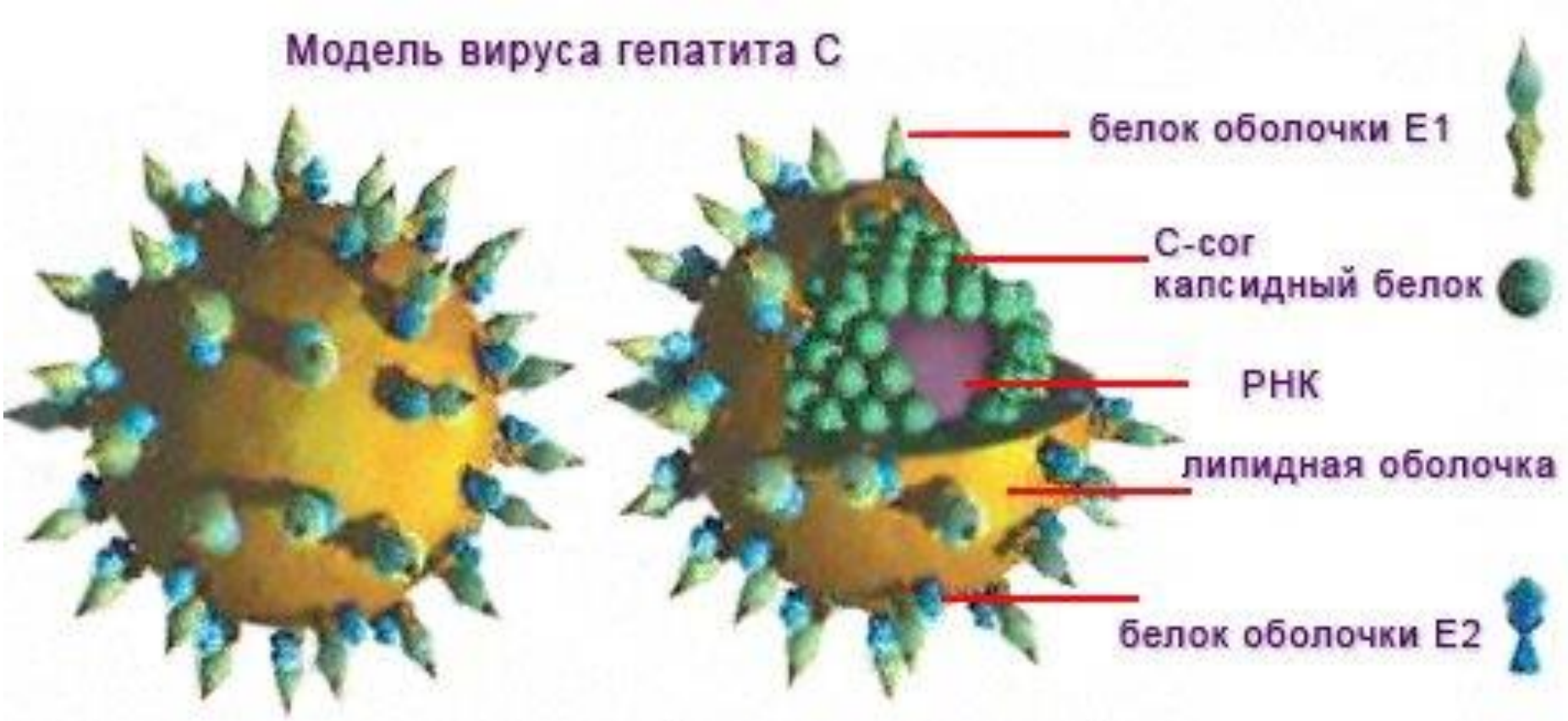
Hepatitis C virus (HCV) belongs to the Flaviviridae family, genus Hepacivirus. HCV is a complexly organized RNA-containing virus of spherical shape, 55-65 nm in diameter.



Structure of Hepatitis C Virus



The capsid is built according to the cubic type of symmetry, contains the structural core protein (core), Hcc antigen and non-structural proteins (NS), which are enzymes necessary for the reproduction of the virus. Lipoprotein envelope contains gp E1 and gp E2/NS1



Variability and genotypes of hepatitis C virus

- The hepatitis C virus is highly variable.
- There are 6 genotypes of the hepatitis C virus: 1 (1a, 1c, 1c), 2 (2a, 2c, 2c), 3c, 4, 5,6.
- Determination of the genotype is of practical importance, since it is believed that infection caused by 1 (especially 1c) and 4 genotypes is difficult to treat.
- In addition, about 100 subtypes of the hepatitis C virus have been identified, the RNA of which differs by more than 25% in the nucleotide sequence.
- There are also many quasi-species of the virus, the RNA of which differs by more than 15% (in one patient, the number of quasi-species of the virus can be in the millions).

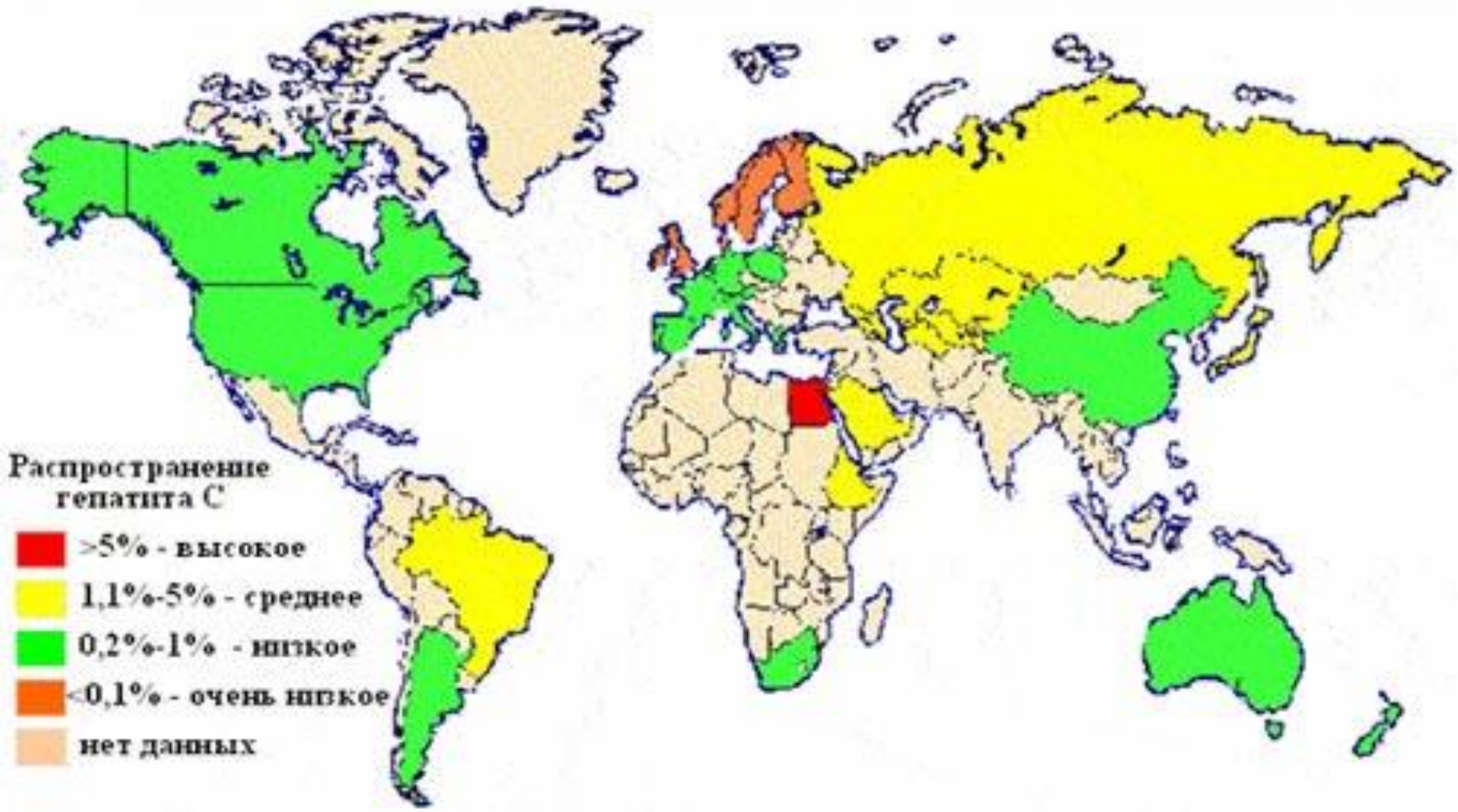
Epidemiology of hepatitis C

- Hepatitis C is anthroponosis.
- The source of infection is patients with acute and chronic hepatitis C.
- Routes of transmission are similar to those for hepatitis B, however, a low concentration of the virus in the blood and other biological fluids reduces the contagiousness index (two times lower than in hepatitis B),
- therefore, the sexual route of infection is less than 10%, and the vertical route is 5-7% of all cases of infection.
- The risk groups are the same as for hepatitis B.

Hepatitis C prevalence

- Globally, chronic hepatitis C infection affects 185 million people (approximately 3% of the world's population).
- Every year, 350,000-500,000 people die from hepatitis C.
- Hepatitis C occurs throughout the world. The regions of Central and East Asia and North Africa are most affected.

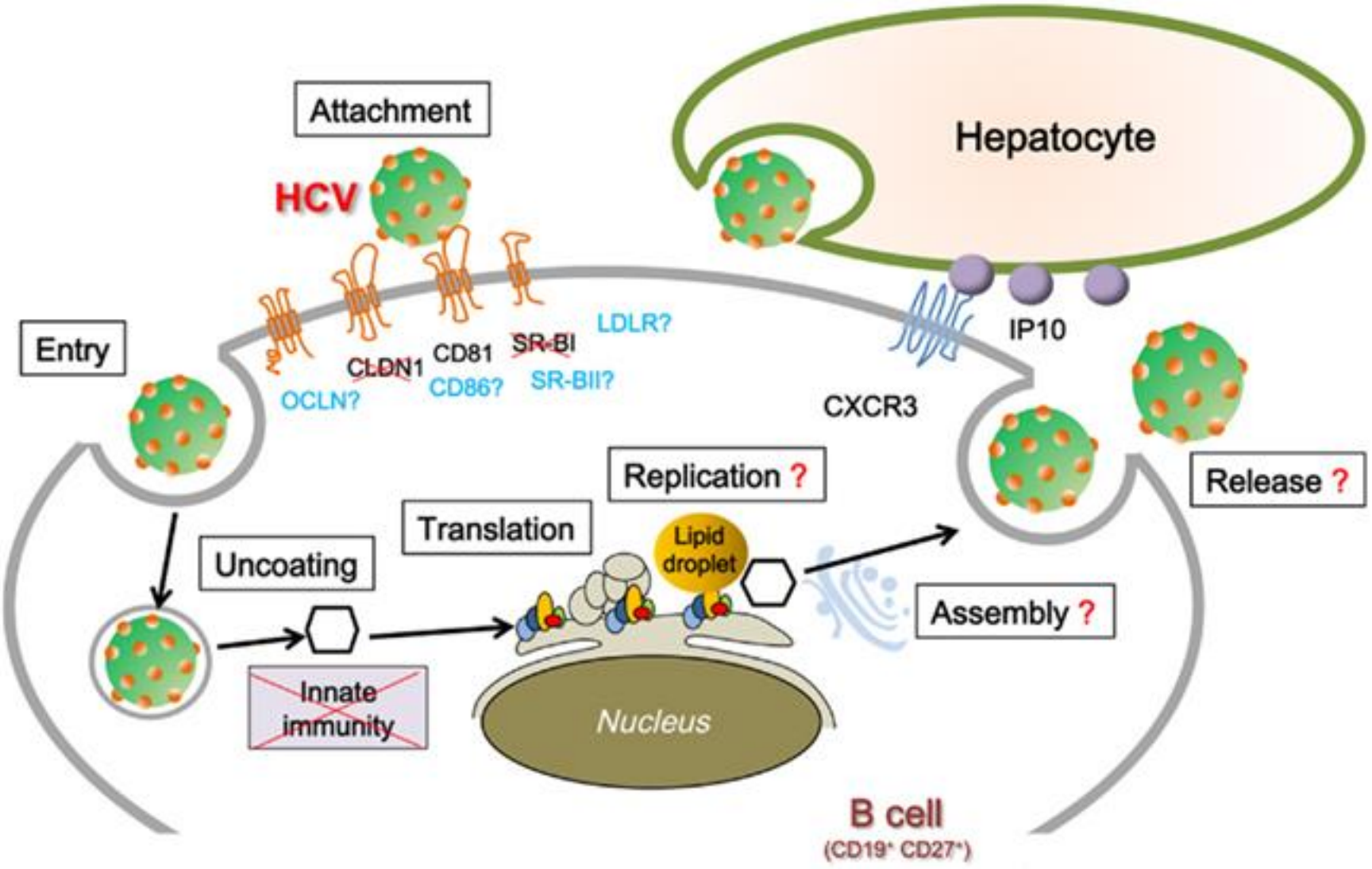
Geographic distribution of hepatitis C



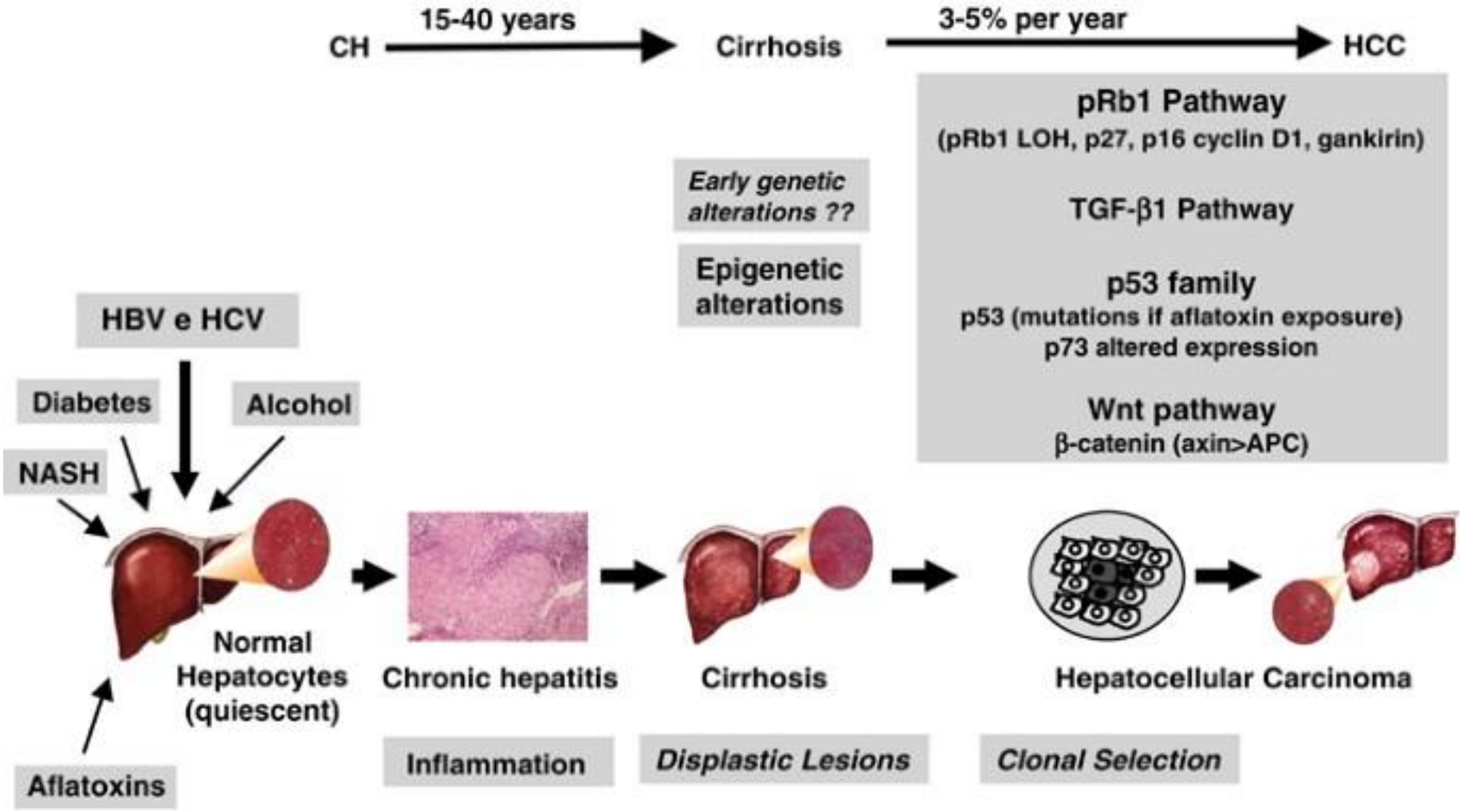
The pathogenesis of hepatitis C

- The hepatitis C virus causes acute and chronic infection.
- The incubation period is 15-150 days.
- Approximately 15-45% of infected individuals clear the virus spontaneously within 6 months of infection without any treatment.
- The remaining 55-85% of individuals develop chronic HCV infection.
- In individuals with chronic HCV infection, the risk of liver cirrhosis is 15-30% within 20 years.
- They also have a risk of developing liver cancer of 2-4% annually.

