Viral Hepatitis

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Viral hepatitis is viral infection of the liver that causes hepatic inflammation which is followed by the classic icteric symptoms of jaundice and the release of liver enzymes

Periods and clinical symptoms of hepatitis

1. Incubation period.

2. Preicteric period.

Initial symptoms:

- Fever, chills.
- Fatigue.
- Nausea, vomiting.
- Loss of appetite (anorexia).
- Abdominal pain.

3. Icteric period.

Later symptoms:

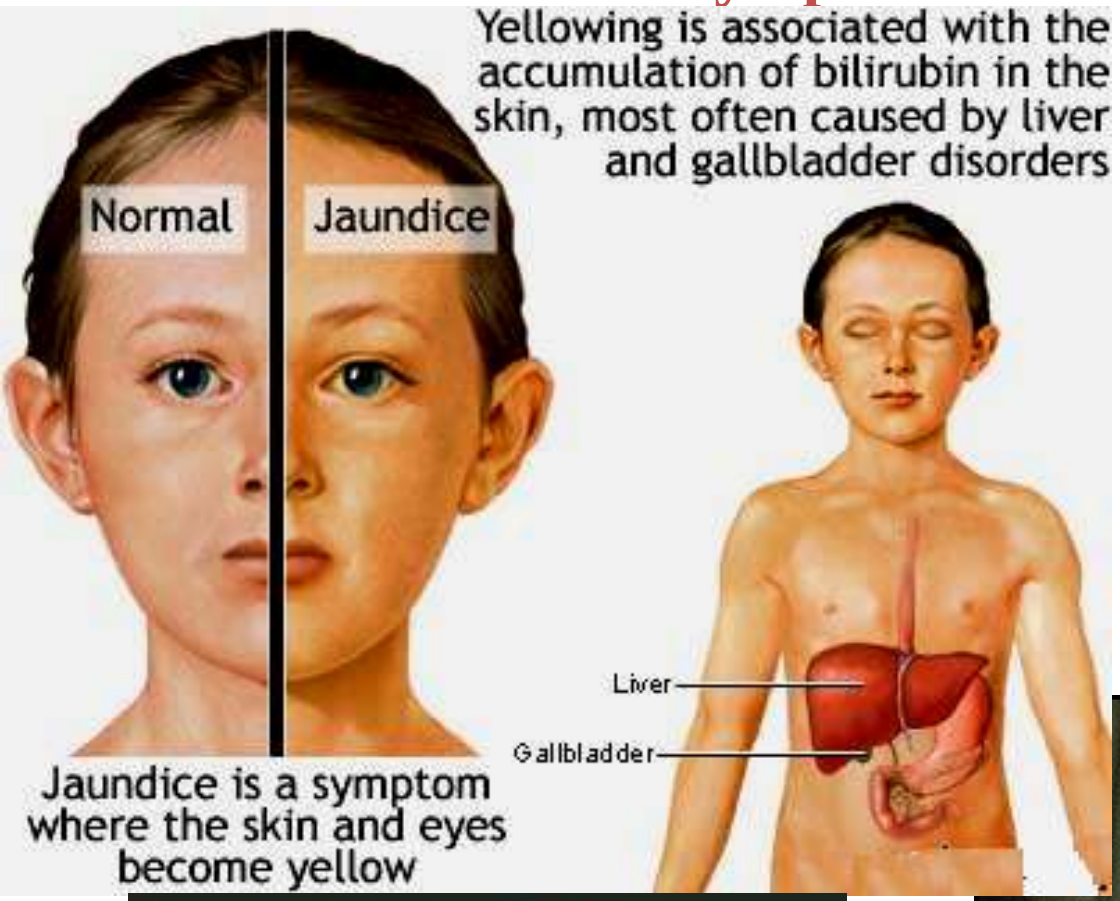
- Jaundice (in 2 of 3 adults).
- Icteric sclera (1-2 of 10 children).
- Dark urine, pale stools.
- Fulminant hepatitis (ascites, bleeding, death).

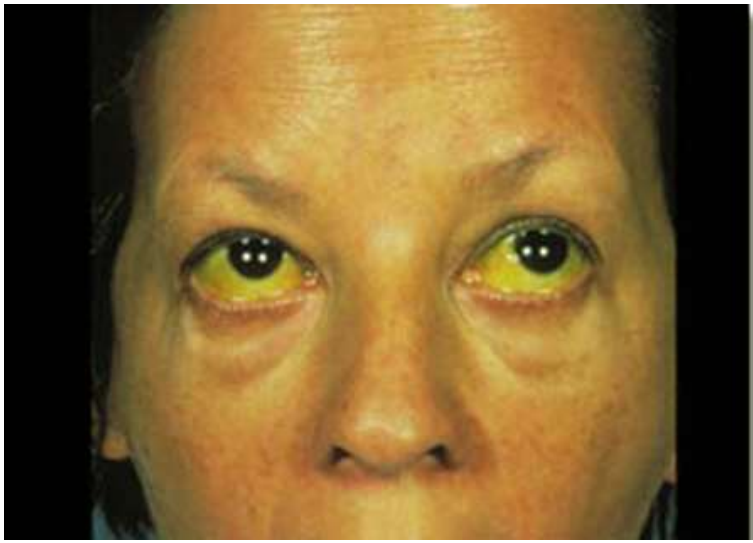
Hepatitis B, C or D also cause:

- Skin rash
- Arthralgia
- Weight loss

4. Recovery.

Icteric symptoms of liver damage





Jaundice/Icterus

- Elevated levels of bilirubin in blood is associated with “dark colored” urine.
- Obstructive jaundice causes impairment of excretion into the small intestine.
- This results in the loss of the “normal yellowing” of the stool.
- The stool is “white”.

Classification of Hepatitis Viruses

Virus	Family	Nucleic acid	Envelope
HAV	Picornaviridae	ss +RNA	No
HBV	Hepadnaviridae	Incomplete circular ds –DNA	Yes
HCV	Flaviviridae	ss +RNA	Yes
HDV	Genus Deltavirus	ss –RNA	Yes
HEV	Hepeviridae	ss +RNA	No

Viral hepatitis

Transmission	
FOOD & WATER BORN	**BLOOD BORN**
Incubation period	
Hepatitis A: 2-6 weeks	Hepatitis B: 2-6 months
Hepatitis E: 2-9 weeks	Hepatitis C: 2-26 weeks
	Hepatitis D: unlimited
Type of hepatitis	
Acute	**Acute, chronic**

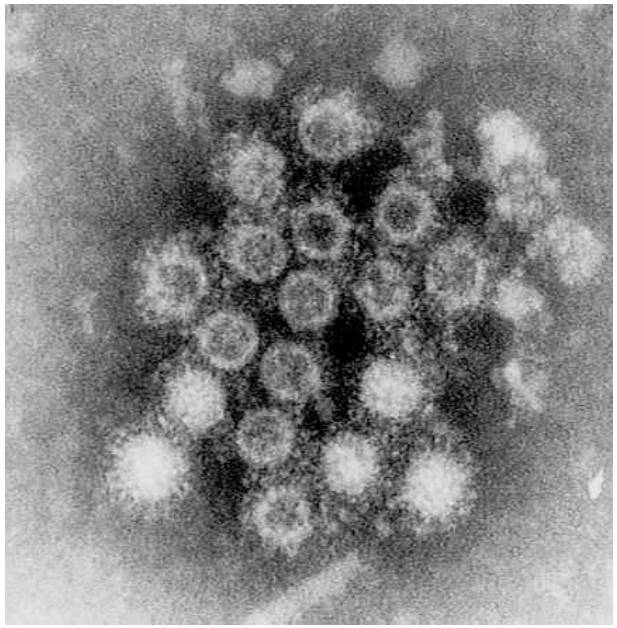
Family Picornaviridae. Hepatitis A virus

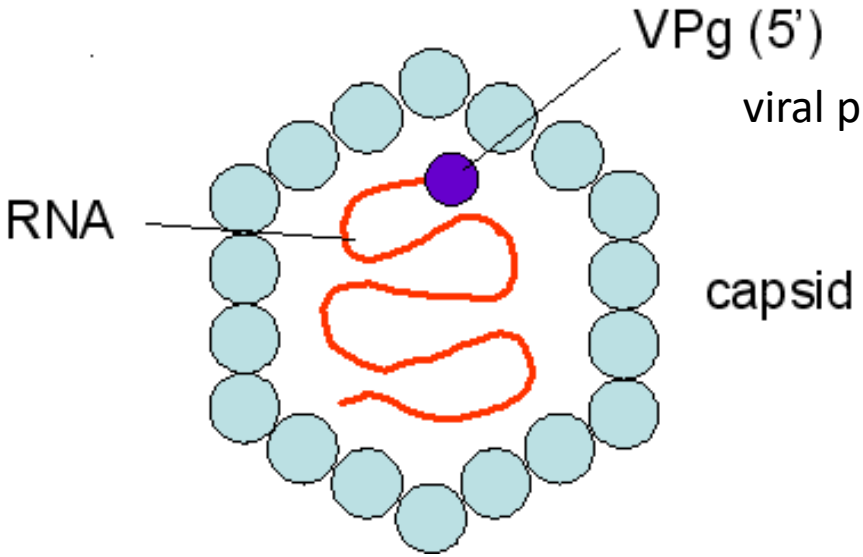
- Small, non-enveloped

RNA virus with

cubical symmetry.