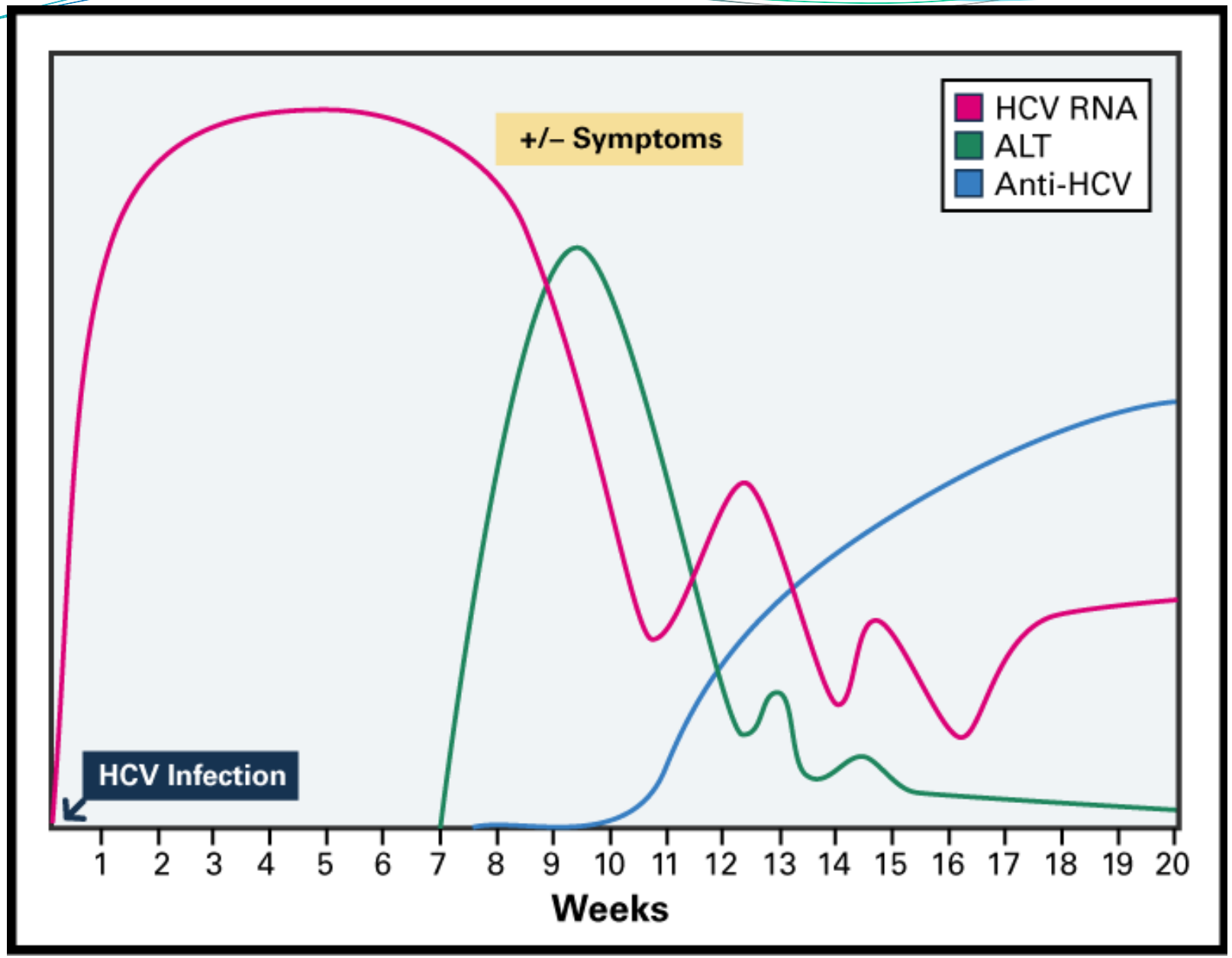
Life cycle hepatitis C



The nature of the changes occurring in the liver in viral hepatitis C



Serological markers of HCV infection



Hepatitis C markers and its laboratory diagnostics

- Determination of infection markers: Virus RNA by PCR - RNA is an indicator of active virus replication, can be detected as early as 1-2 weeks after infection and is the "gold standard" of diagnosis. PCR is the method of choice for early diagnosis of viral hepatitis
- Anti-HBC antibodies in 80% of cases are detected at 5-6 weeks from the moment of infection and in 90% of individuals - at 12 weeks after infection.
- To clarify the diagnosis, the presence of IgM and IgG to the nuclear (core) antigen (HCC-ag) and antibodies to non-structural NS proteins of the virus are determined.
- The presence of IgM antibodies to Hcc-ag indicates a current infection (acute or chronic in the developmental stage).
- The detection of IgG to Hcc-ag indicates infection with a virus or a past infection.
- Antibodies to non-structural proteins are found in the chronic stage.

Viral Hepatitis: Transmission and Incubation Periods

Incubation Period:

- Hepatitis A: 2-6 weeks
- Hepatitis E: 2-9 weeks

Type:

"Acute" types of hepatitis

Transmission:

Food & Water borne

Incubation Period:

- Hepatitis B: 2-6 months
- Hepatitis C: 15-150 days
- Hepatitis D: Unlimited (Restricted by Hep. B)

Type:

"Chronic" type of Hepatitis

Transmission:

Blood borne

Viral Hepatitis Clinic (1)

- **In the prodromal period, there are: asthenic-vegetative, dyspeptic, febrile, respiratory (catarrhal or influenza-like), arthralgic and general toxic syndromes. The activity of ALT and AST increases, the level of bilirubin increases, the urine darkens.**
- **During the peak period: all syndromes of the prodromal period intensify, jaundice syndrome appears (with an icteric form), urine acquires the color of dark beer, feces become discolored, the size of the liver increases, it becomes painful on palpation.**

Viral hepatitis clinic (2)

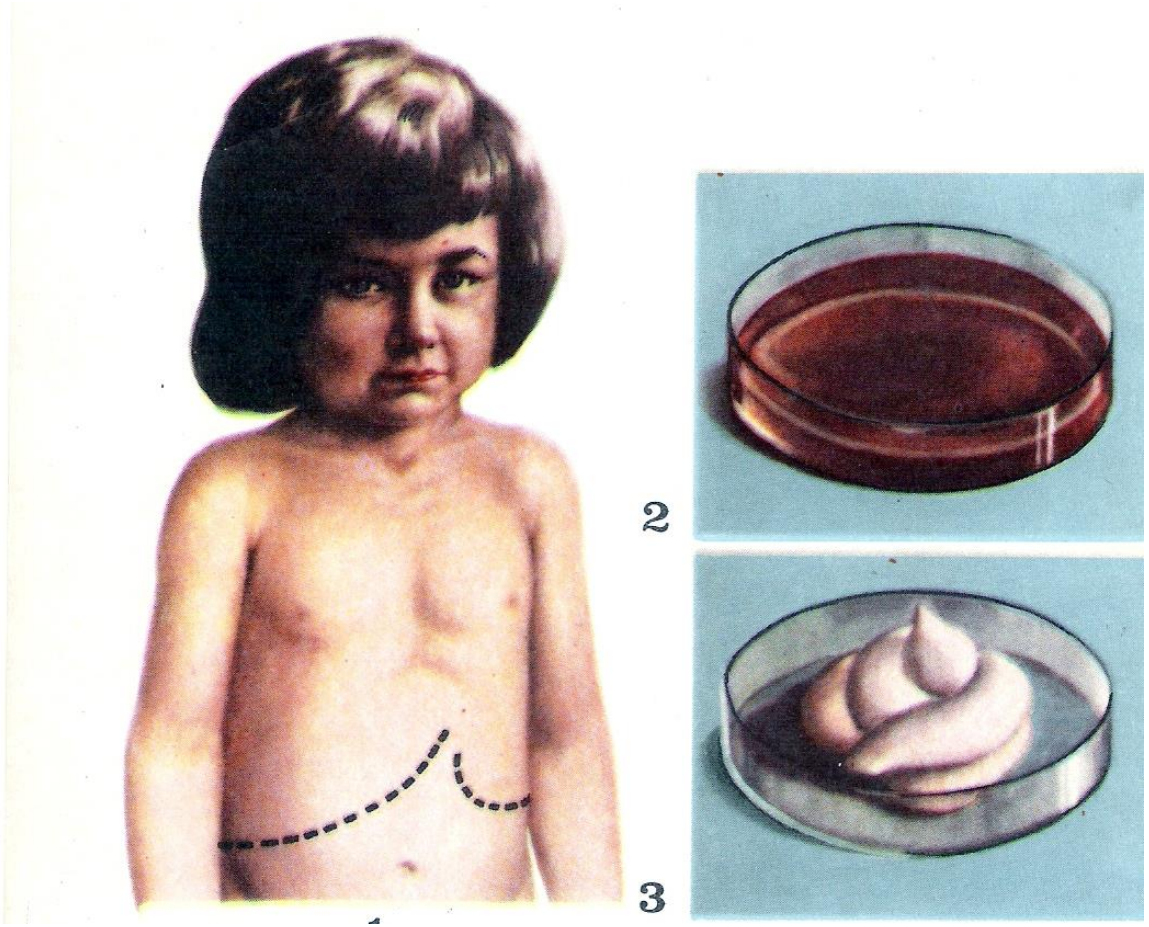
- **The resolution of the disease depends on a number of factors:**

- if reparative processes prevail over alternative ones, then the stage of recovery begins;

- if liver damage and homeostatic shifts progress, then the condition of patients is aggravated, encephalopathy, dysfunction of the adrenal glands may develop;

- with hepatitis B and C, a third option is possible - chronicization of the process.

Some clinical symptoms of viral hepatitis



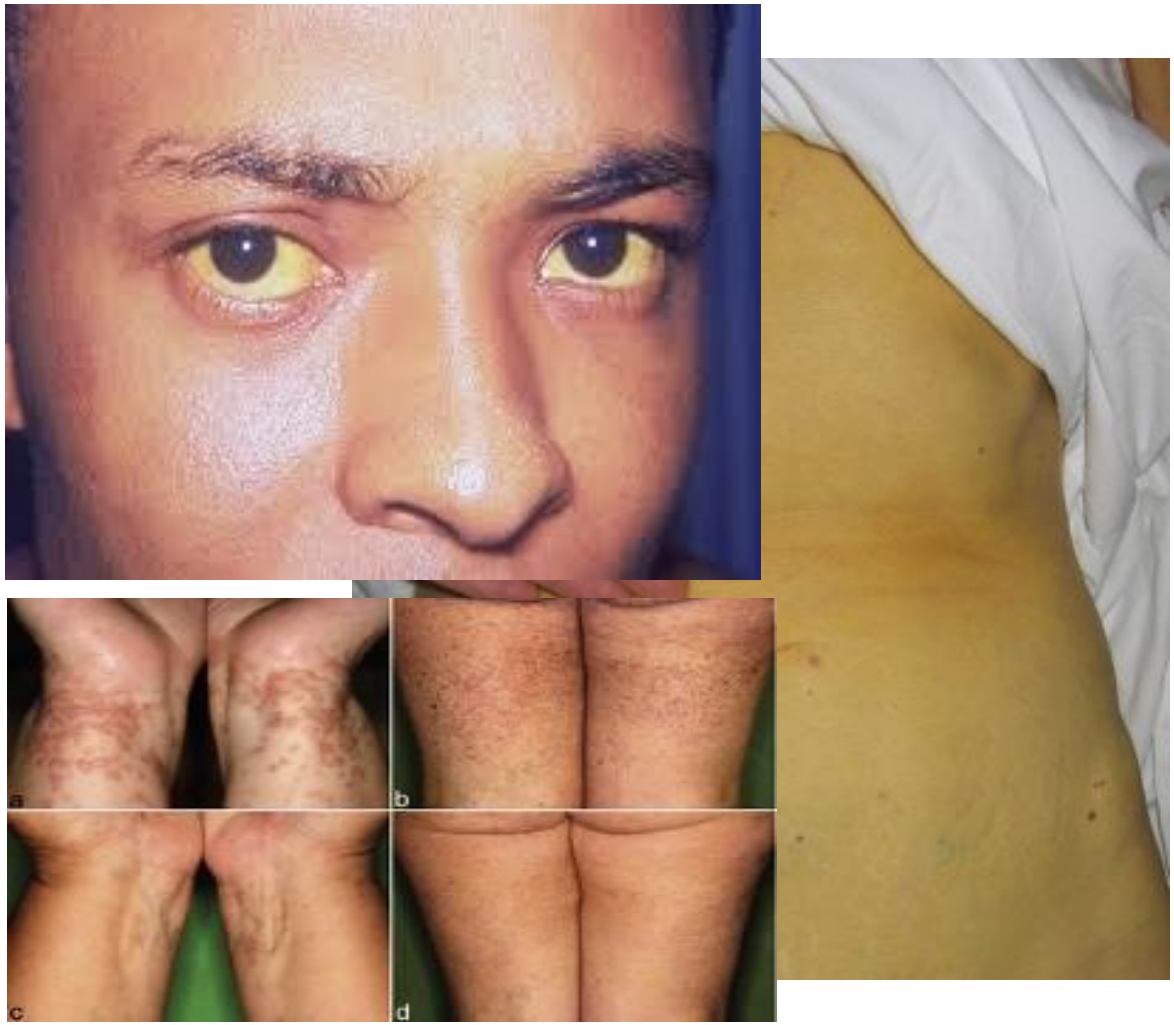
Pale coloured stools

Dark urine

Yellow eyes and skin

Unexplained weight loss

Some clinical symptoms of viral hepatitis



Some clinical symptoms of viral hepatitis

Diagnosis of viral hepatitis

- **Clinical diagnostics using physical (palpation and percussion of the liver) and instrumental (ultrasound, CT, NMR and liver biopsy, as well as its fibroscanning) research methods**
- **Laboratory studies: a change in the picture of peripheral blood (leukopenia with lymphocytosis, monocytosis and eosinophilia against the background of normal ESR), an increase in the level of bilirubin in the blood and urine and a bilirubin index, an increase in the activity of some liver enzymes (aminotransferases, alkaline phosphatase and gamma-glutamyl transpeptidase), an increase thymol test, decrease in prothrombin index and plasma coagulation factors.**
- **Specific diagnostics: identification of specific markers of infection with hepatitis viruses (viruses, their antigens, antibodies to them and their nucleic acids). It is carried out by serological and molecular methods.**

Preventation

Table 5. Viral hepatitis: supporting signs, prevention and action to be taken

	Incubation	Signs and symptoms	Prevention	Treatment
Hepatitis A	Average: 28 days Range: 15–50 days	Children often asymptomatic Abrupt onset Malaise, anorexia, nausea, fever, jaundice	Vaccine Food and water hygiene Personal hygiene	Slow recovery Supportive care No chronic carrier status
Hepatitis B	Average: 75 days Range: 30–180 days	Commonly asymptomatic Abdominal pain, anorexia, nausea, fatigue, jaundice	Vaccine Avoid contact with blood or body fluids	Supportive care Antivirals for chronic disease, long-term expensive therapy
Hepatitis C	2 weeks to 6 months	Many asymptomatic Abdominal pain, anorexia, nausea, fatigue, jaundice	Avoid contact with blood or body fluids	Supportive care Antivirals or interferon for chronic disease
Hepatitis D	Co-infection with hepatitis B	Similar to hepatitis B but more severe	Avoid contact with blood or body fluids	Supportive care
Hepatitis E	Average: 6 weeks. Range: 2–8 weeks	Can be asymptomatic Acute hepatitis, fever, malaise, nausea, jaundice—can last up to 4 weeks	Food and water hygiene Personal hygiene Avoid raw meat	Supportive care

From: Field et al, 2010; Dawood, 2012; World Health Organization, 2013c, Zuckerman, 2013

The likelihood of contracting blood-borne infections when pricked with a contaminated needle

Pathogen	Average risk, %	Range, %
HİV	0,23	1 - 2,38
HCV (hepatit C)	0,75	1 - 10,3
HBV (hepatit B)	10	2,5 - 30

Universal Precautions

- **Proper, full use of protective equipment;**
- **Wash hands and other parts of the skin;**
- **Prevention of accidental and other occupational risks of infection**

HIV, HIV infection, AIDS

- **HIV - Human Immunodeficiency Virus (HİV - Human Immunodeficiency Virus);**
- **HIV infection (HIV - infection) is a long-term infectious disease that develops as a result of infection with the human immunodeficiency virus (HIV) and is characterized by progressive damage to the immune system.**
- **AIDS - Acquired Immunodeficiency Syndrome (AIDS - Acquired Immunodeficiency Syndrome) - the terminal stage of HIV infection, characterized by deep damage to the immune system, in particular, a decrease in the number of CD4 + lymphocytes, multiple opportunistic infections and neoplastic processes**

History of the discovery and study of HIV/AIDS (1)

- June 5, 1981 - The message “Pneumocystis pneumonia. Los Angeles" by Donald Francis et al. on the detection of 5 cases of severe (in two cases - fatal) pneumocystis pneumonia in young homosexual people, observed in three clinics in Los Angeles from October 1980 to May 1981;
- A month later, in the 26th issue of this bulletin, a publication by A. Fridman et al. “Kaposi's sarcoma and pneumocystis pneumonia among male homosexuals. New York and California" on the detection of pneumocystis pneumonia in 26 more homosexual men, 8 of whom were also diagnosed with Kaposi's sarcoma

History of discovery and study of HIV/AIDS (2)

- At the end of 1981, CDC specialists gave a provisional definition of the disease and developed temporary criteria for its diagnosis: 1) the presence of T-cell deficiency, 2) the presence of pneumocystis pneumonia and other infections caused by opportunistic pathogens, and 3) the presence of Kaposi's sarcoma in persons younger than 60 years and/or brain lymphoma.
- In early 1982, in a CDC report, Michael Gottlieb and colleagues at the University of California named the disease Acquired Immune Deficiency Syndrome and first coined the acronym AIDS.

History of the discovery and study of HIV/AIDS (3)

•1983 - L.Montagnier, F.Barre-Sinoussi et al. (France) described in the journal "Science" a virus isolated from an AIDS patient - Lymphadenopathy associated virus (LAV)

•1984 - R. Gallo et al. (USA) also isolated a new virus, which they called Human T-cell leukemia virus III (HTLV-III)

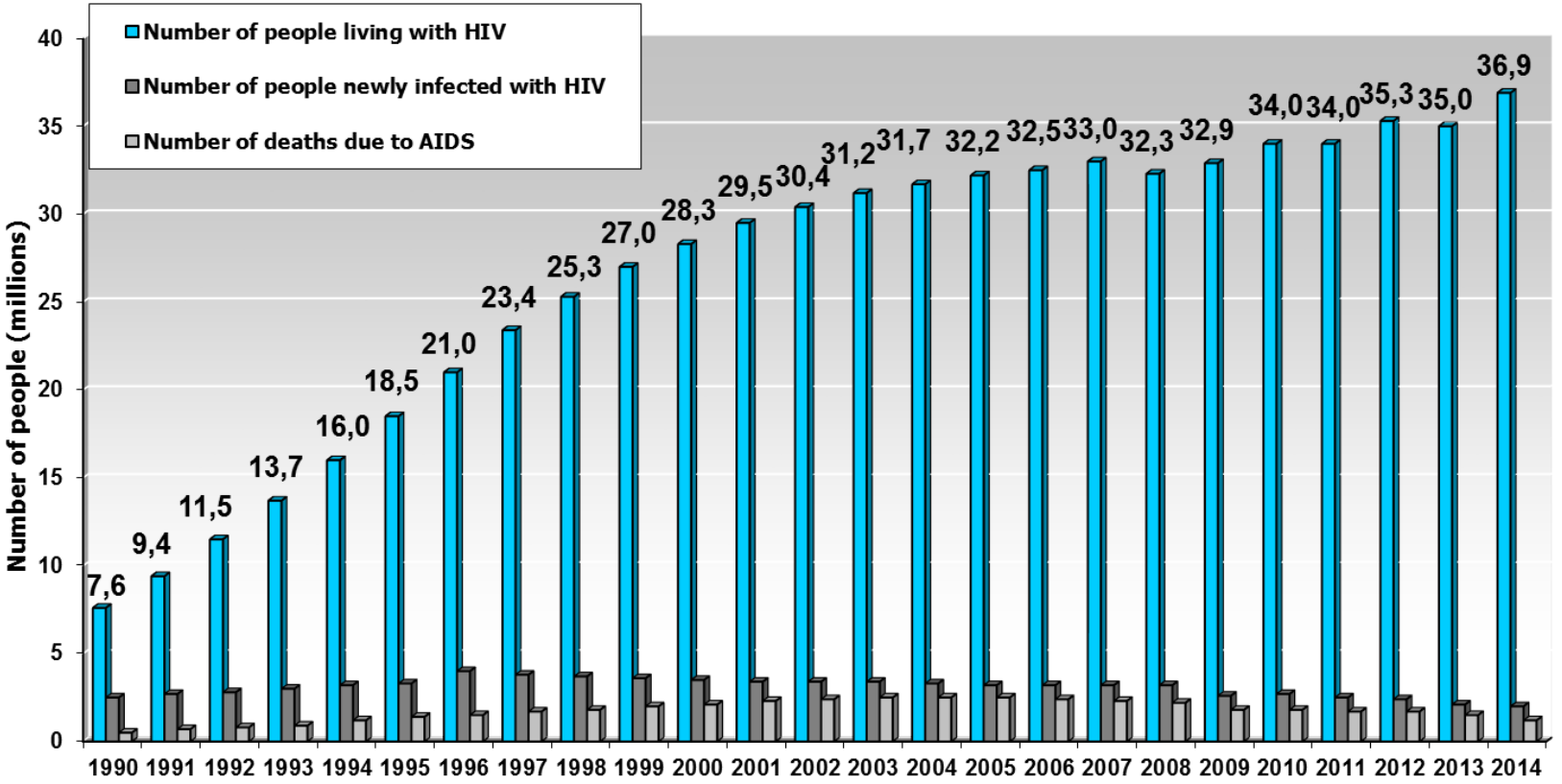
•Since the end of 1984, the causative agent of AIDS has been designated as LAV/HTLV-III.

•1986 - at the 2nd International AIDS Conference, in order to unify the nomenclature, it was decided to name the causative agent Human Immunodeficiency Virus (HİV), or human immunodeficiency virus (HIV).

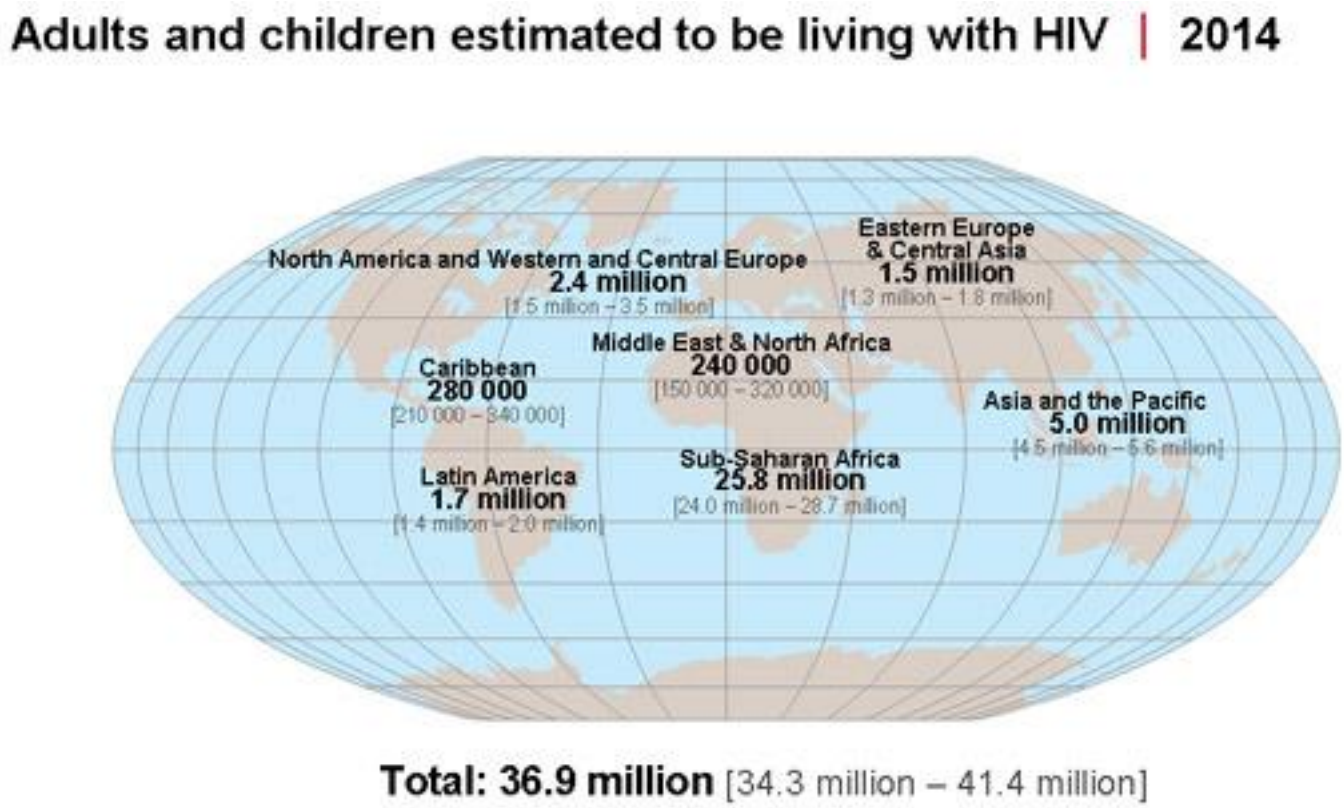
History of the fight against HIV/AIDS

- **1987 - Introduction of the first drug for the treatment of AIDS**
- **1988 - December 1 declared by the United Nations as World AIDS Day**
- **1995 - use of highly active retroviral therapy (HAART) drugs**
- **1996 - Establishment of a joint United Nations program on AIDS**
- **2001 - UN General Assembly, adoption of the resolution "Global Crisis-Global Action«**
- **2011 - UN General Assembly, adoption of a new resolution on HIV/AIDS.**

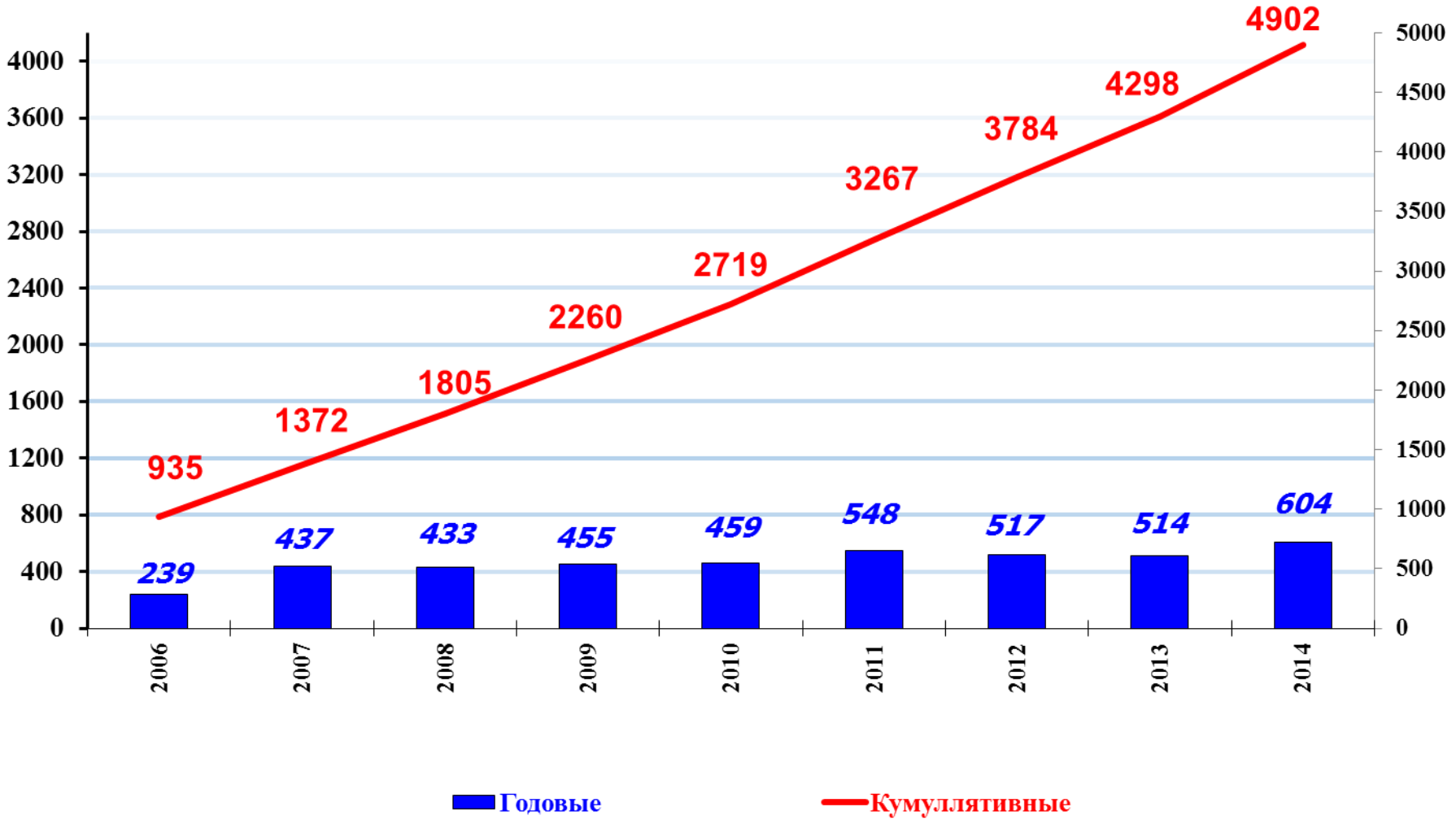
Number of people living with HIV, new HIV infections and AIDS deaths worldwide(1990 - 2014)



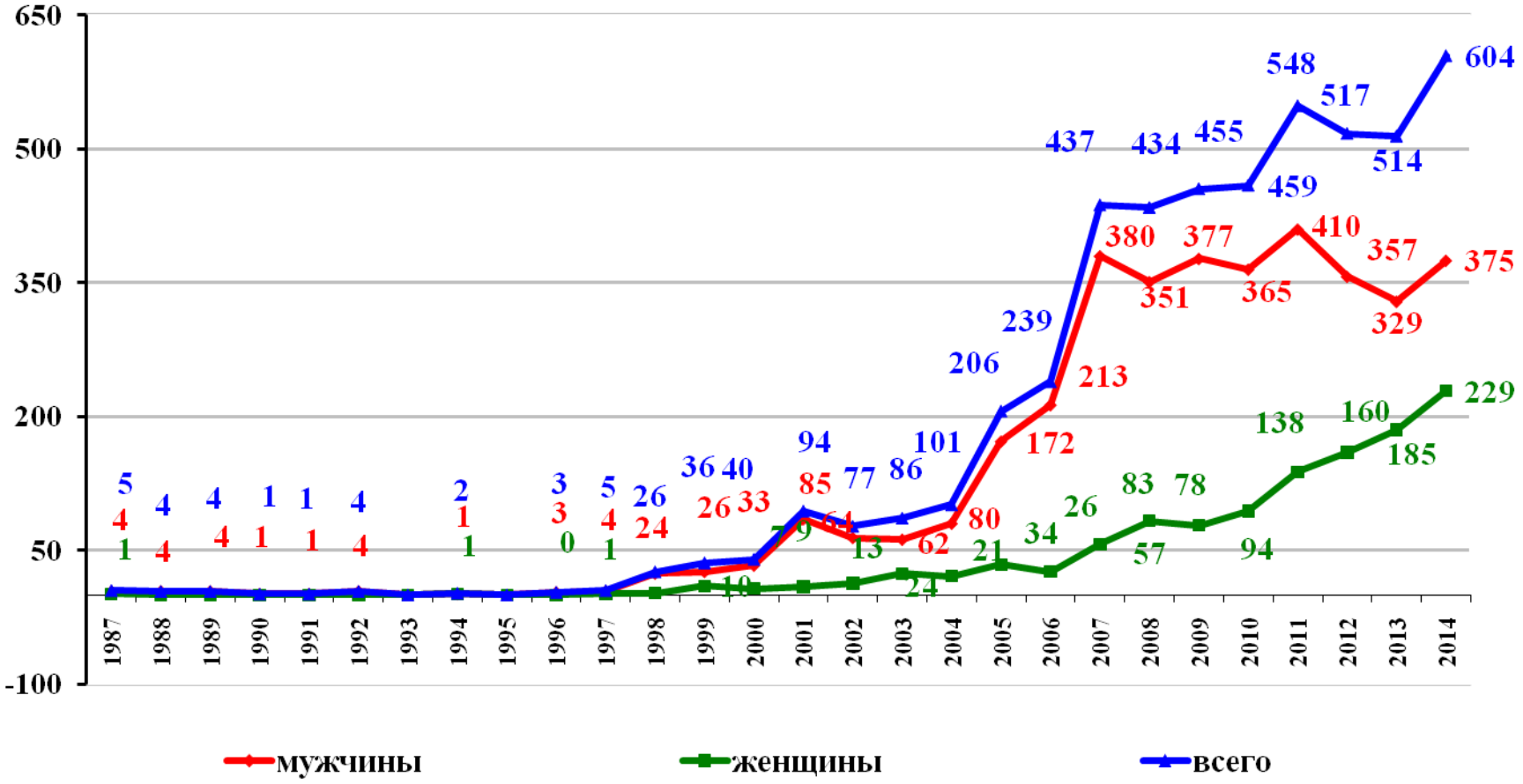
Estimated number of adults and children living with HIV 2014



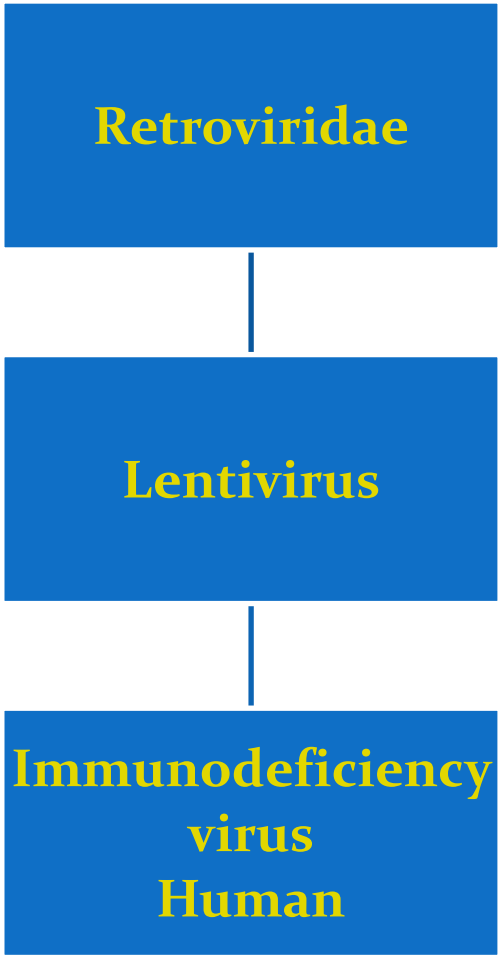
Dynamics of detection of HIV cases in Azerbaijan (2006-2014)