- One stable serotype only





Characteristics of HAV

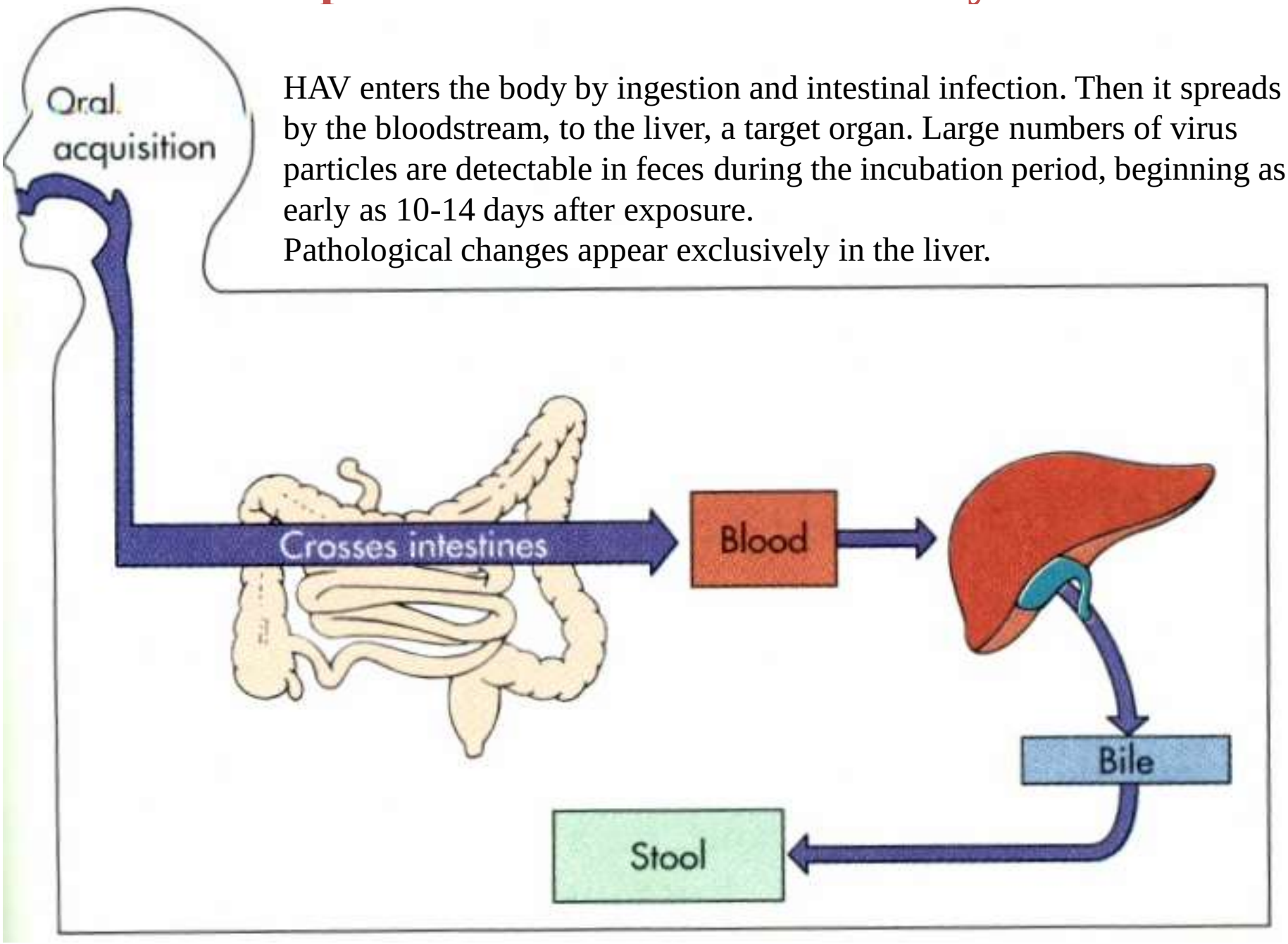
- **Stable to:**
  - Saltwater, groundwater (months)
  - Acid at pH 1
  - Solvents (ether, chloroform)
  - Detergents
  - Drying
  - Temperature:
    - 4^0C: weeks
    - 56^0C for 30 minutes
    - 61^0C for 20 minutes
- **Inactivated by:**
  - Chlorine treatment of drinking water
  - Formalin

Hepatitis A (infectious hepatitis)

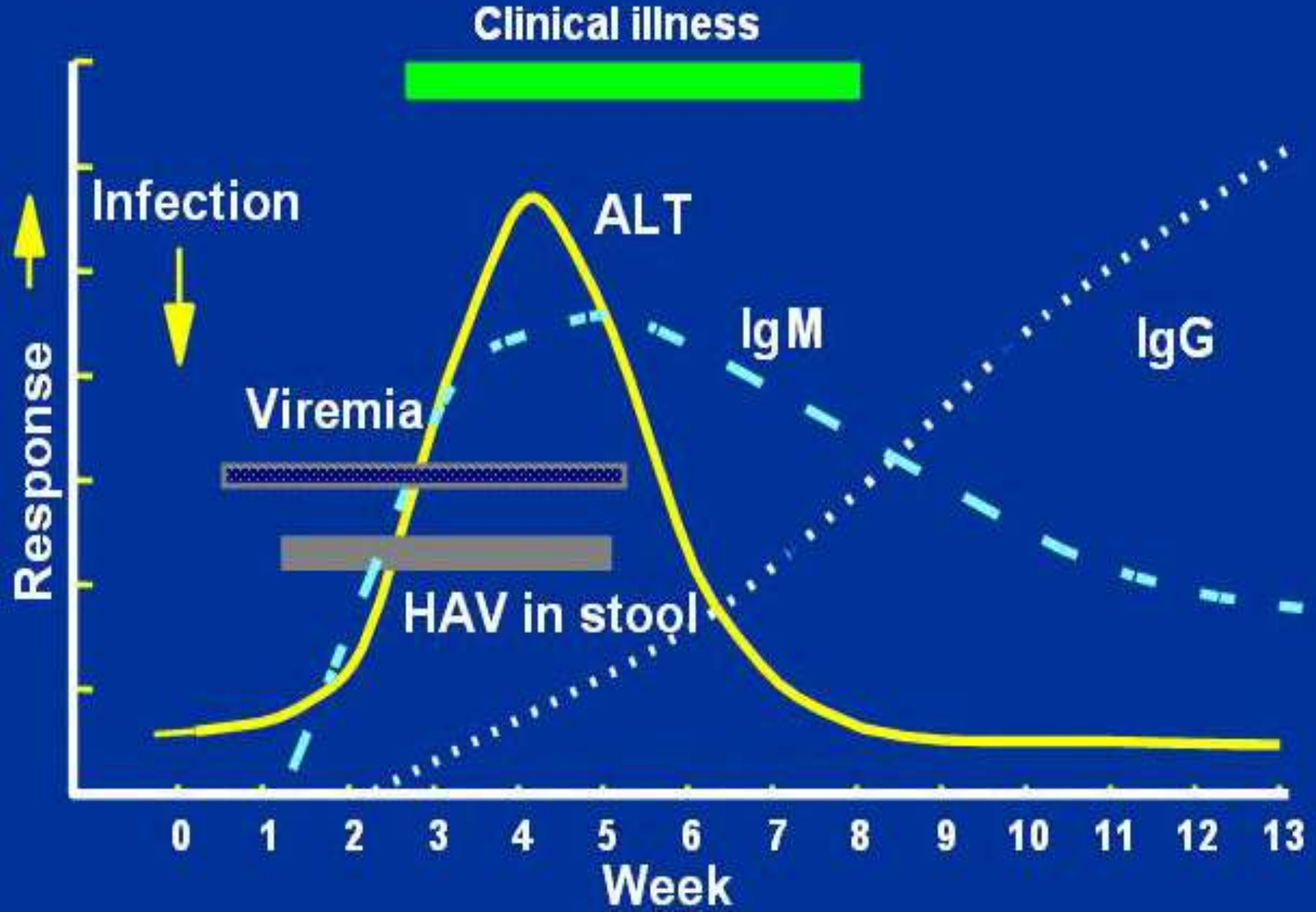
- 1) is spread:
  - by the fecal-oral route by ingestion of contaminated food and water;
- 2) contagious period extends 2-3 weeks before and 8-10 days after onset of jaundice. Virus may cause asymptomatic shedding.
- 3) does not cause chronic liver disease.
- 4) immunity is life-long.

Spread of HAV within the body

HAV enters the body by ingestion and intestinal infection. Then it spreads by the bloodstream, to the liver, a target organ. Large numbers of virus particles are detectable in feces during the incubation period, beginning as early as 10-14 days after exposure.
Pathological changes appear exclusively in the liver.