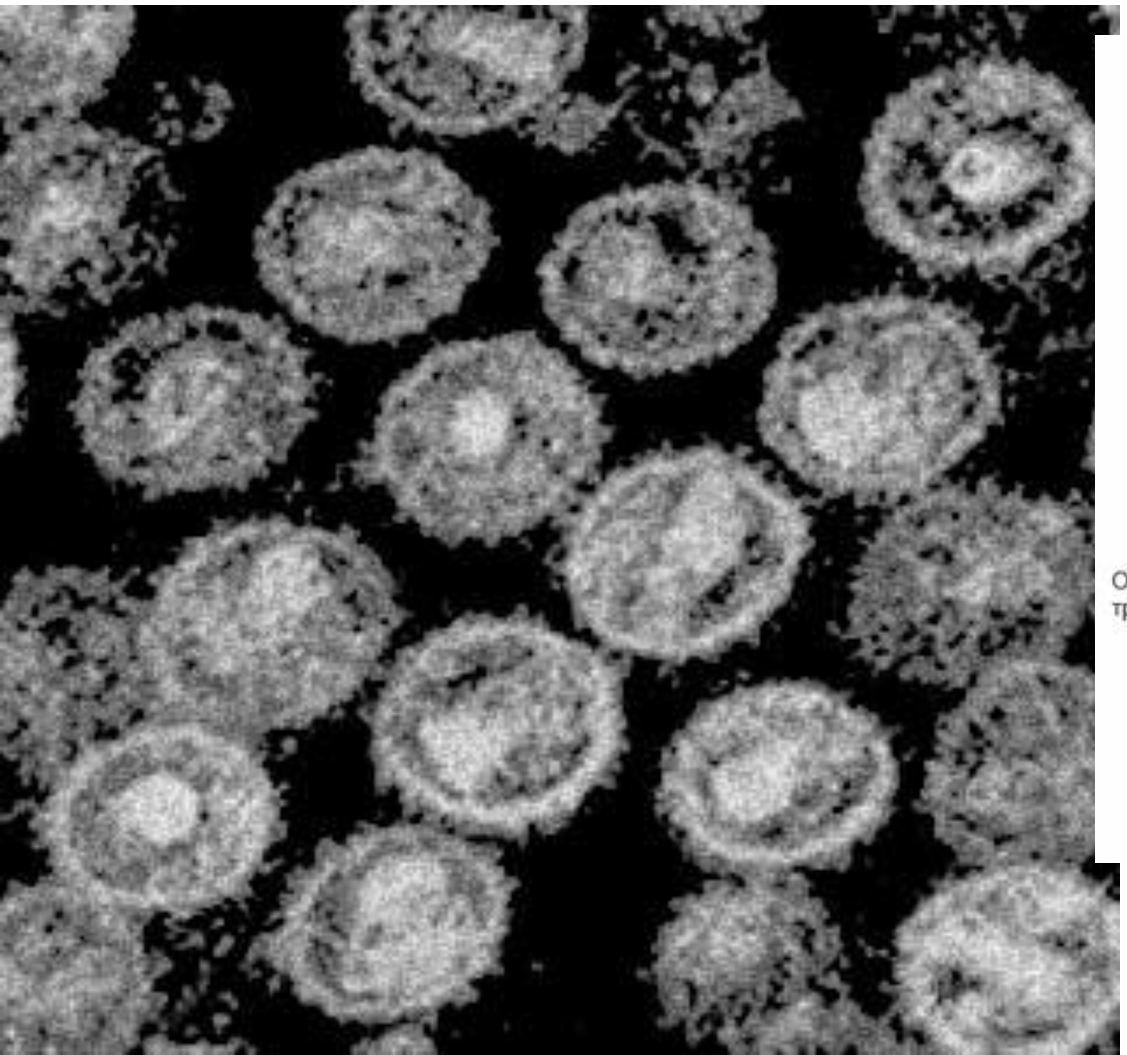
Dynamics of detection of HIV infection in Azerbaijan and gender distribution of HIV-infected people (1987 - 2014)

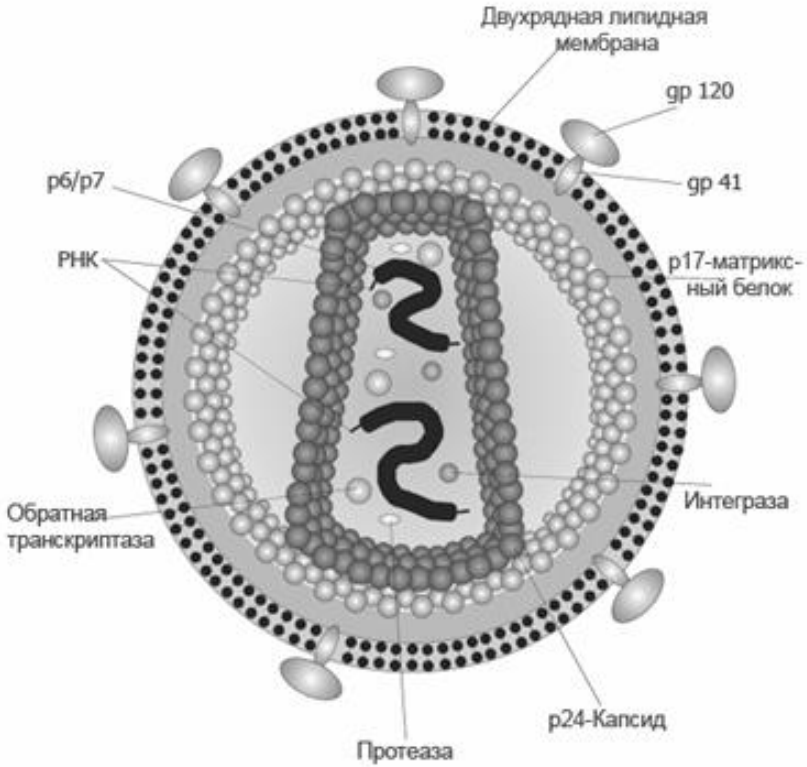


Human immunodeficiency virus (taxonomy)

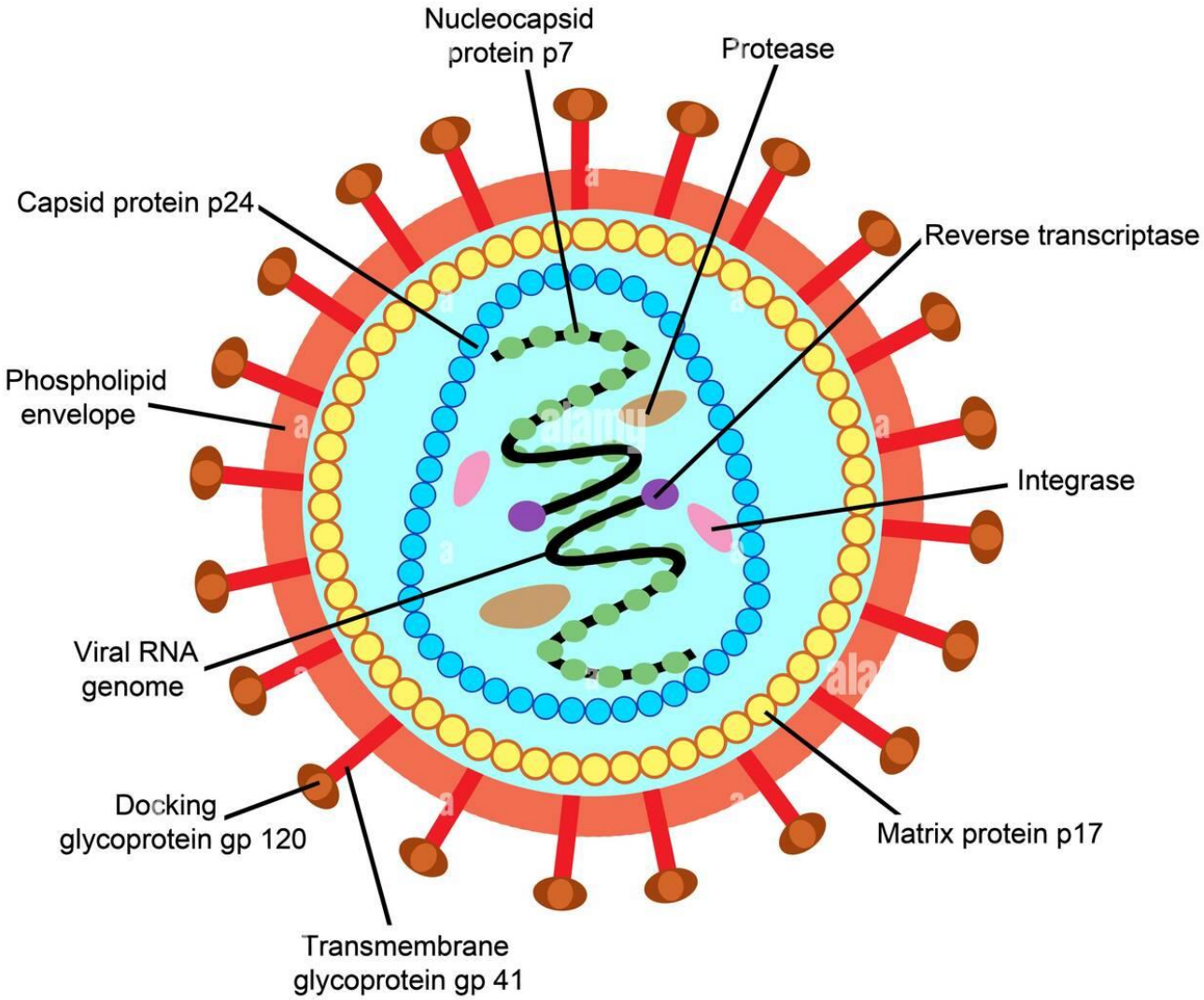


Human immunodeficiency virus (electronogram and diagram)

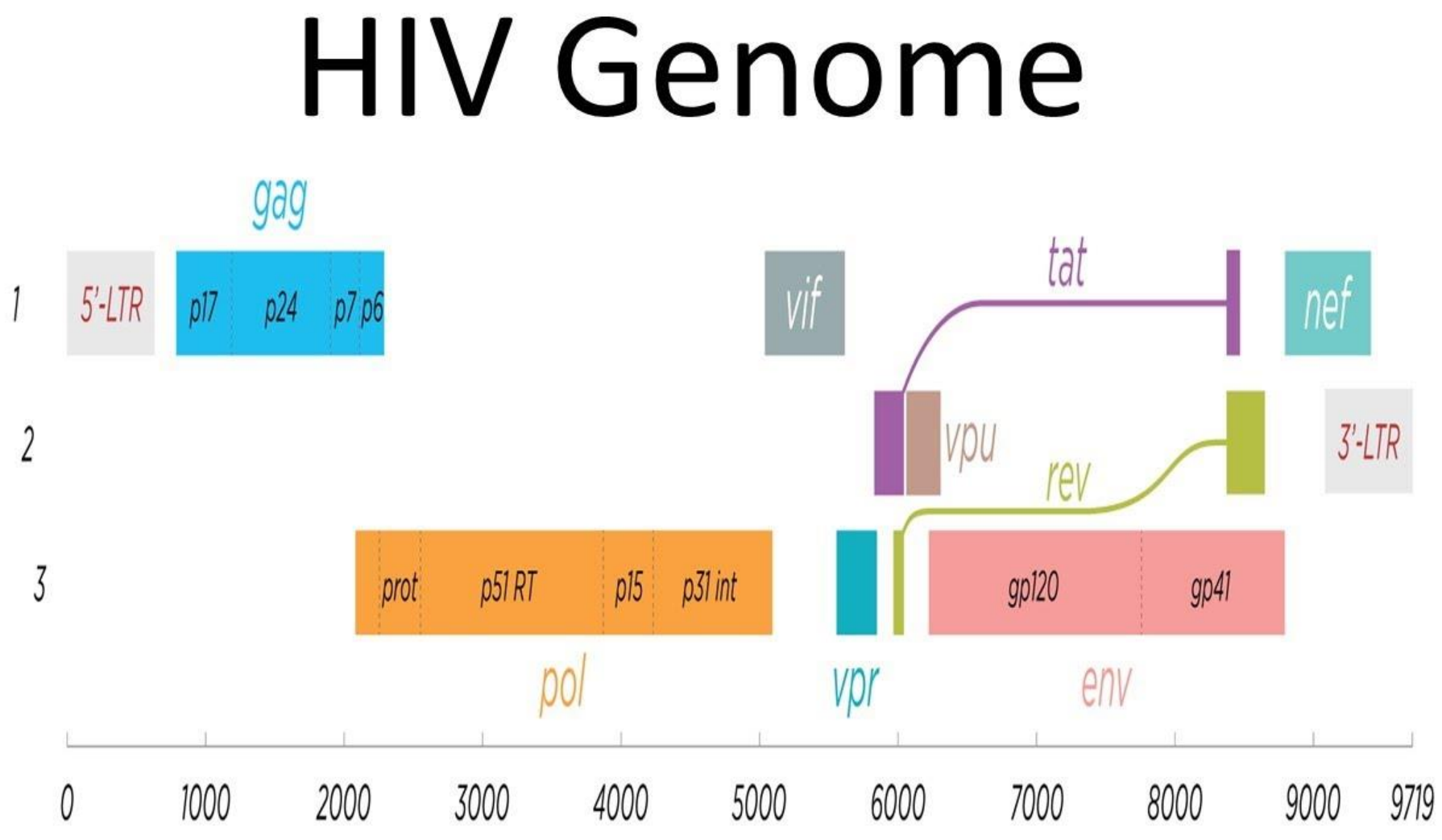




HUMAN IMMUNODEFICIENCY VIRUS - HIV



HIV genome


HIV Genome
gag
1
5'-LTR
p17
p24
p7
p6
vif
tat
nef
2
vpu
rev
3'-LTR
3
prot
p51 RT
p15
p31 int
gp120
gp41
pol
vpr
env
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
9719

HIV genes (1)

1. **Structural genes:**

- **Env (envelope) - encodes the translation of the gp160 precursor protein, which during processing is cleaved into two virion envelope proteins - gp120 and gp41;**
- **Gag (group-Specific antigens) encodes the translation of a precursor protein with a molecular weight of 55 kDa, which is cleaved into p17, p24, p7, p6 during processing. Gag forms the capsid;**
- **Pol (polymerase) - encodes the synthesis of protease (p52/53), reverse transcriptase (p64/66/68), RNase (p15 and integrase (p31/32)**

HIV genes (2)

2. Regulatory genes (main):

- **Tat (transactivator of transcription) - encodes a regulatory protein necessary for the full biosynthesis of viral RNA and capable of increasing the synthesis of viral proteins by more than 1000 times;**
- Nef (negative regulatory factor) - encodes a protein that leads to the suppression of mRNA transcription and, as a result, to a decrease in the synthesis of viral proteins;

HIV genes (3)

3. Regulatory genes (auxiliary):

- **Rev (regulator of viral expression) - encodes a protein that accelerates the process of viral messenger RNA transport from the nucleus to the cytoplasm;**
- **Vif (viral infectivity factor) - encodes a protein that increases the infectious ability of newly formed virions;**
- **Vpr (virus protein regulatory) - encodes a protein that provides the activating function of the long terminal repeat (LTR)**
- **Vpu (virus protein unknown) - absent from HIV-2, encodes a protein that plays a functional role in the assembly of virions and their separation from the host cell;**

HIV variability

- HIV variability is associated with a high mutation rate (spontaneous mutation rate 1:10,000)Причины высокой скорости мутаций:
- high reproduction rate (up to 1010 new virions can be formed per day)

- in the process of reverse transcription, genetic errors occur regularly (with a frequency of 3x10 -5) - point mutations, while there are no repair mechanisms

- During reverse transcription, recombinations occur at a high frequency

HIV genetic heterogeneity

- Genetic heterogeneity - the presence of different genetic variants of the virus
- A quasi-species is a genetically close, but at the same time heterogeneous and constantly changing virus population, represented by virions (and viral RNA) that differ from each other in nucleotide sequences in viral RNA by up to 10%.
- The body of an HIV-infected person in the preclinical phase contains 106, and at the AIDS stage - 108 quasispecies

HIV genetic groups

- There are 3 groups of HIV - M (major), N (new) and O (outline)
- According to the composition of nucleotide sequences in viral RNA, genetic groups differ by 25-40%
- Within the group, genetically heterogeneous "clades" (subtypes) are distinguished, which differ in genetic composition by 20-30%.

Phenotypic manifestations of variability

- Depending on the rate of reproduction and infectivity:

highly infectious and reproduce quickly (rapid/high)

- low-infectious and poorly reproduced (slow / low)

- By cytopathic action:

- weakly reproducing and not forming syncytium

- reproduce rapidly, but do not form syncytium

- rapidly reproducing and forming syncytium

- According to cellular tropism:

- лимфоцитотропные

- моноцитотропные

HIV antigens

All structural and regulatory proteins of HIV have antigenic properties and cause the formation of corresponding antibodies. HIV antigens are divided into:

- **The core antigens of the virion - core ("gag" gene) - are group-specific and are common with other retroviruses;**
- **Virion envelope antigens - env ("env" gene) - are species-specific and unique to HIV**

Epidemiological features of HIV infection

Source of infection

Infected person at all stages of the disease

HIV-infected biofluids:

→blood

→ sperm

→ secret of the cervix

→ mother's milk

→cerebrospinal fluid

Ways of getting HIV

- Sexual:

With homo- and heterosexual contact with an HIV-infected person;

Parenteral:

- when transfusing HIV-infected blood and its preparations;
- when using HIV-contaminated medical instruments and/or solutions, including when injecting drug use;
- when transplanting organs from an HIV-infected donor.