EVENTS IN HEPATITIS A VIRUS INFECTION



Clinical finding

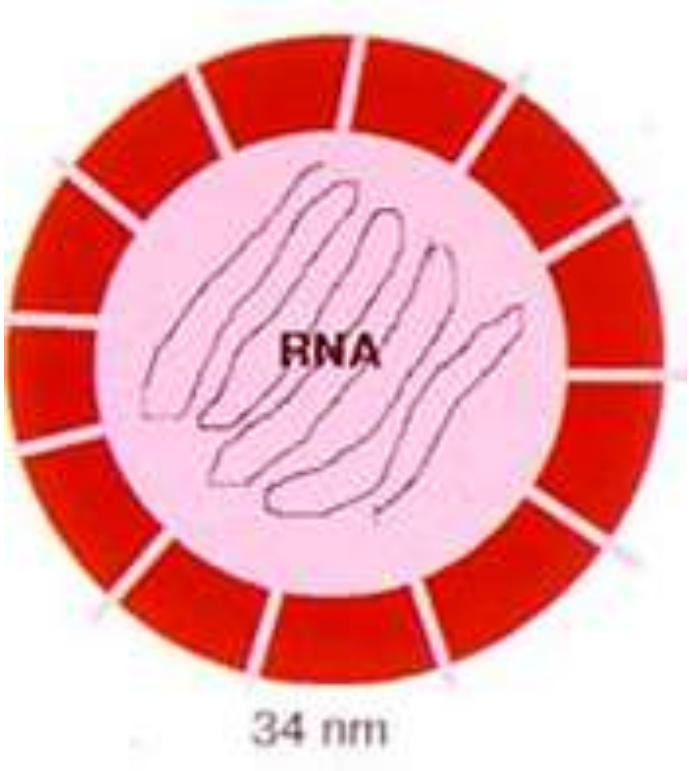
- Swelling and tenderness of liver
- Jaundice -yellow tinge in the skin and eyes
- dark urine
- transaminase, alkaline phosphatase levels increased

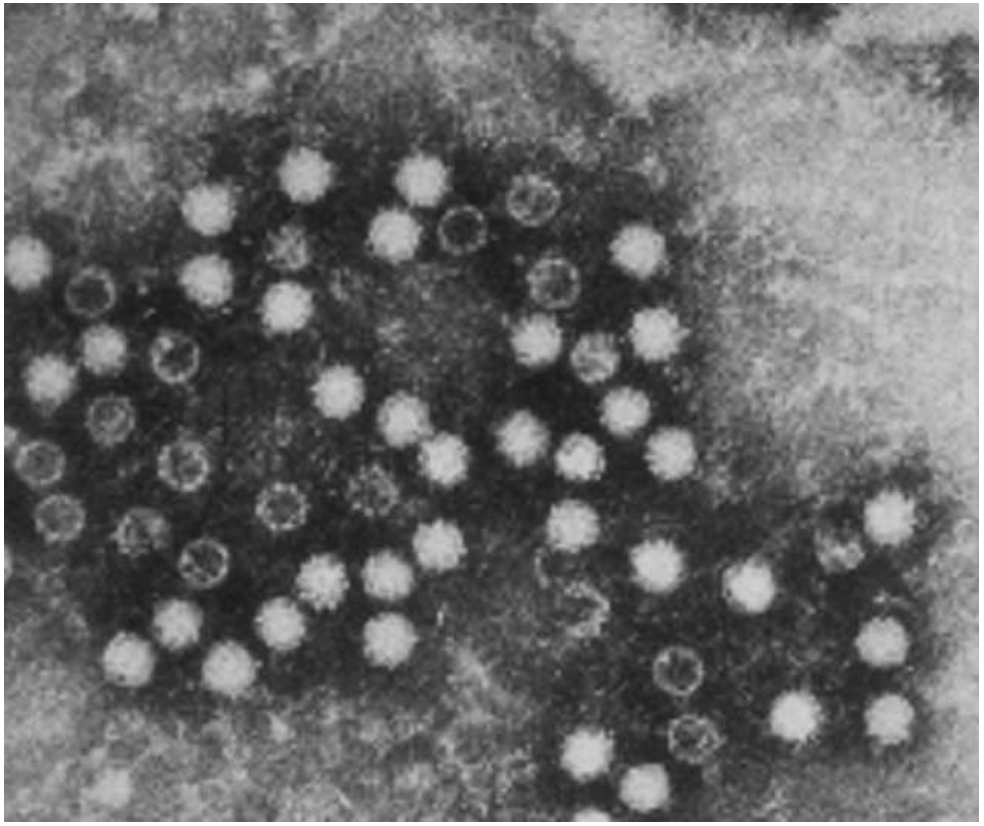
Laboratory diagnosis of hepatitis A

- **Biochemical tests** to study liver function:
  - **The Bilirubin.**
  - **Alanine aminotransferase** (ALT).
  - **Aspartate aminotransferase** (AST).
- **Serology: ELISA**
  - Acute infection: IgM.
  - Past Infection i.e. immunity: IgG.
- **Direct demonstration:**
  - ELISA (detection of antigen in stool),
  - RT-PCR of faeces.

Family Hepeviridae. Hepatitis E virus

- non-enveloped, cubic symmetry, 32-34 nm,
- ss + RNA virus
- 4 genotypes





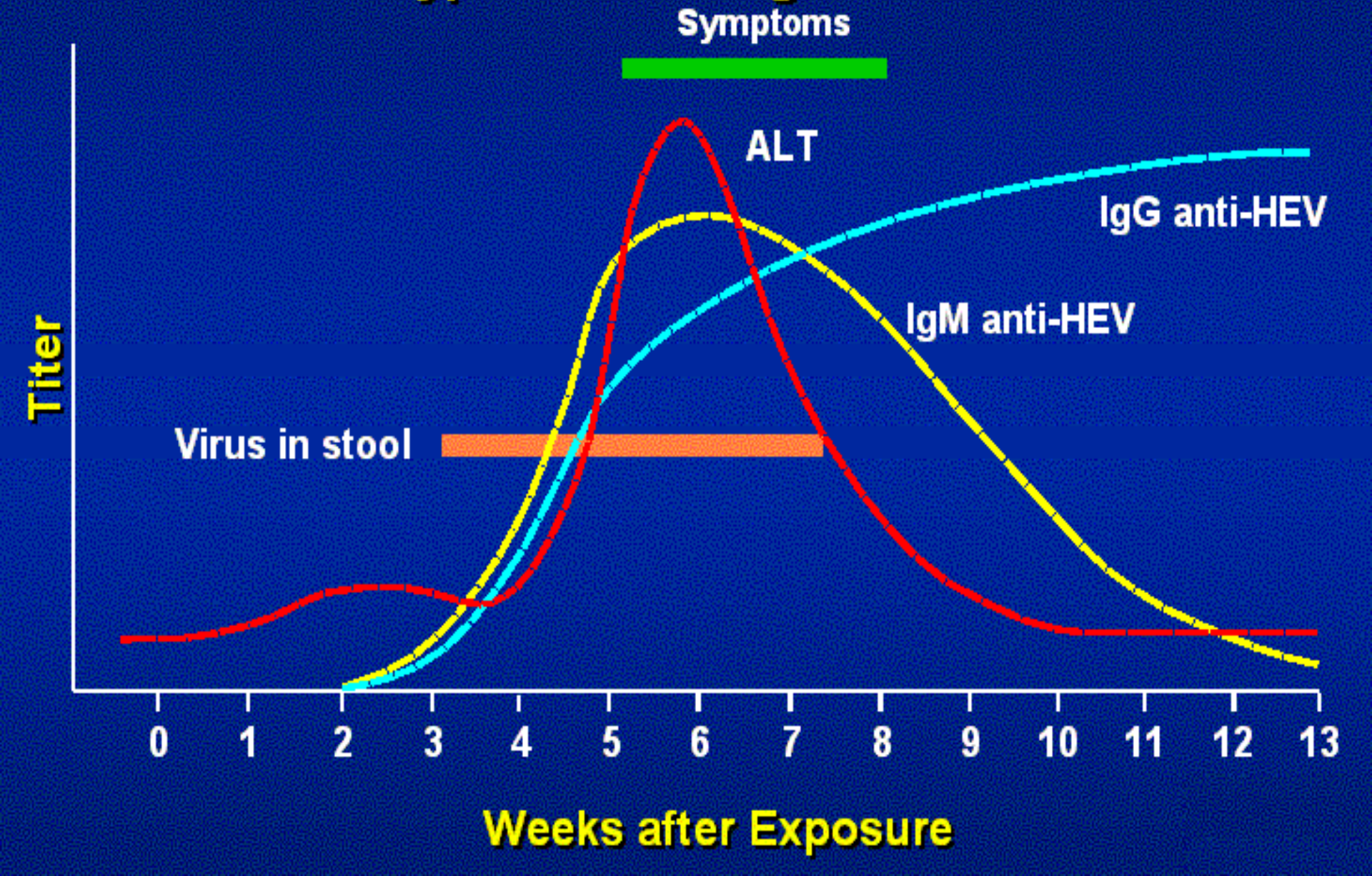
Epidemiology of HEV infection

- Contagious period extends from before to after symptoms.
- Transmission - via fecal-oral route by ingestion of contaminated food and water.
- It causes only acute disease.
- Life long immunity.
- HEV infection is especially serious in pregnant women (mortality rate about 20 %).