Perinatal:

from an HIV-infected mother to her child during pregnancy and childbirth (vertical);

- during breastfeeding (horizontal).

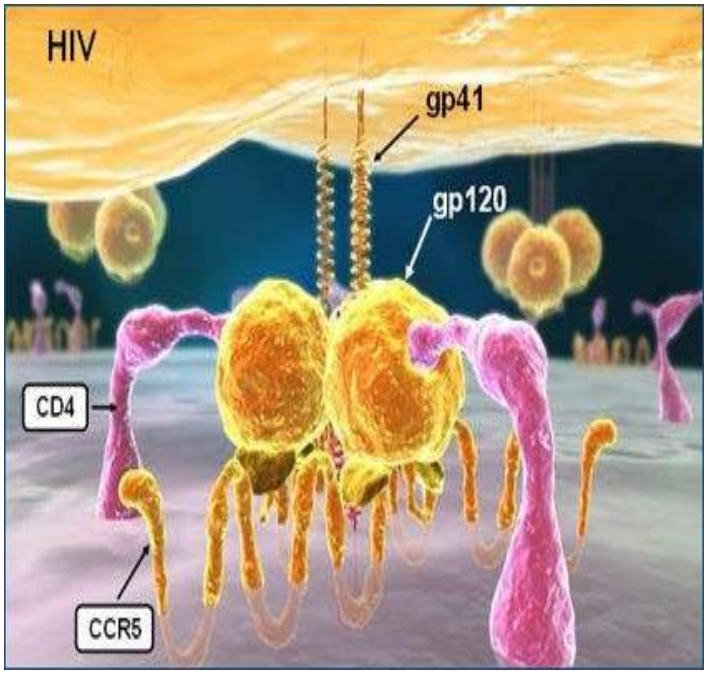
Probability of HIV transmission (WHO)

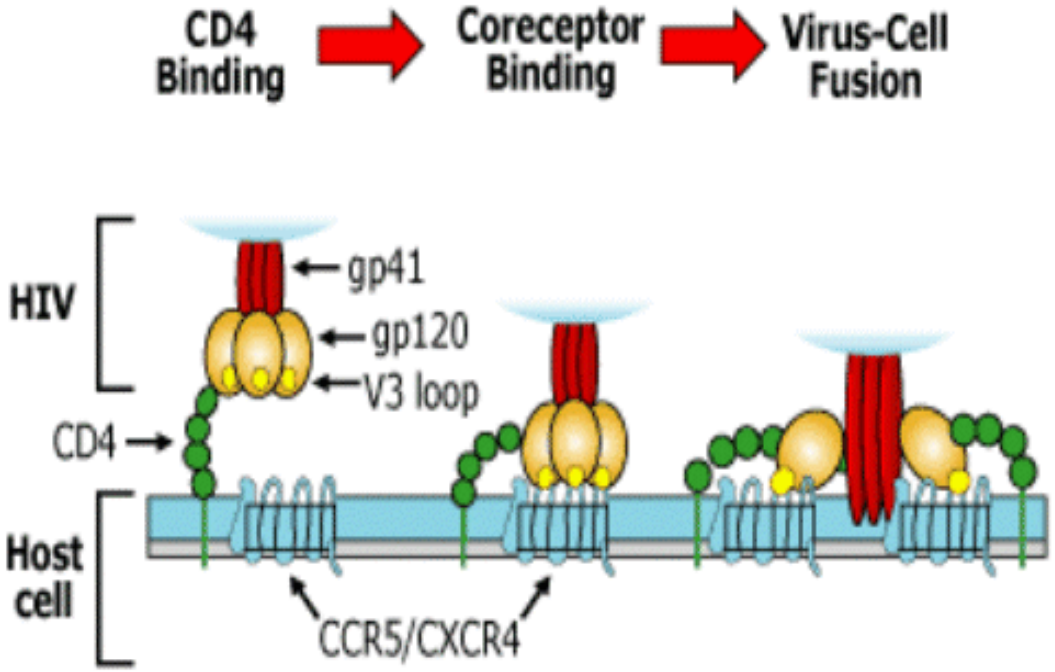
Transmission route	Transmission probability, %
Blood transfusion	92,5
Mother to child transmission of HIV	15 - 30
Sharing needles and syringes to administer drugs	0,8
Anal intercourse: passive partner	0,5
Percutaneous needle prick	0,3
Mucosal contact	0,1
Vaginal intercourse: women	0,15 – 1,01
Anal intercourse: active partner	0,065
Vaginal intercourse: men	0,01 - 0,15
Oral intercourse: passive partner	0,01
Oral intercourse: active partner	0,005

HIV persistence in the environment

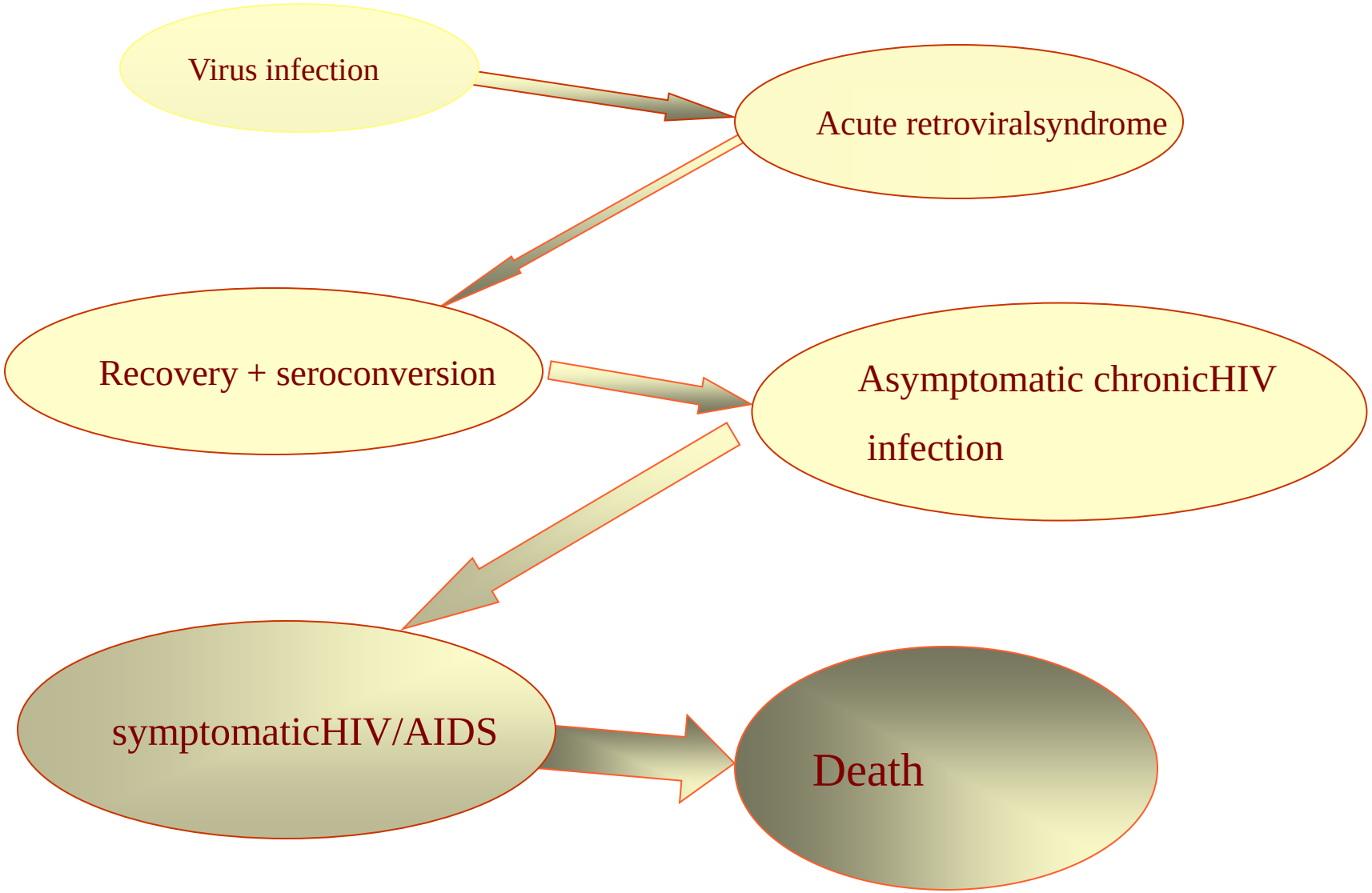
- **HIV is sensitive to all known disinfectants;**
- **Dies when heated to 56 ° C for 30 minutes;**
- **For HIV, solar and artificial UV radiation, all types of ionizing radiation are detrimental;**
- **When plasma is dried at 25 ° C, it dies after 7 days, at 30 ° C - after 3 days, at 55 ° C - after 5 hours;**
- **In a liquid medium at a temperature of 23-27 ° C, it remains active for 15 days, at 36 ° C - 11 days;**
- **It remains in frozen blood and serum for many years;**
- **In frozen semen, it lasts for several months.**

Attachment of HIV to a target cell

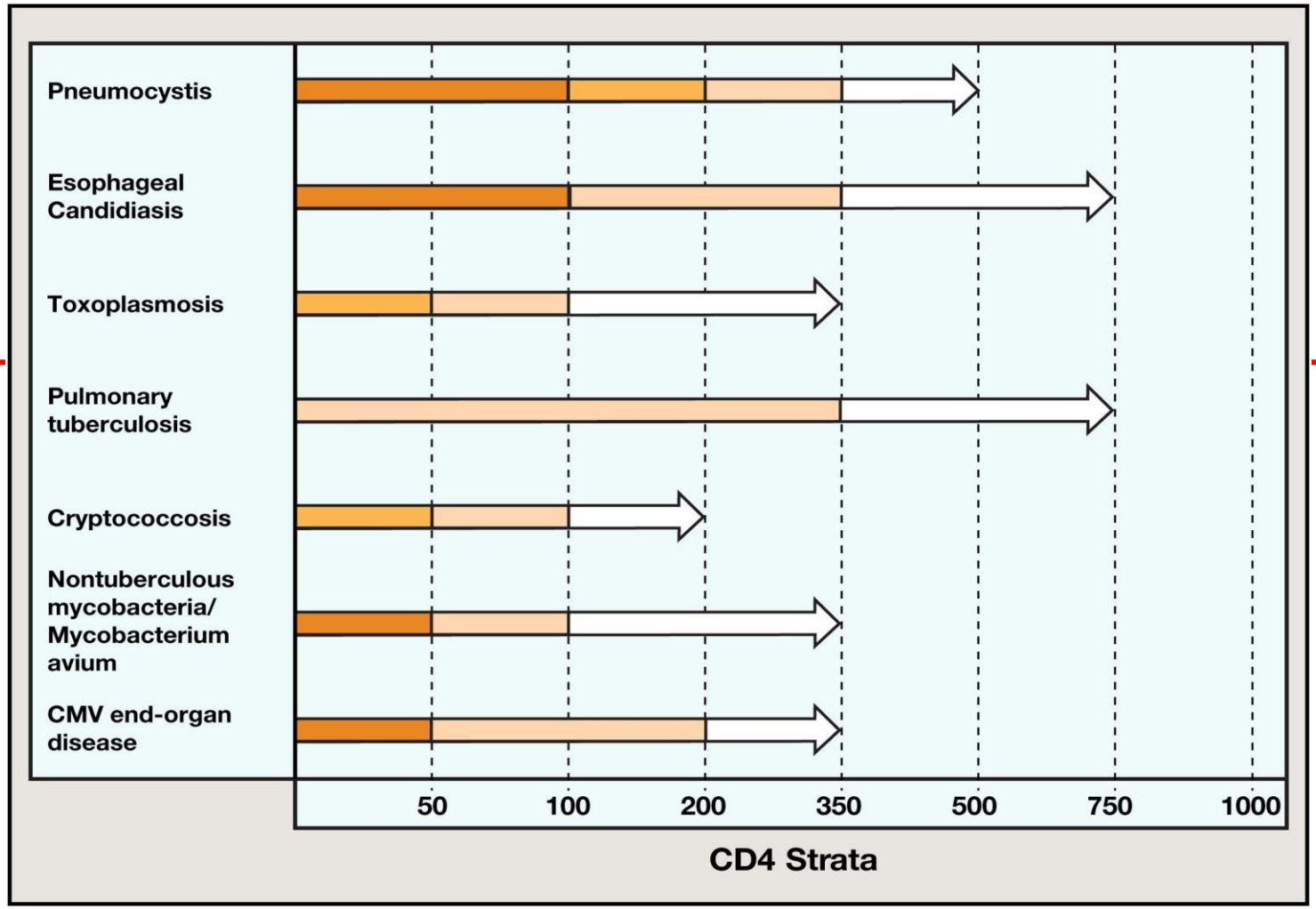




Development of HIV infection without antiretroviral therapy



ASSOCIATION BETWEEN THE RISK OF OPPORTUNISTIC INFECTIONS AND THE NUMBERLYMPHOCYTES CD4+

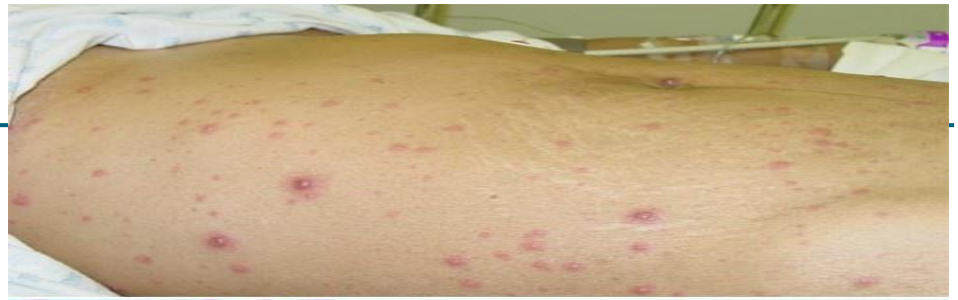


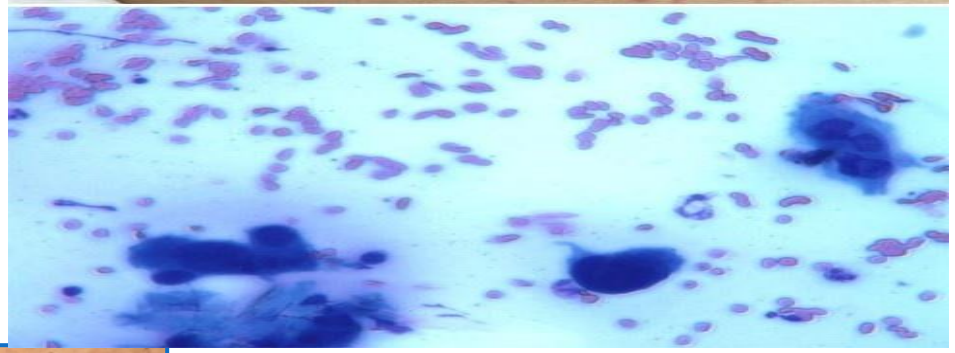
Clinical classification of HIV infection

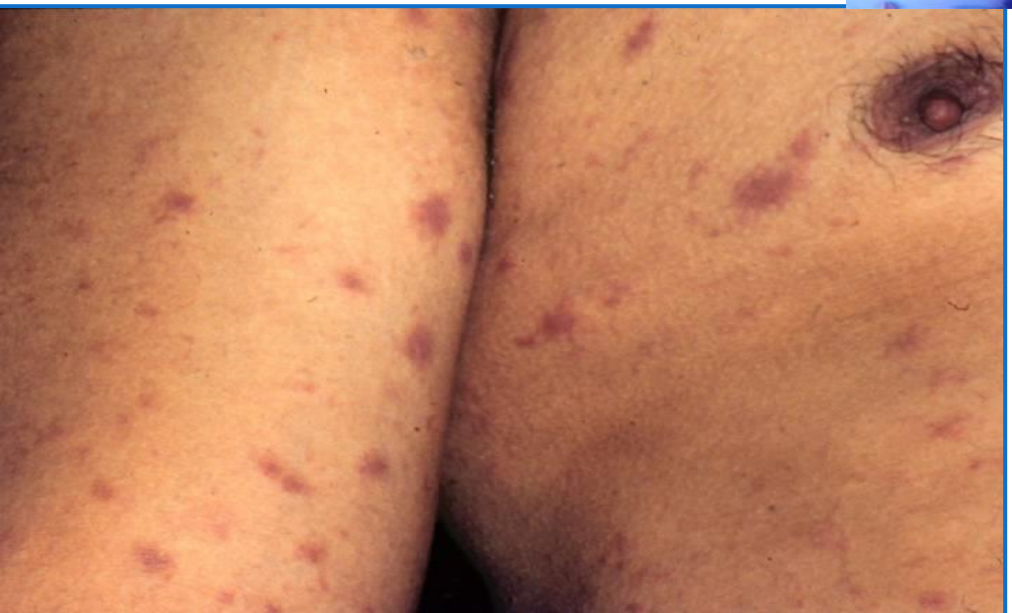
- The incubation period from the moment of infection to the clinical manifestations of an acute infection or the production of antibodies is from 3 weeks to 3 months.
- Stage of primary manifestations (acute retroviral syndrome) - about a year
- Subclinical stage, slow development of immunodeficiency, lasts 6-7 years (asymptomatic period)
- Stage of secondary diseases, significant immunodeficiency, ending 10-12 years after the onset of the disease
- The terminal stage, manifested by the irreversible course of secondary diseases (AIDS)