- Transmission through placenta results in death of fetus.

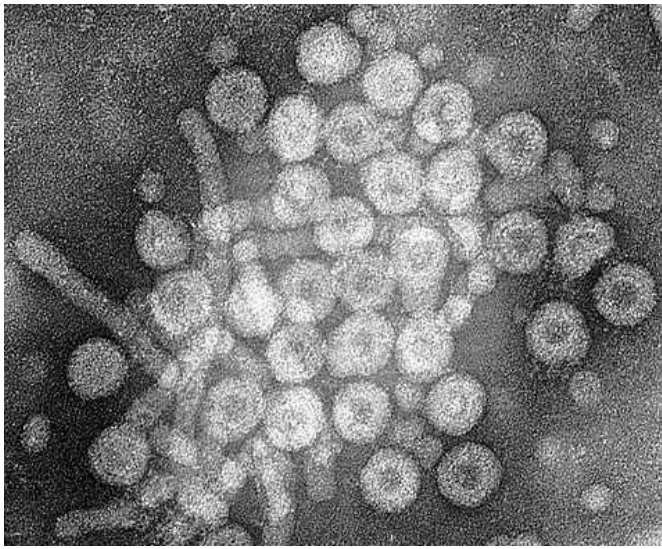
Hepatitis E Virus Infection

Typical Serologic Course

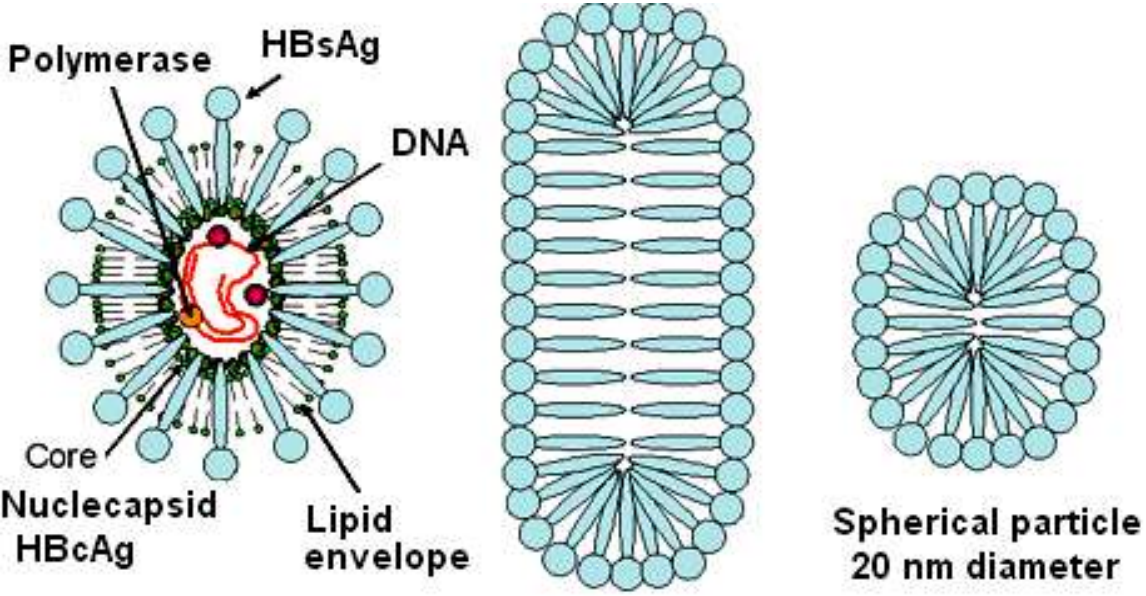


Family Hepadnaviridae. Hepatitis B virus

The hepatitis B virion (Dane particle):
- outer lipid envelope with the **surface antigen (HBsAg)**.
- an electron-dense core (nucleocapsid): ds circular DNA and polymerase surrounded by the **core antigen (HBcAg).**

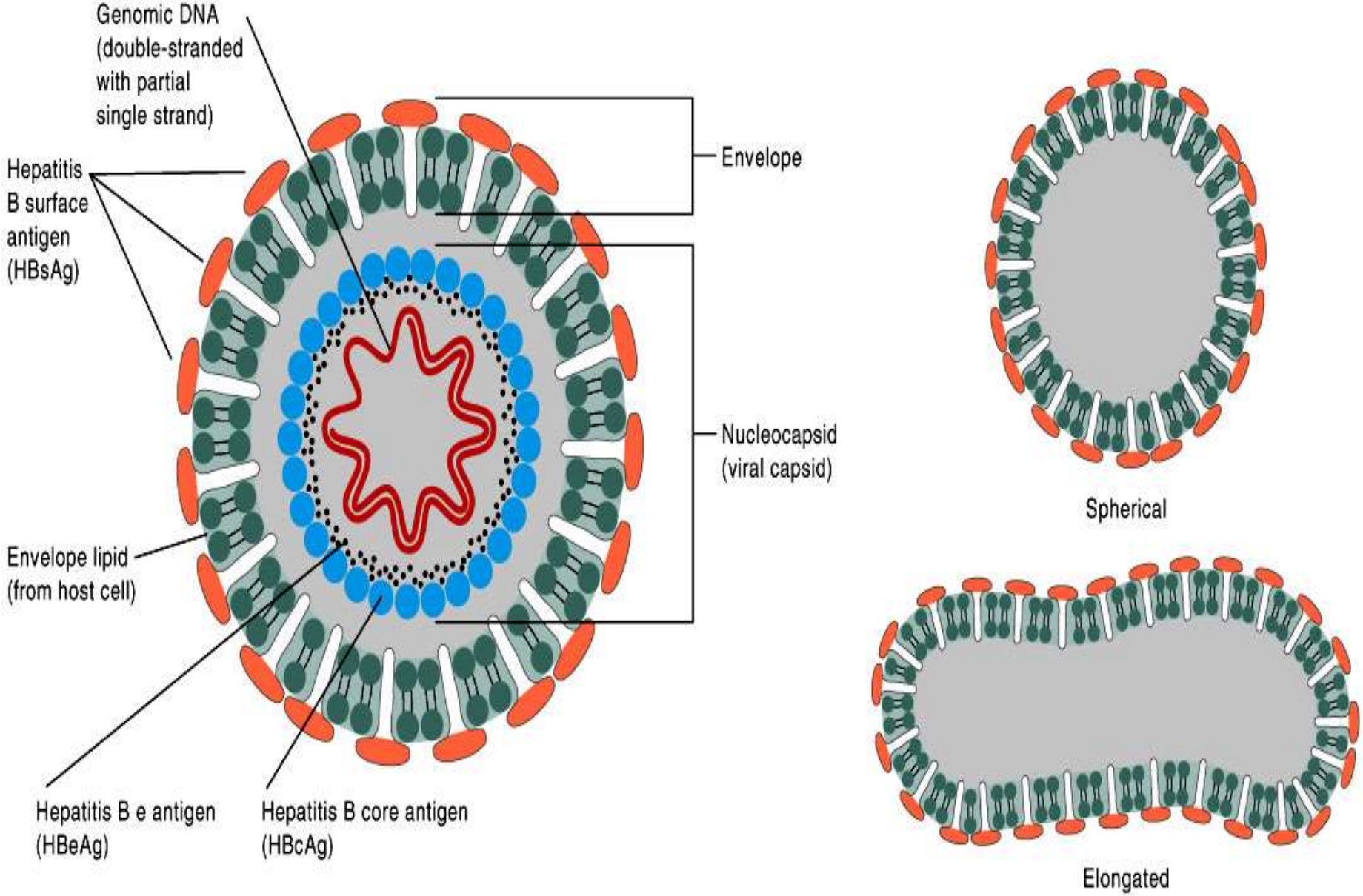


The HBsAg is produced in excess by the infected hepatocytes and is secreted in the form of **spherical and filamentous particles**.



HBeAg is the soluble component of the core, with is released during active infection.

HBxAg is a transactivator of viral transcription that appears to contribute to Hepatocellular carcinoma (HCC) by altering patterns of host gene expression.