Symptoms of acute HIV infection

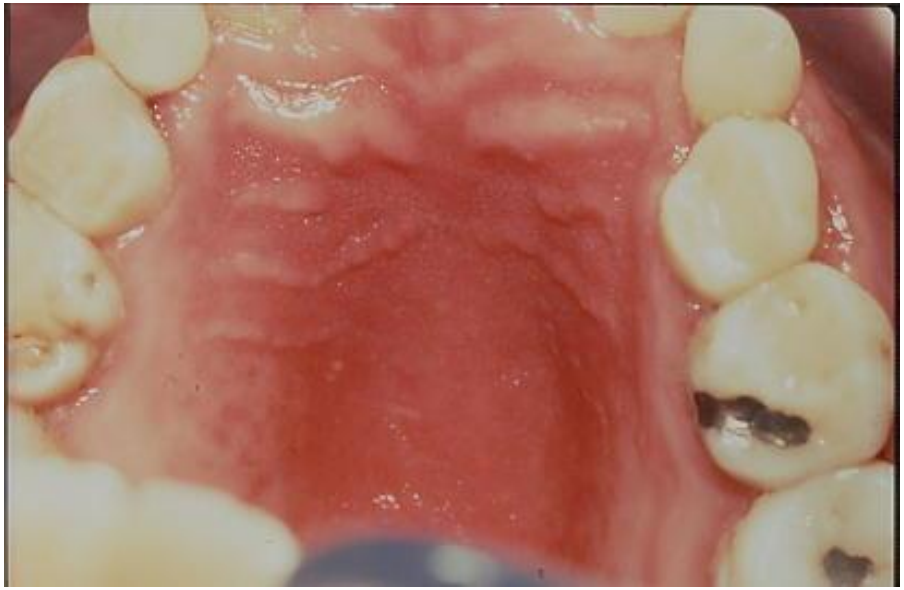
Symptoms of acute HIV infection

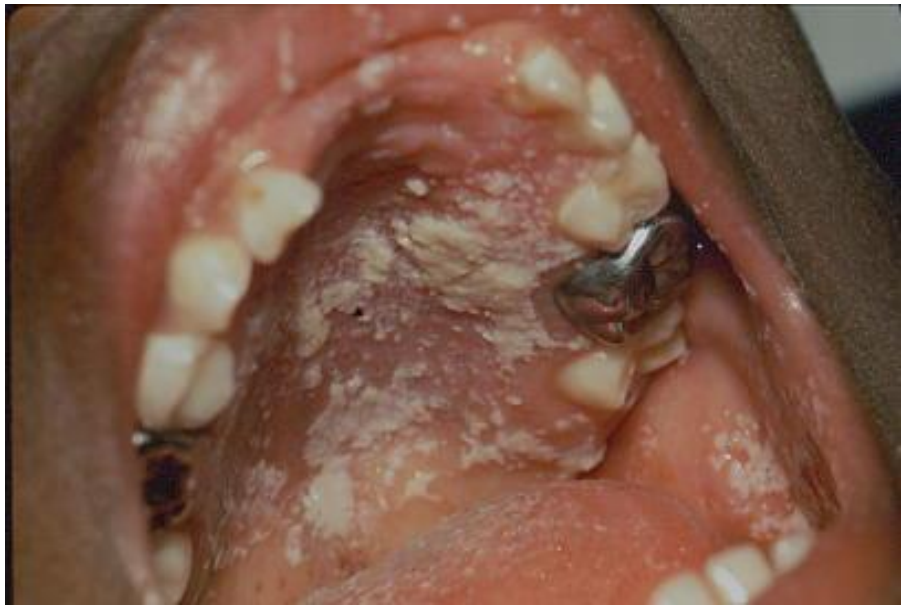




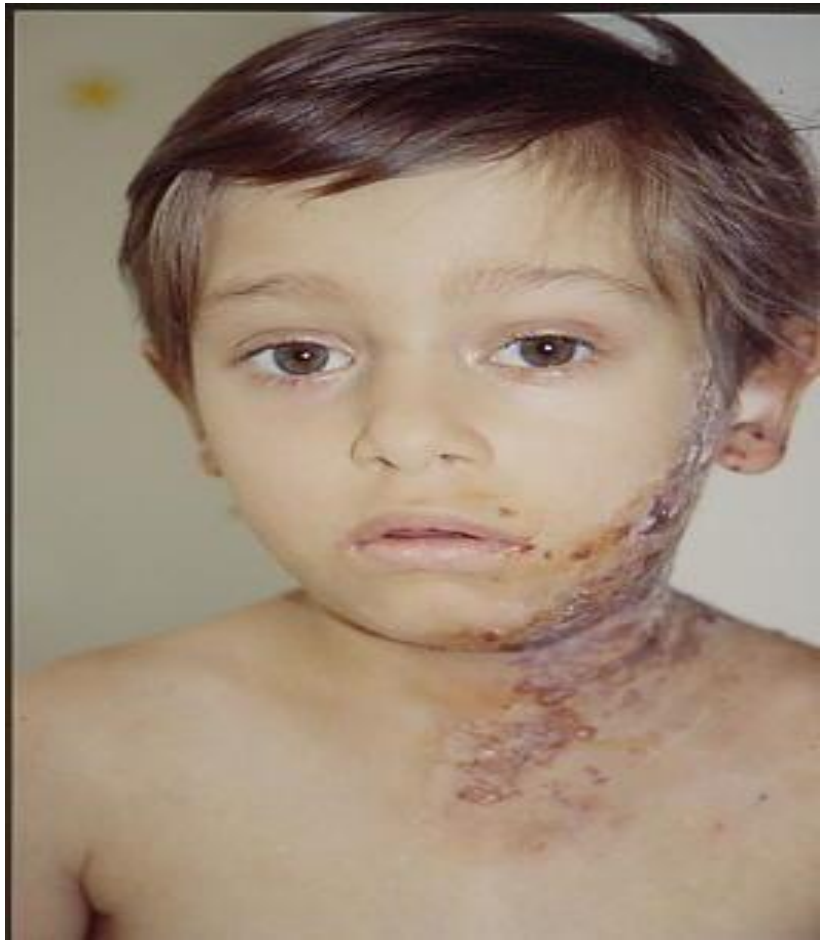


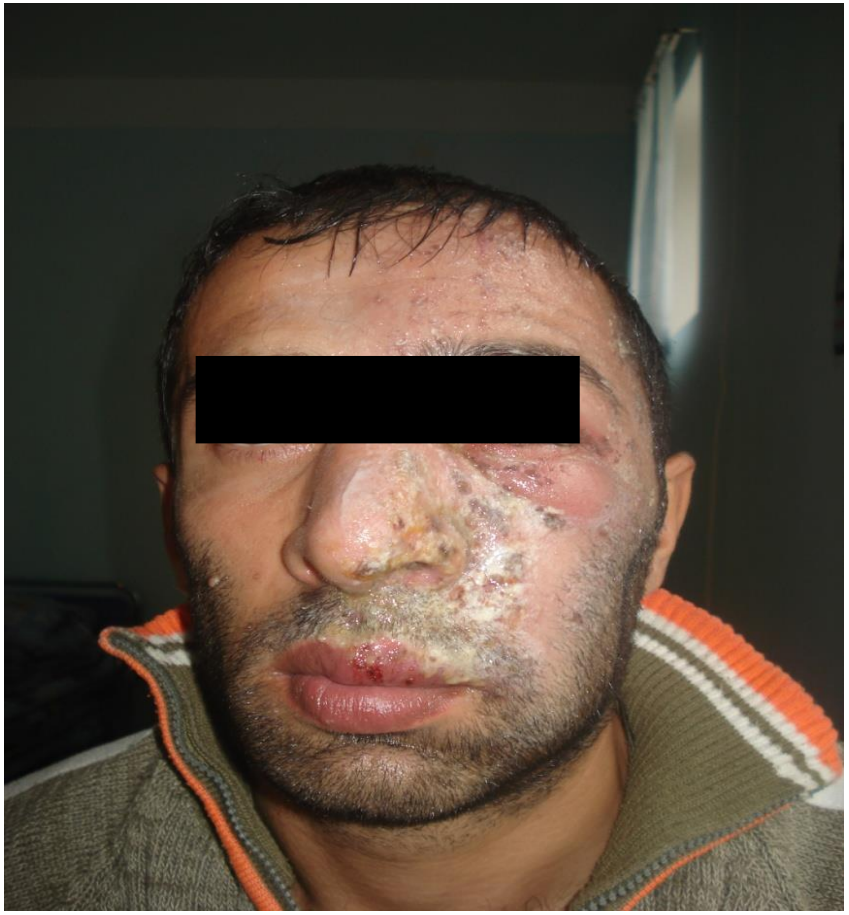
oral candidiasis





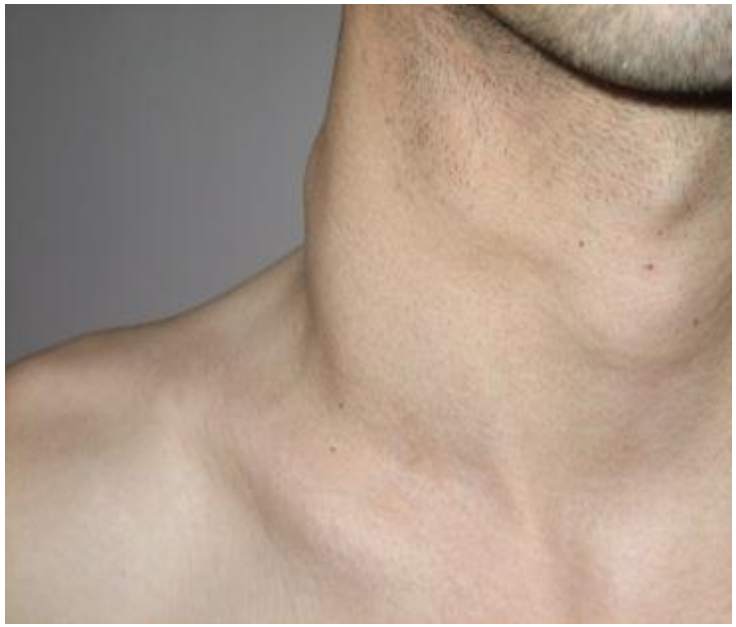
Varicella zoster

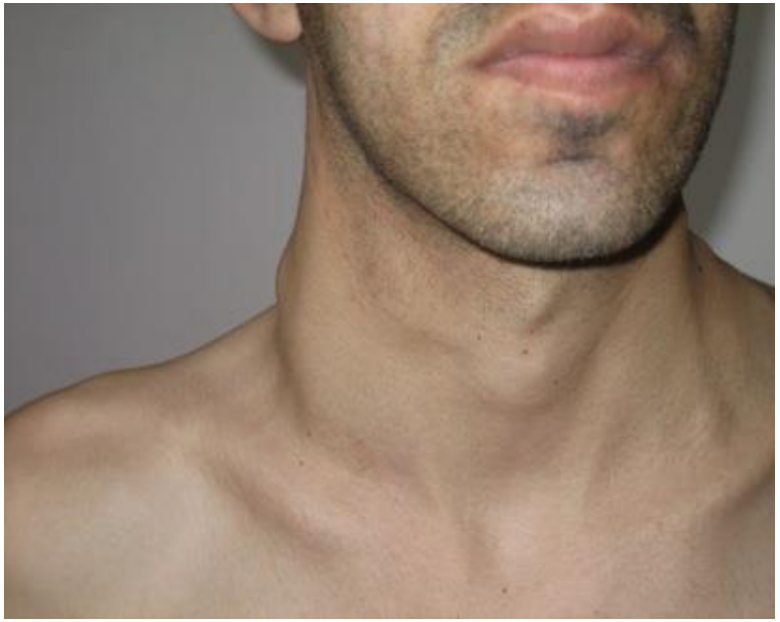




Respublika QİÇS-lə Mübarizə Mərkəzinin arxivindən

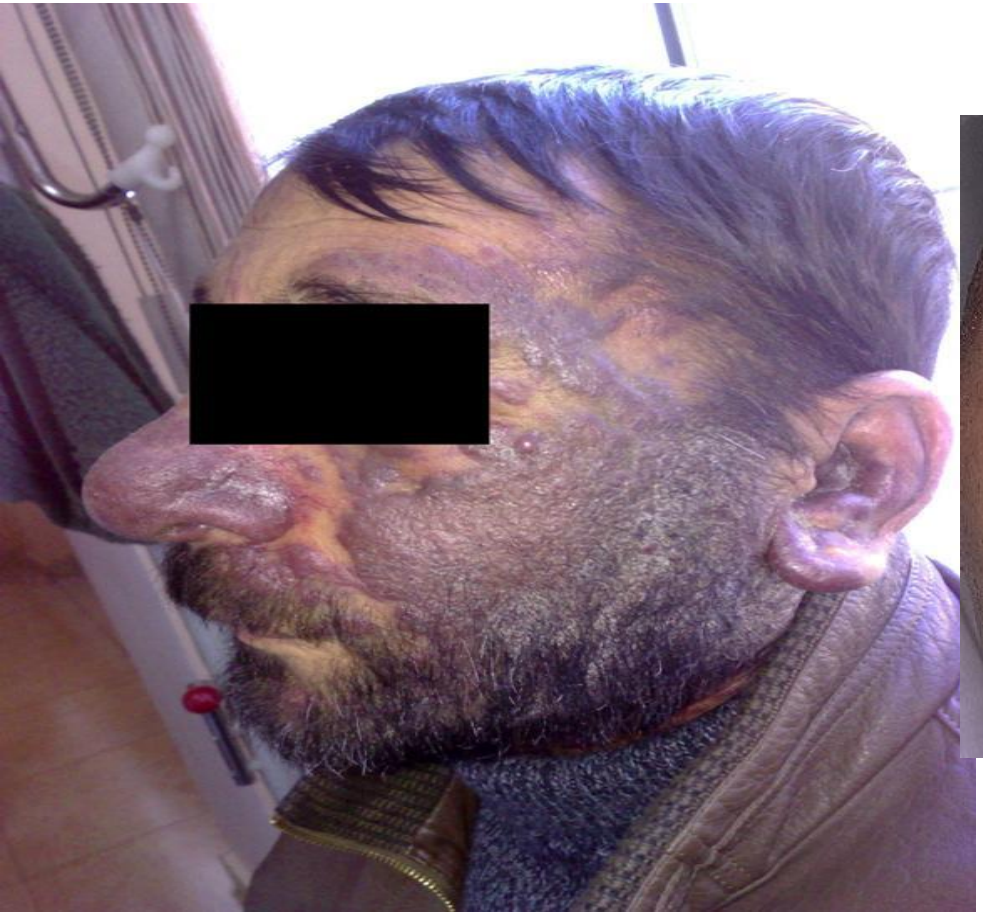
Extrapulmonary TB in AIDS

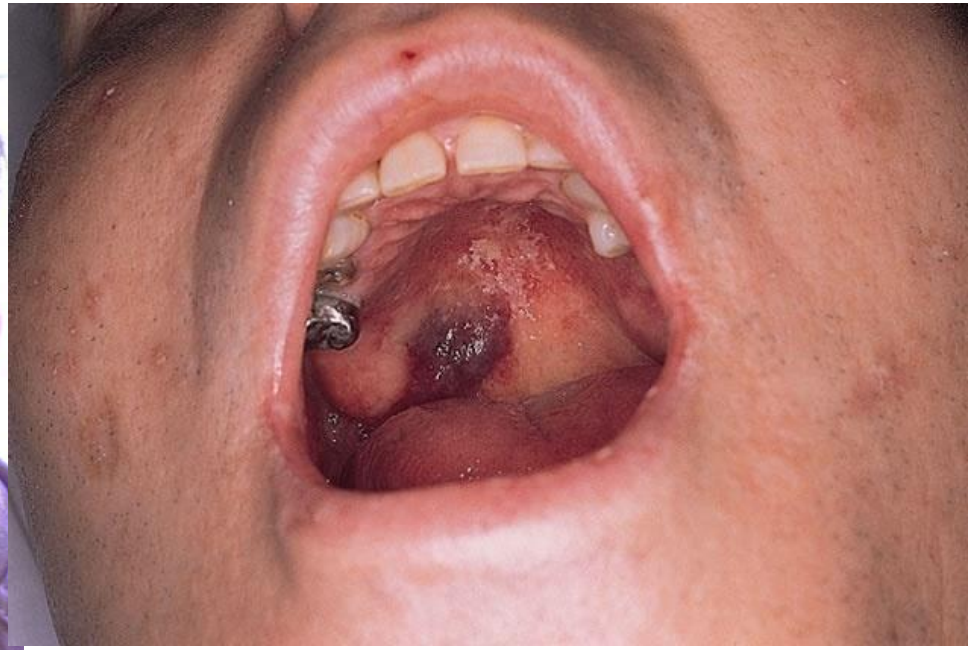




Respublika QİÇS-lə Mübarizə Mərkəzinin arxivindən

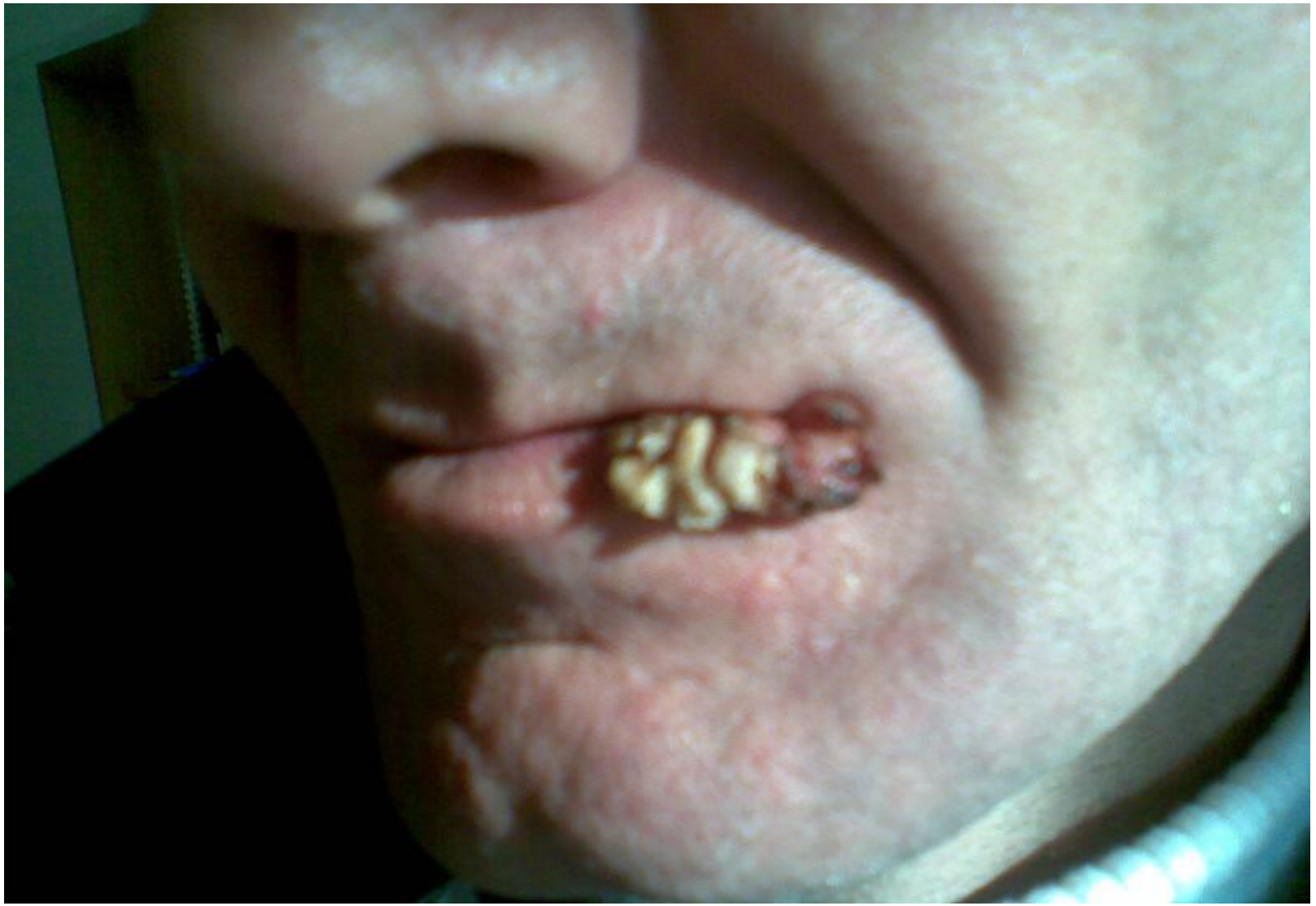
AIDS - Kaposi's Sarcoma





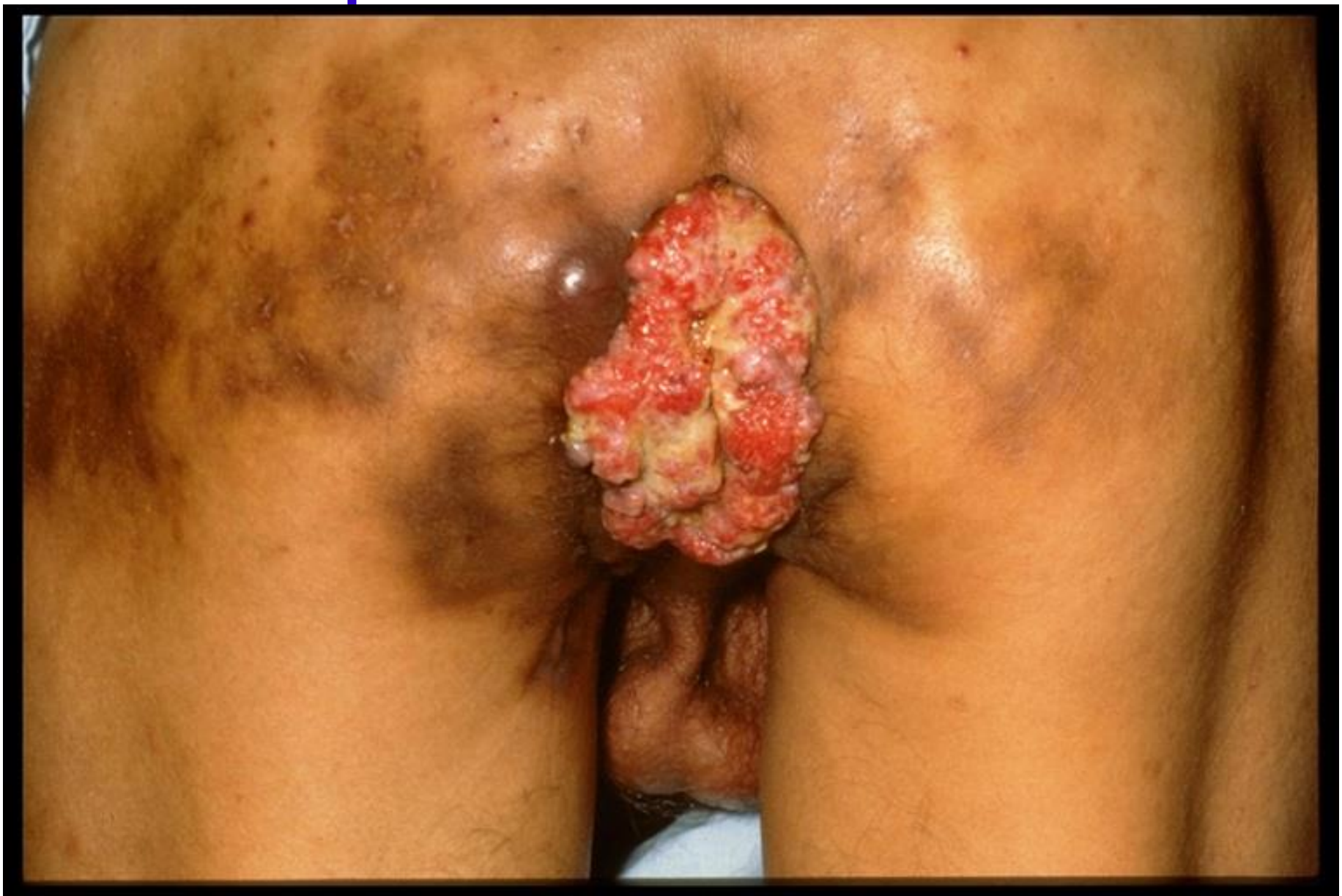
Respublika QİÇS-lə Mübarizə Mərkəzinin arxivindən