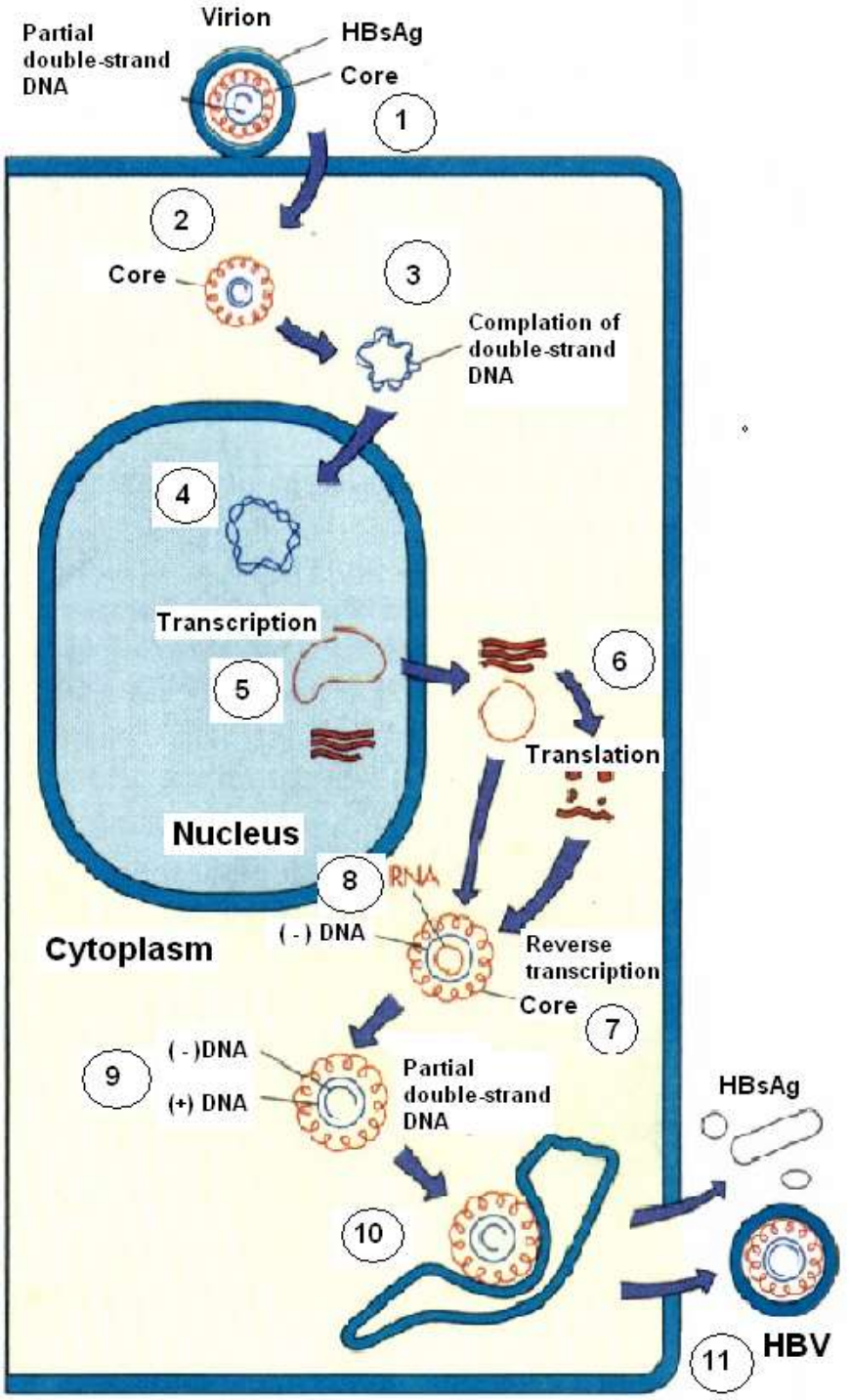


(a) Complete infectious virion

(b) Viral envelope particles containing HBsAg

1. Attachment to the cell surface receptor, fusion and releasing the core into the cytoplasm.
2. The core proteins dissociate from the DNA.
3. Completion of ds DNA by DNA polymerase and entering the nucleus.
4. Formation of a circular episome.
5. Transcription of mRNAs.
6. Translation.
7. RNA is encapsidated by core proteins.
8. Inside the core, the RNA is transcribed to minus strand DNA by polymerase called reverse transcriptase.
9. Transcription the minus strand DNA into a plus strand DNA.
10. Budding the virus through the endoplasmic reticulum and/or Golgi Body membranes from which it acquires HBsAg.
11. Shedding of viruses embedded in a lipid bilayer and empty envelopes from HBsAg.

- **10^{11} new virions are produced every day during acute infection**



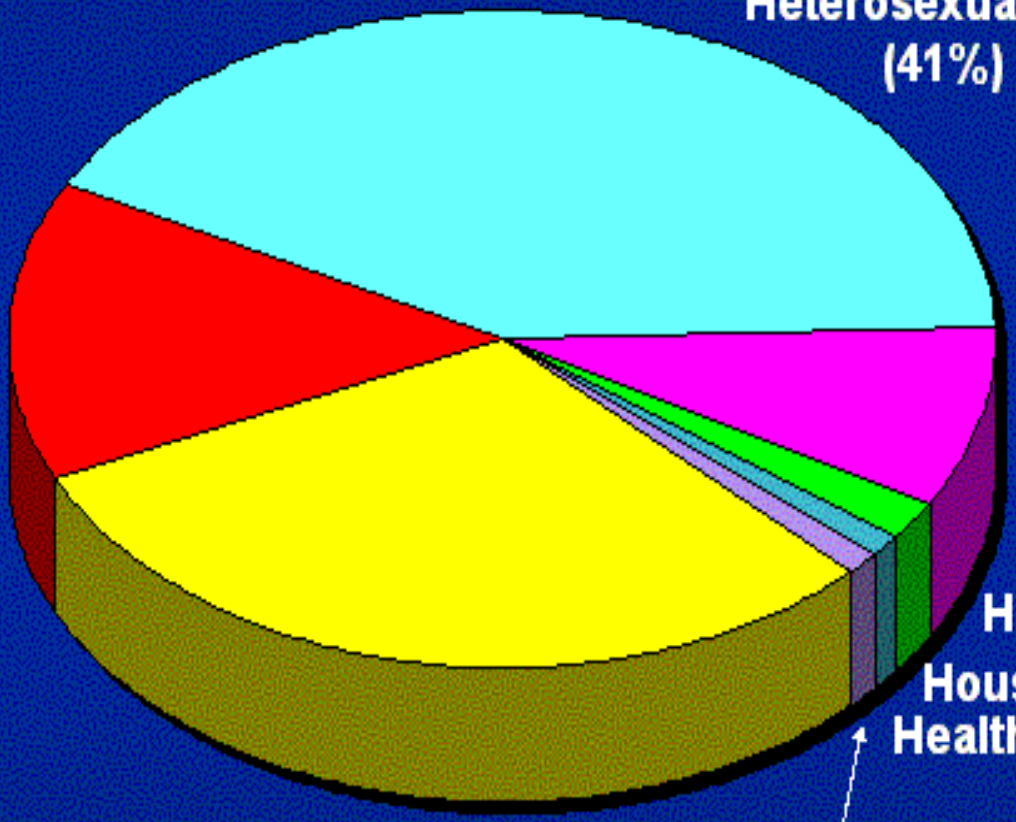
Characteristics of HBV

- **Stable to:**
  - Acid at pH 2,3
  - UV radiation
  - Phenol
  - Temperature:
    - 100^0 C for 5 minutes retains infectious activity
    - 20^0 C for 3 months
    - 4^0 C (in a refrigerator) for 6 months
  - Survival:
    - in dried blood for 4-5 months,
    - in frozen plasma for 15-20 years,
    - the presence of gross amounts of blood may interfere with the germicidal action of disinfectants.
- **Inactivated by:**
  - Autoclaving (120^0 C for 20 min).
  - Boiling for 60 minutes.
  - Chloramine 1-2% for 2 hours.
  - Ethanol 70-80% for 2 min.
  - Formalin 1,5 % for 2 min.
  - Hydrogen peroxide

Hepatitis B (serum hepatitis)

- 1) **Transmission:**
  - parenterally,
  - sexually,
  - vertically (from mother to fetus),
  - close contact (hemocontact).
- 2) chronic hepatitis in 10% to 15% of adult patients, 30-90% of young patients
- 3) is causally associated with primary hepatocellular carcinoma and cirrhosis.

Risk Factors for Acute Hepatitis B



* Includes sexual contact with acute cases, carriers, and multiple partners.

Epidemiology of HBV infection

- Virus is shed during both symptomatic and asymptomatic periods.
- **Transmission:**

  - In blood, semen, vaginal secretions, saliva and mother's milk.

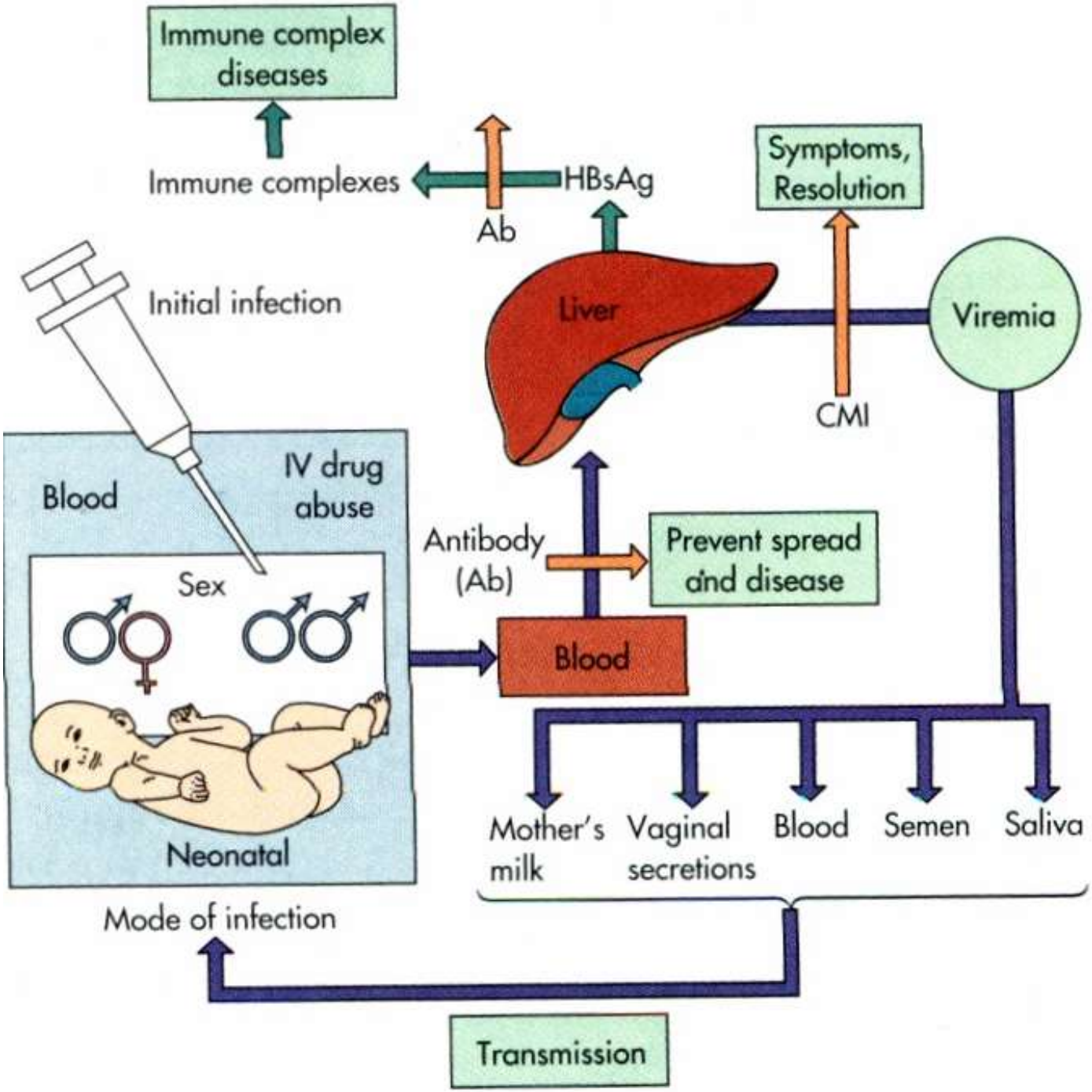
  - Via transfusion, needle stick injury, injecting drug use, sex, child-birth, and breast-feeding.

Concentration of hepatitis B virus in body fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
	breast milk	tears

Concentration HBV in the blood 10^9 virions per 1 ml

Spread of HBV in the body



Symptoms of typical acute viral hepatitis B infection

Fever, rash, arthritis — 15%

Jaundice

Dark urine

Malaise 95%

Anorexia 90%

Nausea 80%

RUQ pain 60%

Itching 10%

Exposure

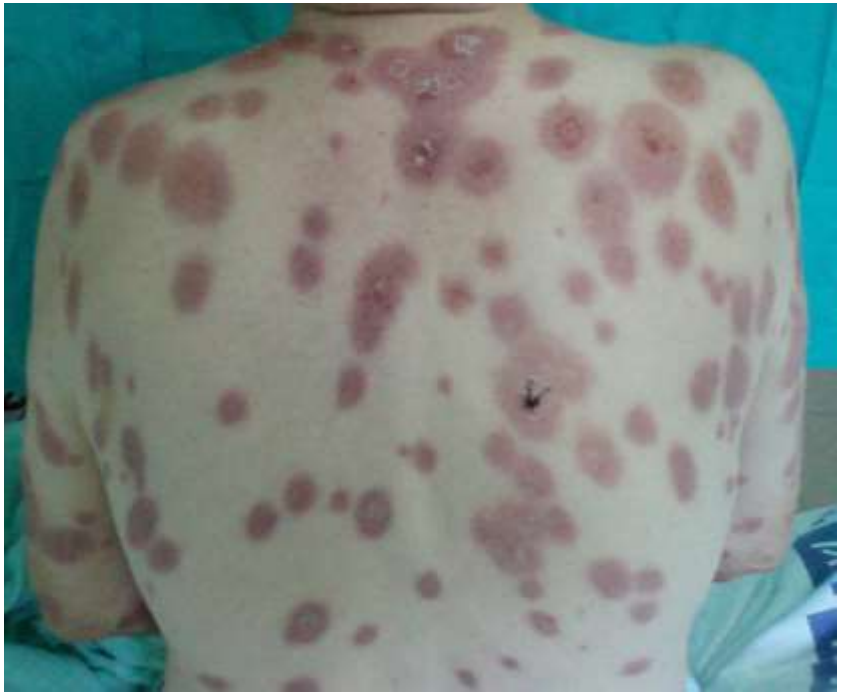
Incubation period | Preicteric | Icteric | Convalescent period

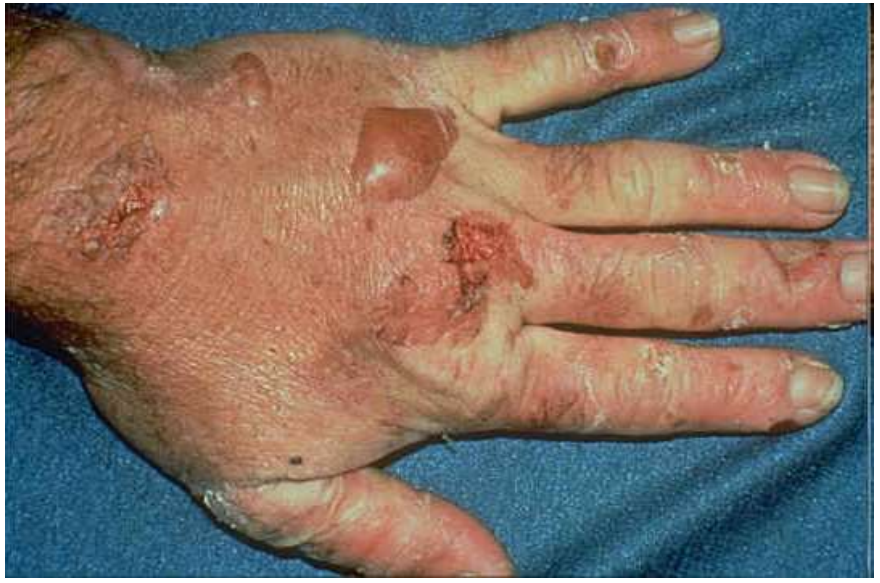
Acute disease

Right Upper Quadrant

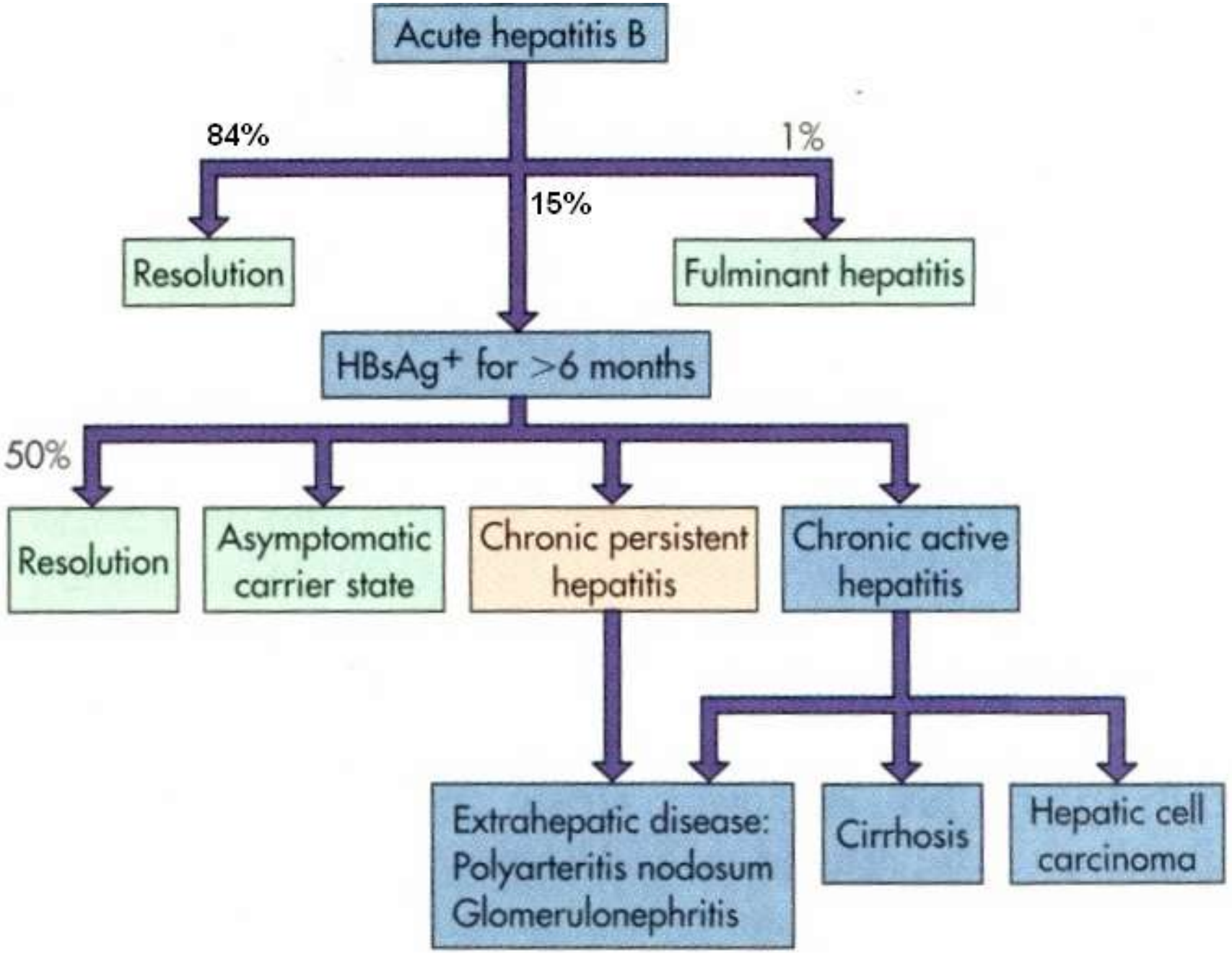
HBV can multiply in monocytes, T- and B-lymphocytes, NK.
Extrahepatic manifestation: glomerulonephritis, vasculitis and **ARTHRITIS-DERMATITIS** (a serum sickness-like syndrome). These patients experience rash, petechiae, purpura, arthralgia and arthritis.