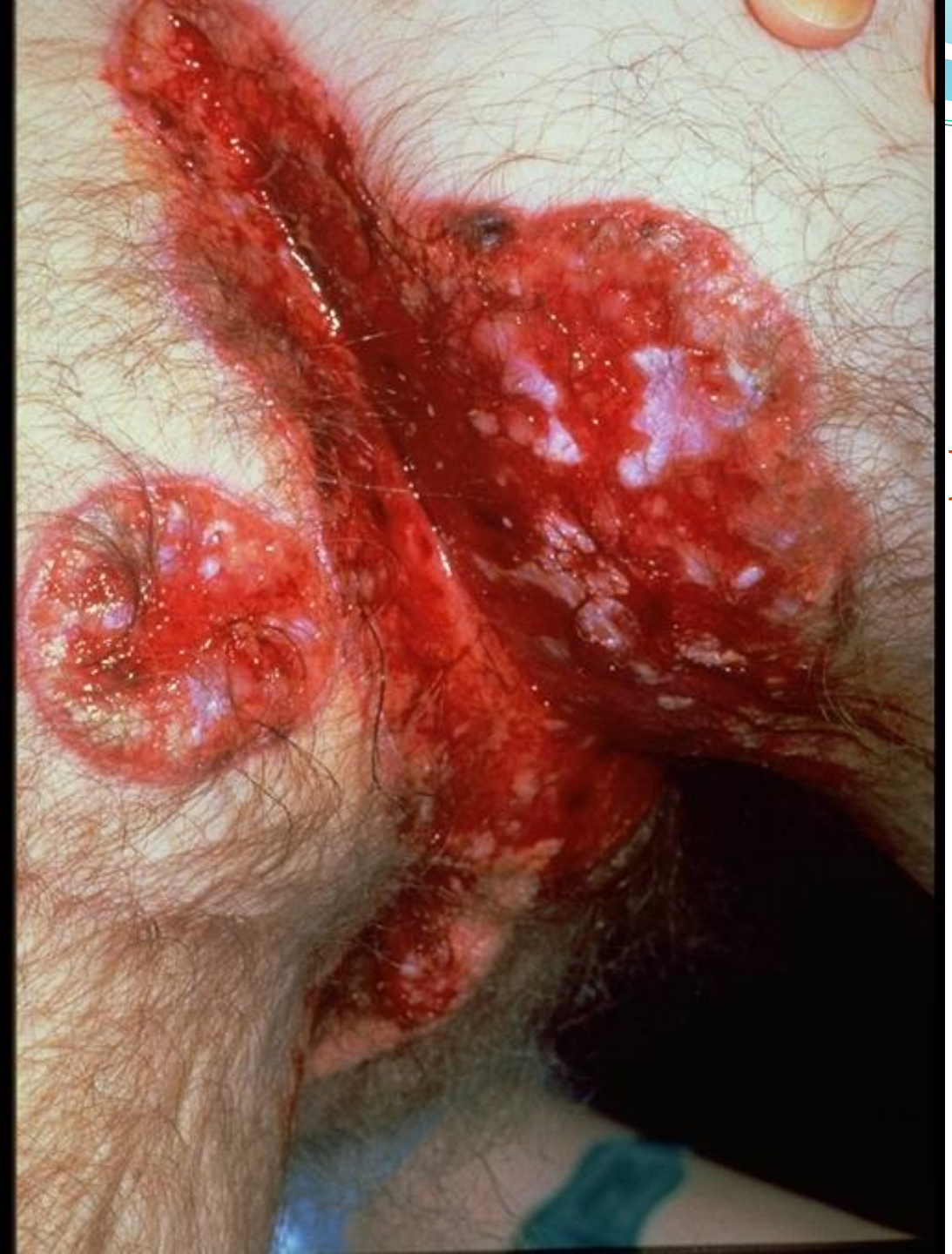
AIDS-carcinoma of the lip



Respublika QİÇS-lə Mübarizə Mərkəzinin arxivindən

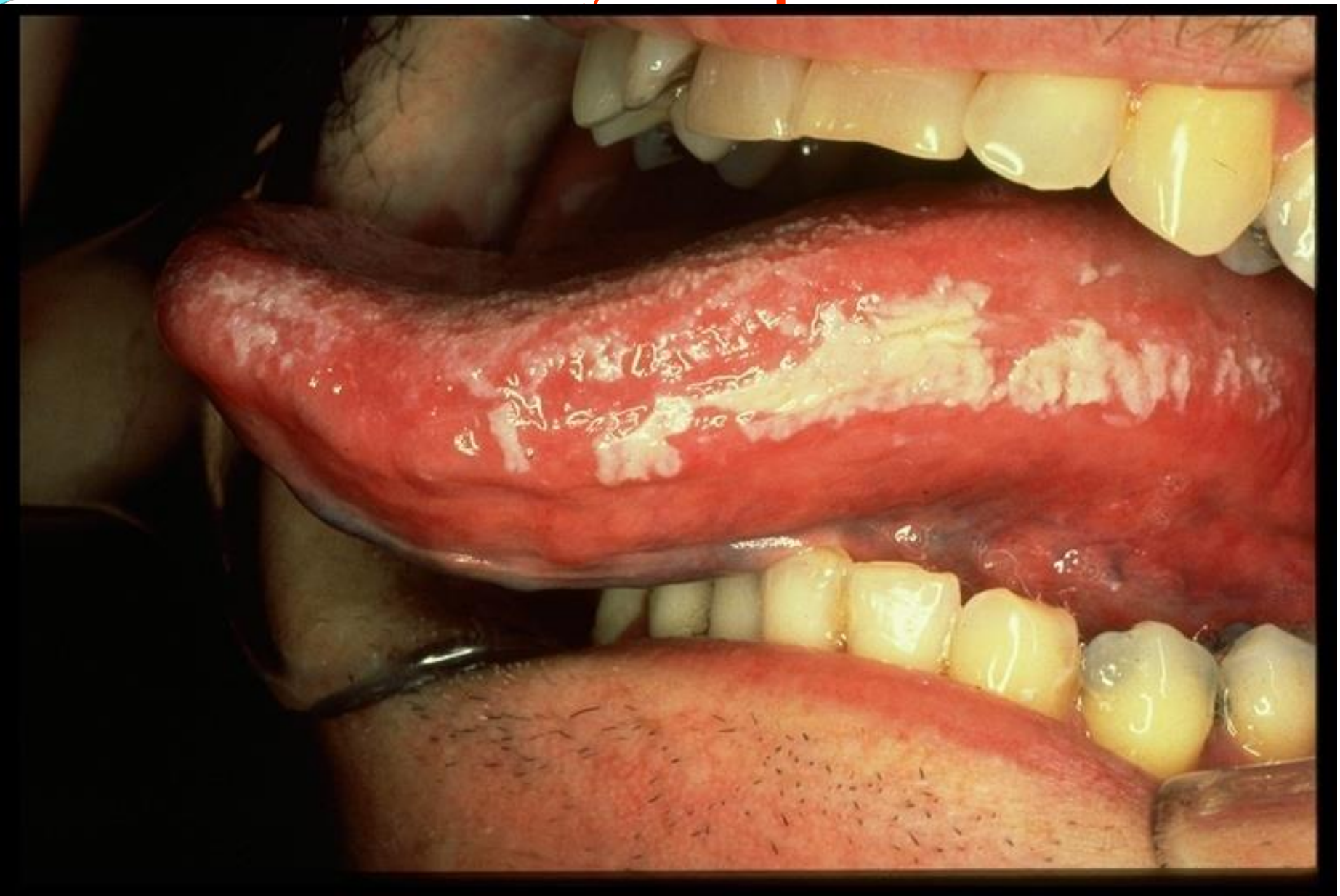
squamous cell carcinoma



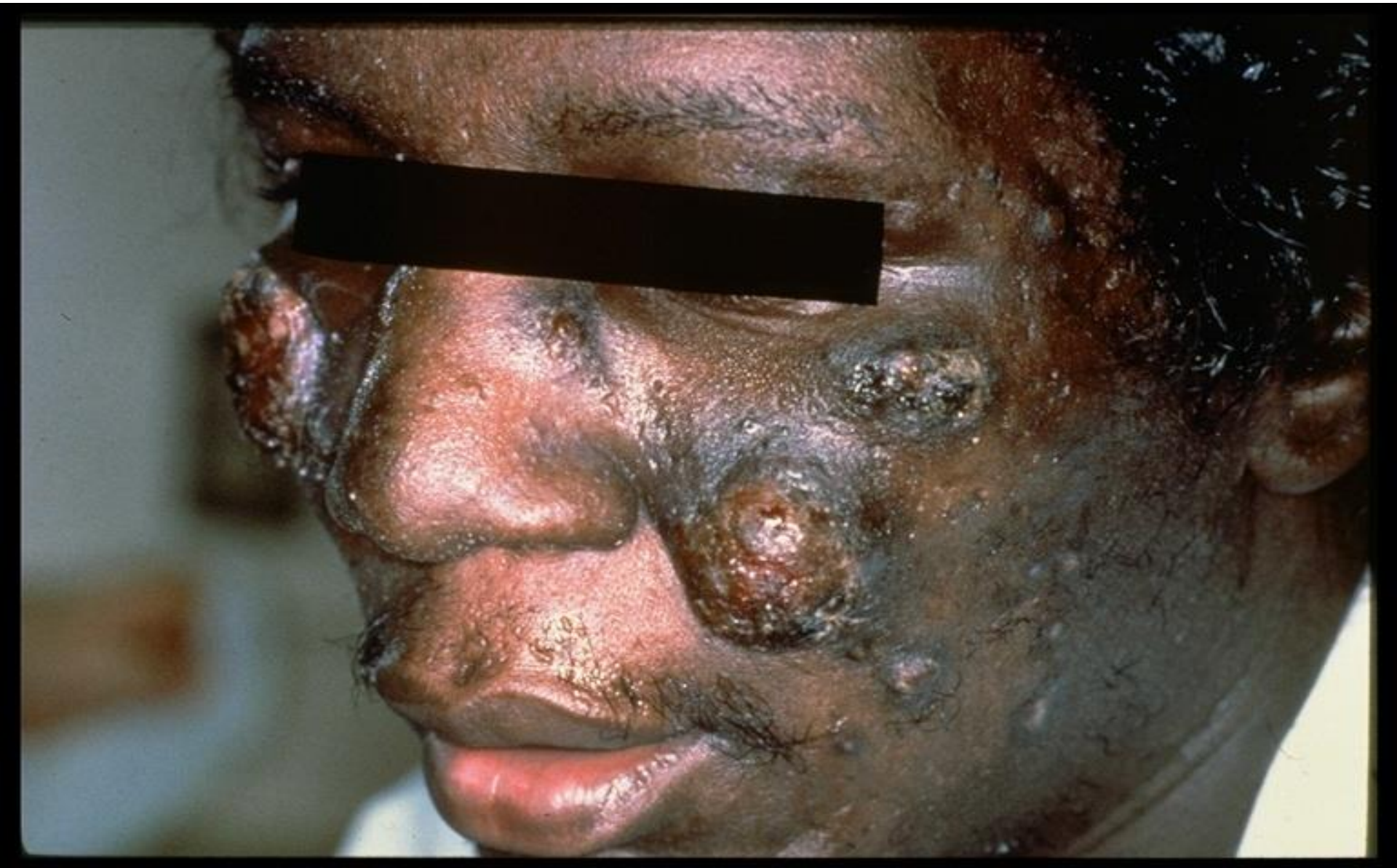


perirectal herpes

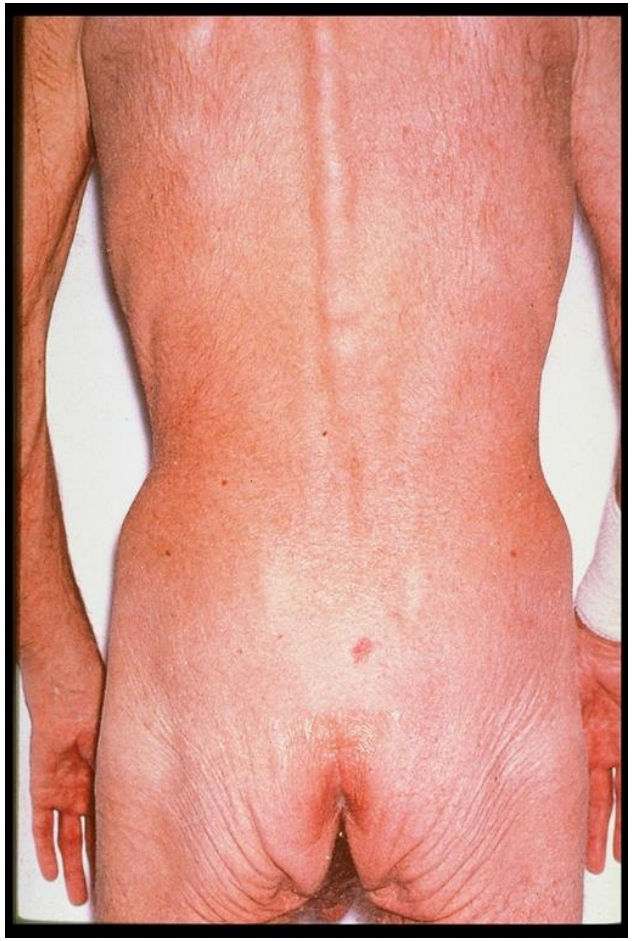
Hairy leukoplakia

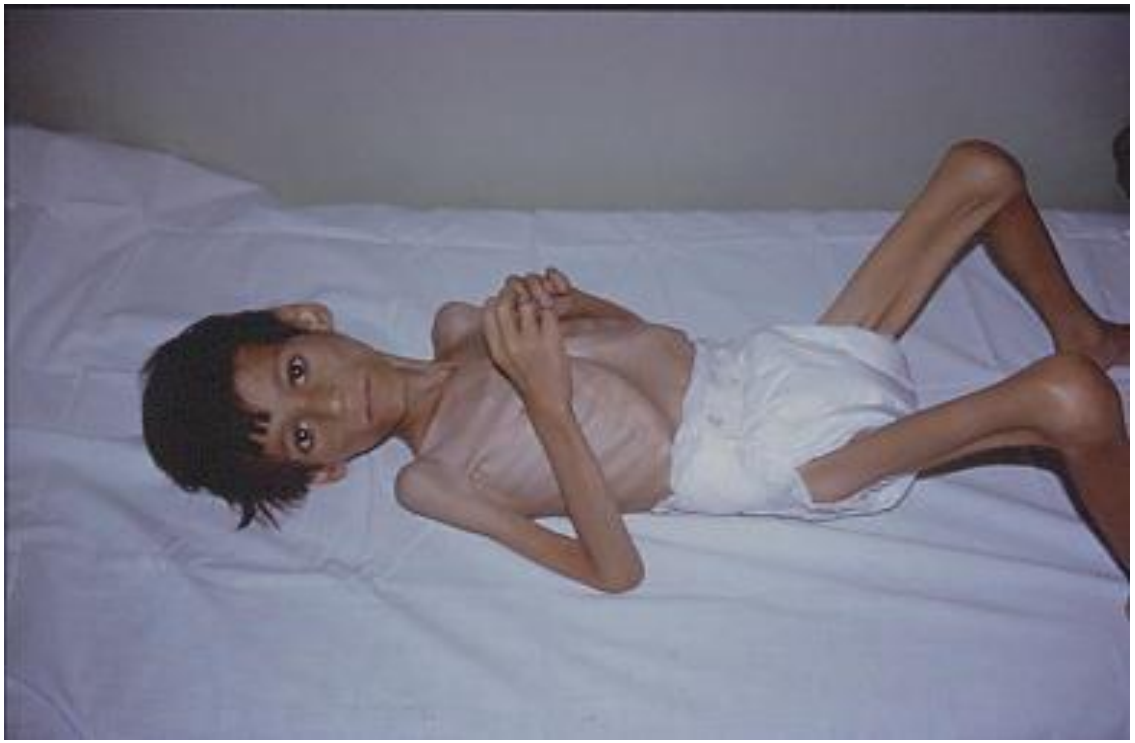


Blastomycosis



HIV WASTING





Diagnosis of HIV infection

Diagnosis of HIV infection is carried out in three main areas:

- **Etiological diagnosis –**

установление факта инфицированности ВИЧ путем выявления в организме специфических маркеров инфицирования этим вирусом;

- **Nosological diagnostics –**

identification of signs of the development of immunodeficiency, in particular, a decrease in the number of CD4 + cells in the blood;

- **Additional diagnostics –**

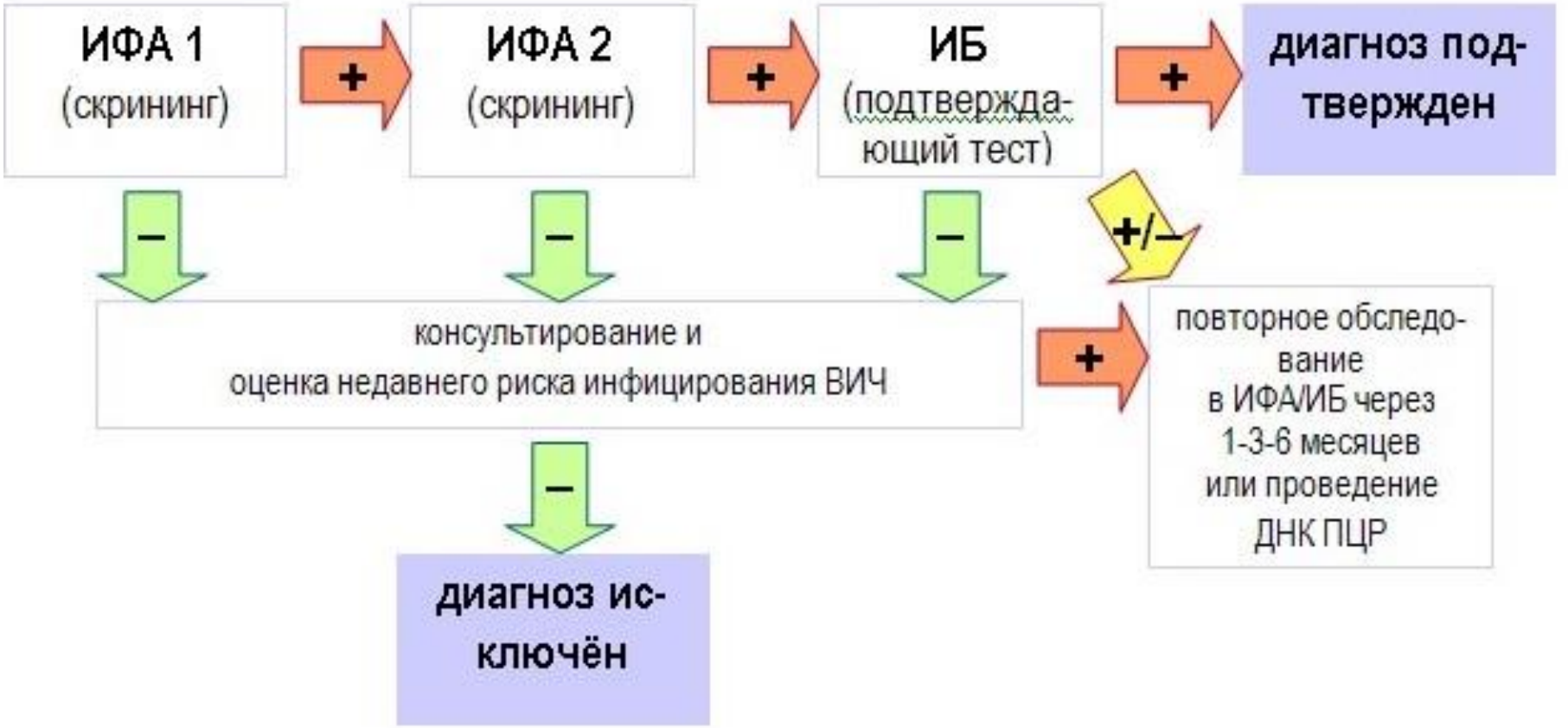
identification of characteristic complications of HIV infection, in particular, markers of secondary infections and tumors.

Etiological (specific) diagnosis of HIV infection

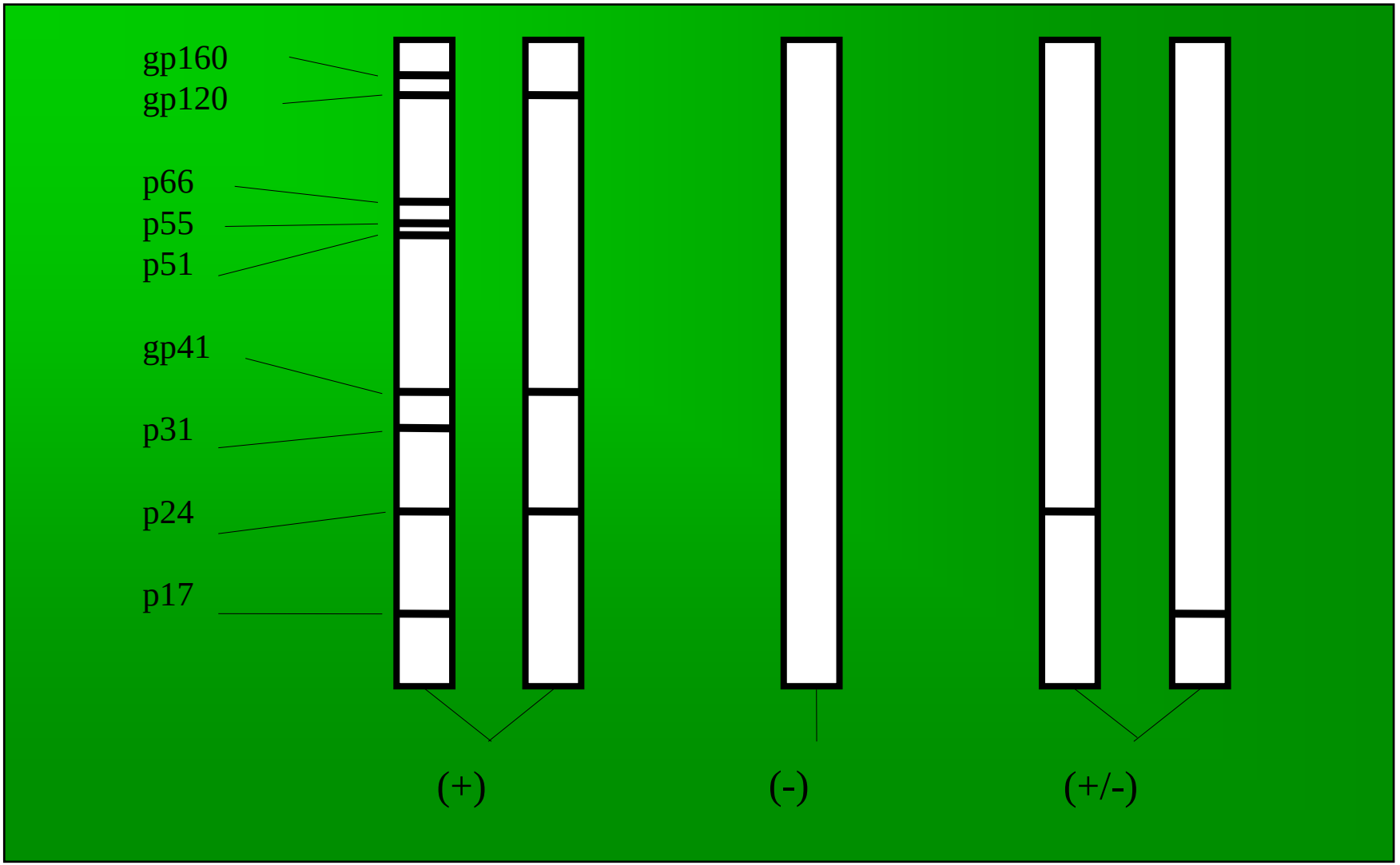
Methods for the specific diagnosis of HIV infection:

- **Serological - based on the detection of HIV antigens and antibodies to these antigens in the blood**
- **Molecular genetic - based on the detection of fragments of the HIV genome in blood and other biofluids and tissues**

Diagnostic algorithm for testing for HIV infection



IMMUNOBLOT