It involves mostly small joints of hands and knees and occurs in the prodromal period, before jaundice appears and resolves within a week.





Clinical outcomes of acute hepatitis B infection



CLINICAL OUTCOMES OF HEPATITIS B

- Acute hepatitis
  - » Self-limiting
  - » Most common
  - » Life long immunity
- Carrier state
  - » Asymptomatic
- Chronic persistent disease
- Chronic active disease
- Fulminant hepatitis
  - » Massive necrosis of liver cells
- Hepatocellular carcinoma

Principal considerations:

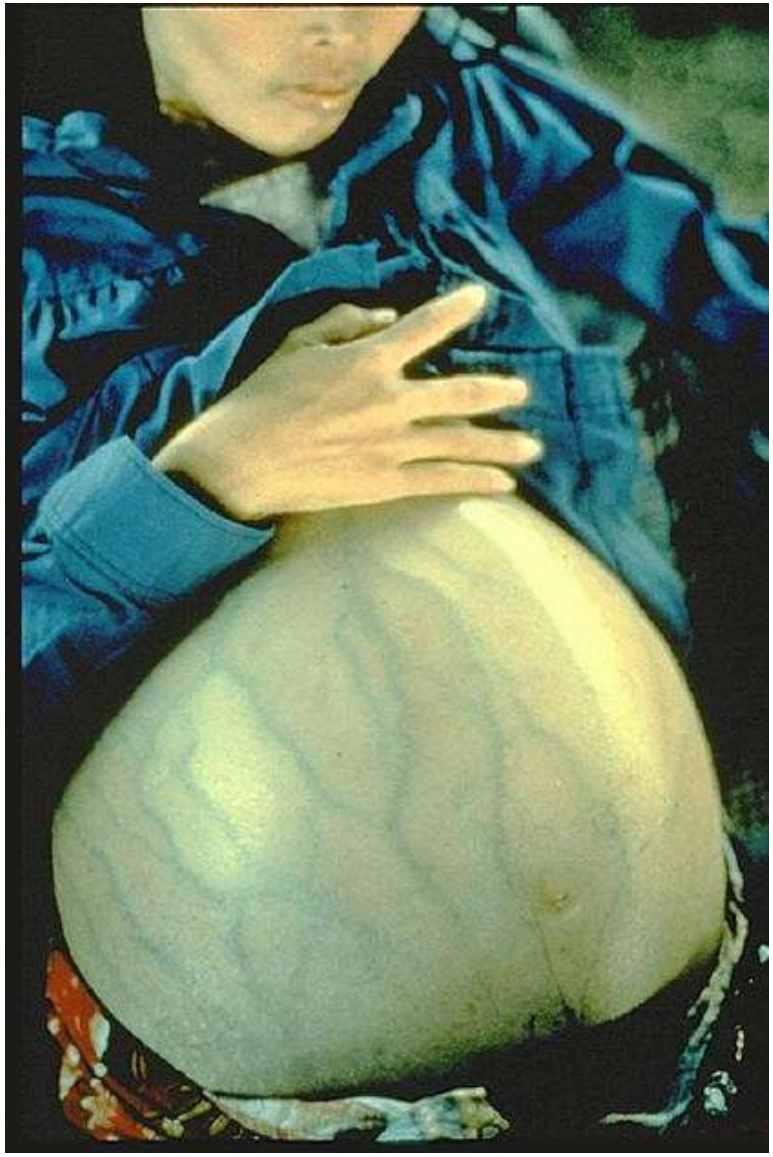
Asymptomatic carrier: the carrier patient never develops antibodies against HBsAg and harbors the virus without liver injury.

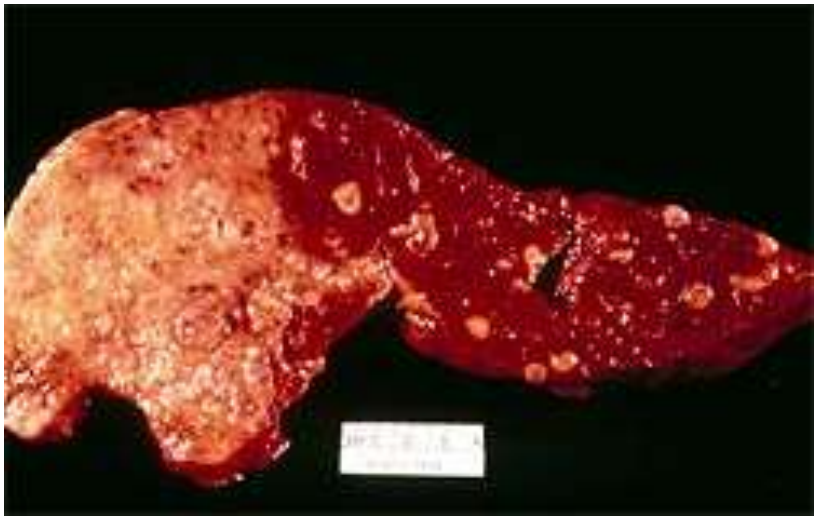
Chronic persistent hepatitis: the patient has a low-grade hepatitis

Chronic active hepatitis: the patient has an acute hepatitis state that continues without the normal recovery (last longer than 6-12 months).

Fulminant hepatitis: severe acute hepatitis with rapid destruction of the liver.

Hepatocellular carcinoma





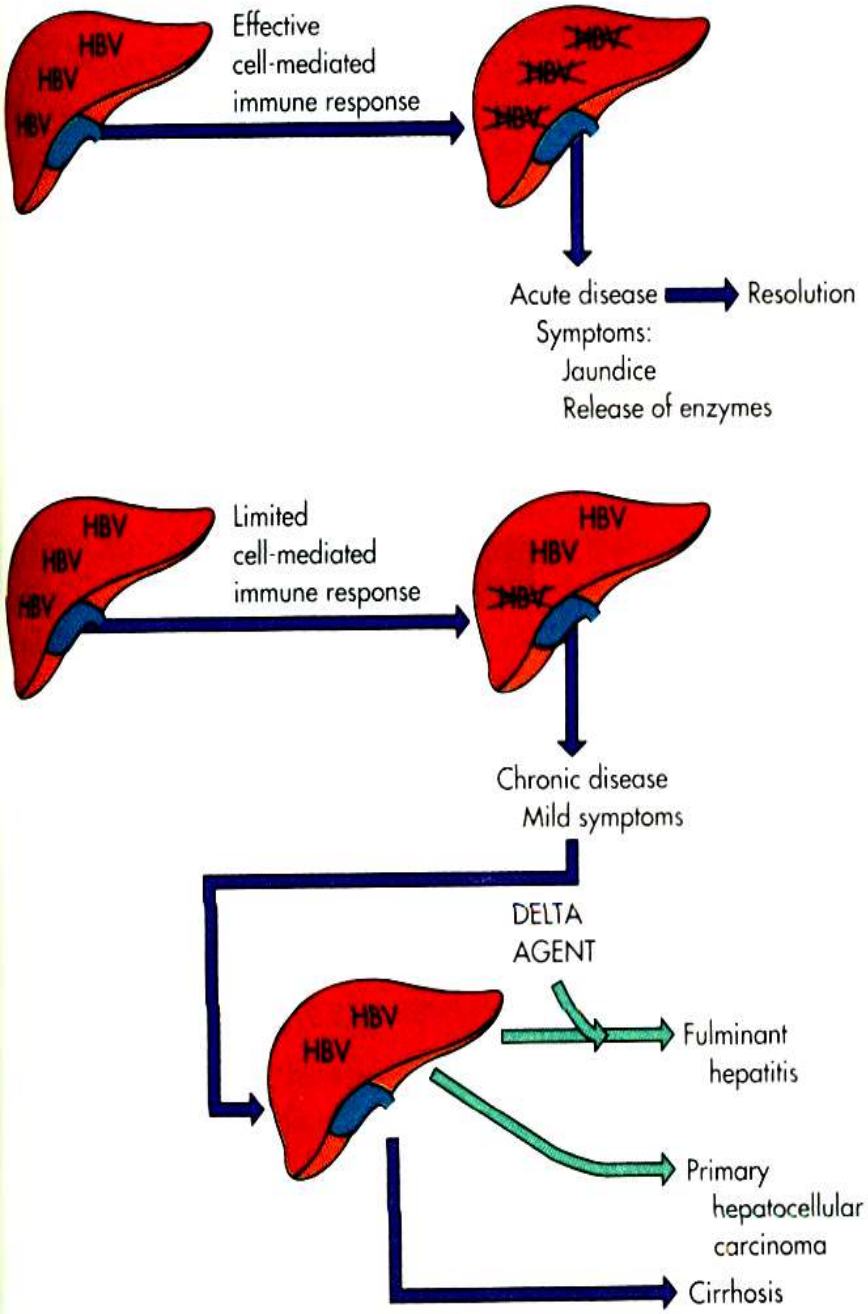
A section of a liver removed at liver transplantation showing a massive HCC (in white) and multiple satellite nodules