Strips from blot. Reading results

- Strip A –

Positive control

- Strip B –

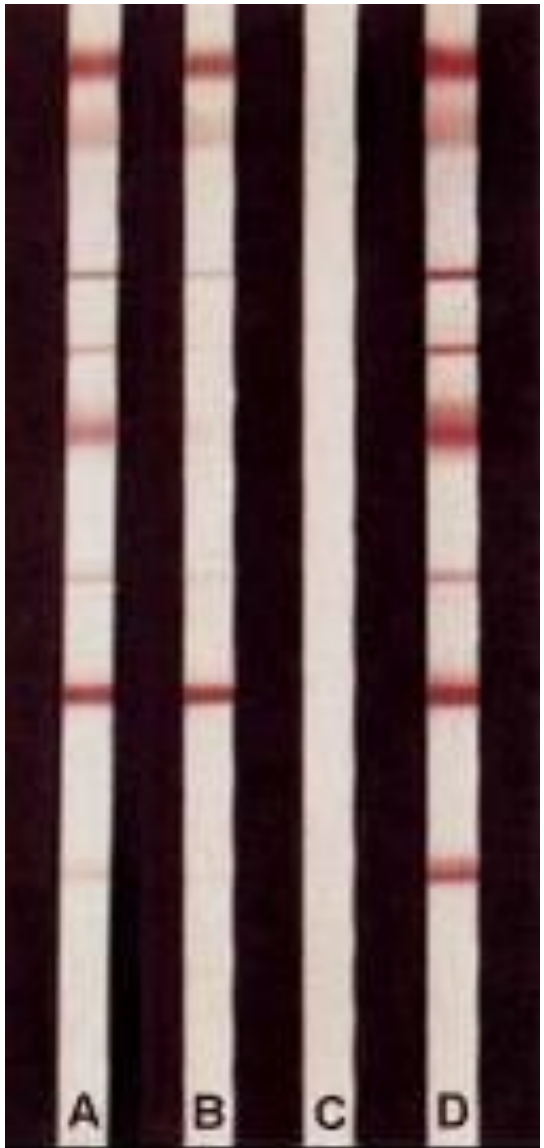
Weak positive control

- Strip C –

Negative control

- Stripe D –

Positive sample (presence of anti-HIV-1 antibodies detected)



HIV TREATMENT

- **Etiotropic (antiretroviral) therapy - ART**
- **Pathogenetic therapy**
- **Treatment of opportunistic and AIDS-associated diseases**

Antiretroviral drugs

Nucleoside reverse transcriptase inhibitors (NRTIs))

- **mechanism of action: nucleoside analogs (“false building material”), need to be activated inside cells**
- **currently approved 7 drugs**

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- **mechanism of action: non-competitive HIV reverse transcriptase inhibitors**
- **currently approved 3 drugs**

Protease inhibitors (PIs)

- **mechanism of action: HIV protease inhibition**
- **currently approved 7 drugs**

Fusion inhibitors

Recommendations about occupational risk of HIV infection

CONTACT of damaged skin and mucous membranes with the following products should be considered

as RISK:

- blood;
- amniotic fluid, pericardial fluid, peritoneal fluid, pleural fluid, synovial fluid, cerebrospinal fluid;
- sperm, vaginal secretion;
- fabrics;
- any other organic fluids that are obviously contaminated with blood

Risk of occupational HIV infection

Transcutaneous contact with an HIV-infected person

blood: 0.3%

Mucosal contact: 0.09%

Intact skin contact: <0.09%