Pathology

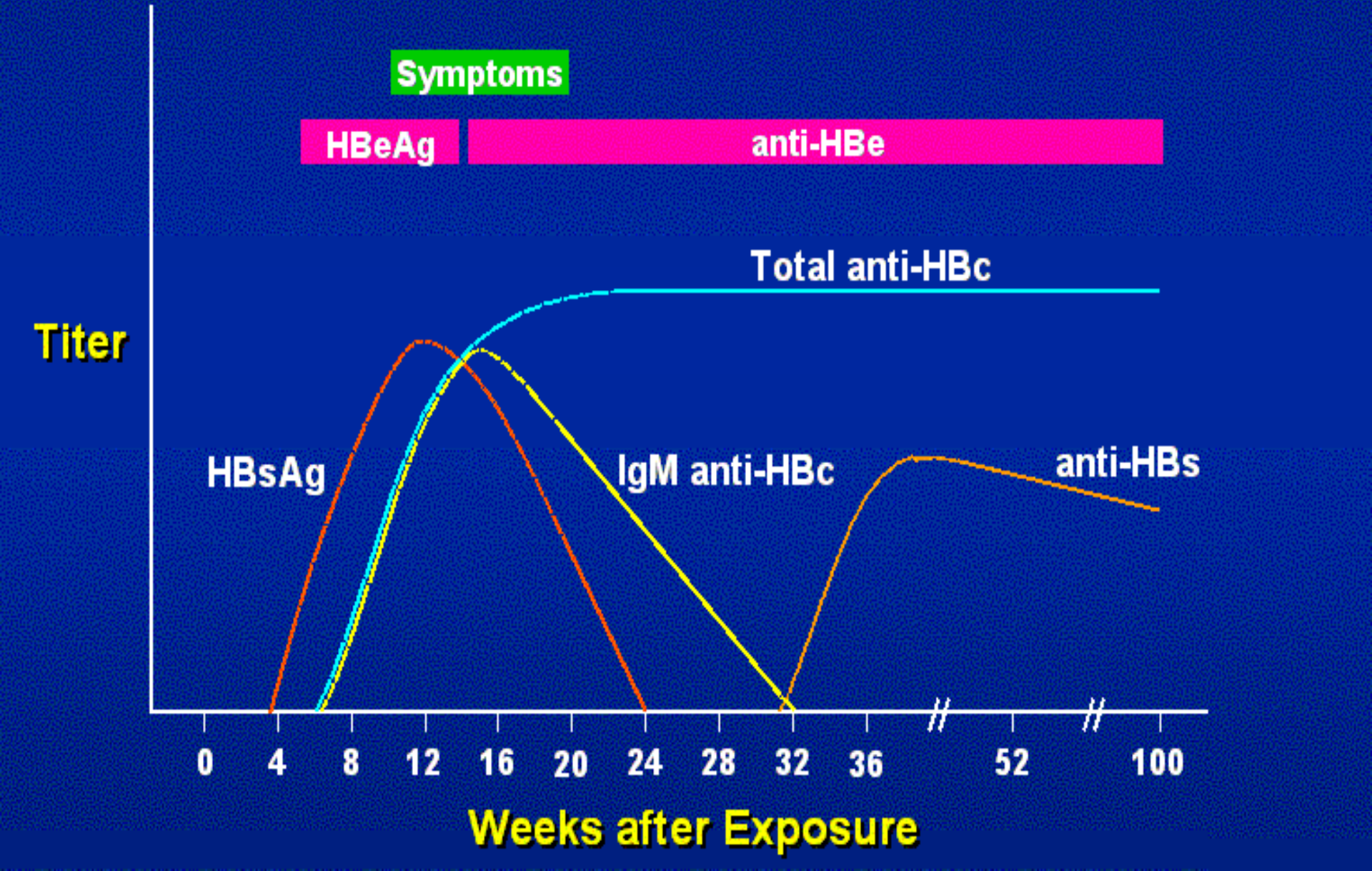
1- Symptoms are immune-mediated, resulting from inflammation and cell-mediated (cytotoxic T cell) responses to HBsAg on the surface of hepatocytes. These resolve the disease.

2-If the cell-mediated immune response is weak, symptoms are mild but the infection does not resolve and chronic hepatitis ensues.

3- Chronic hepatitis leads to cirrhosis and hepatocellular carcinoma. Both of these are fatal in the absence of a liver transplant

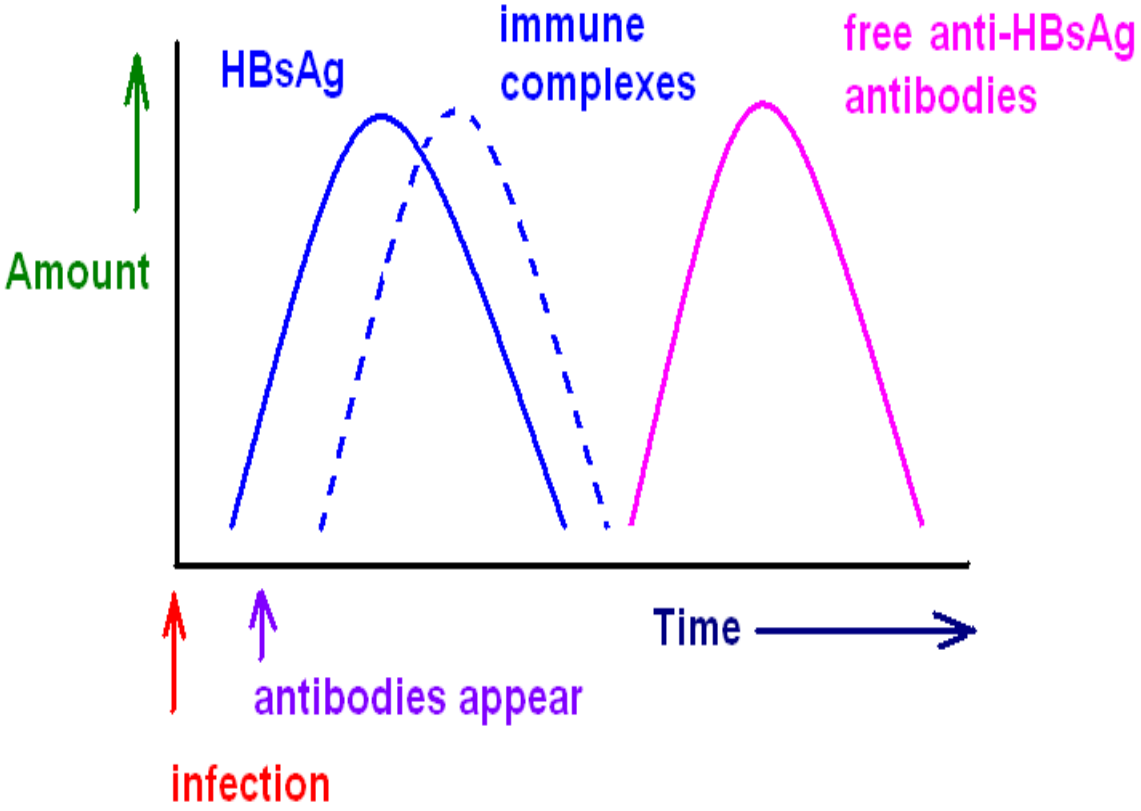


Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



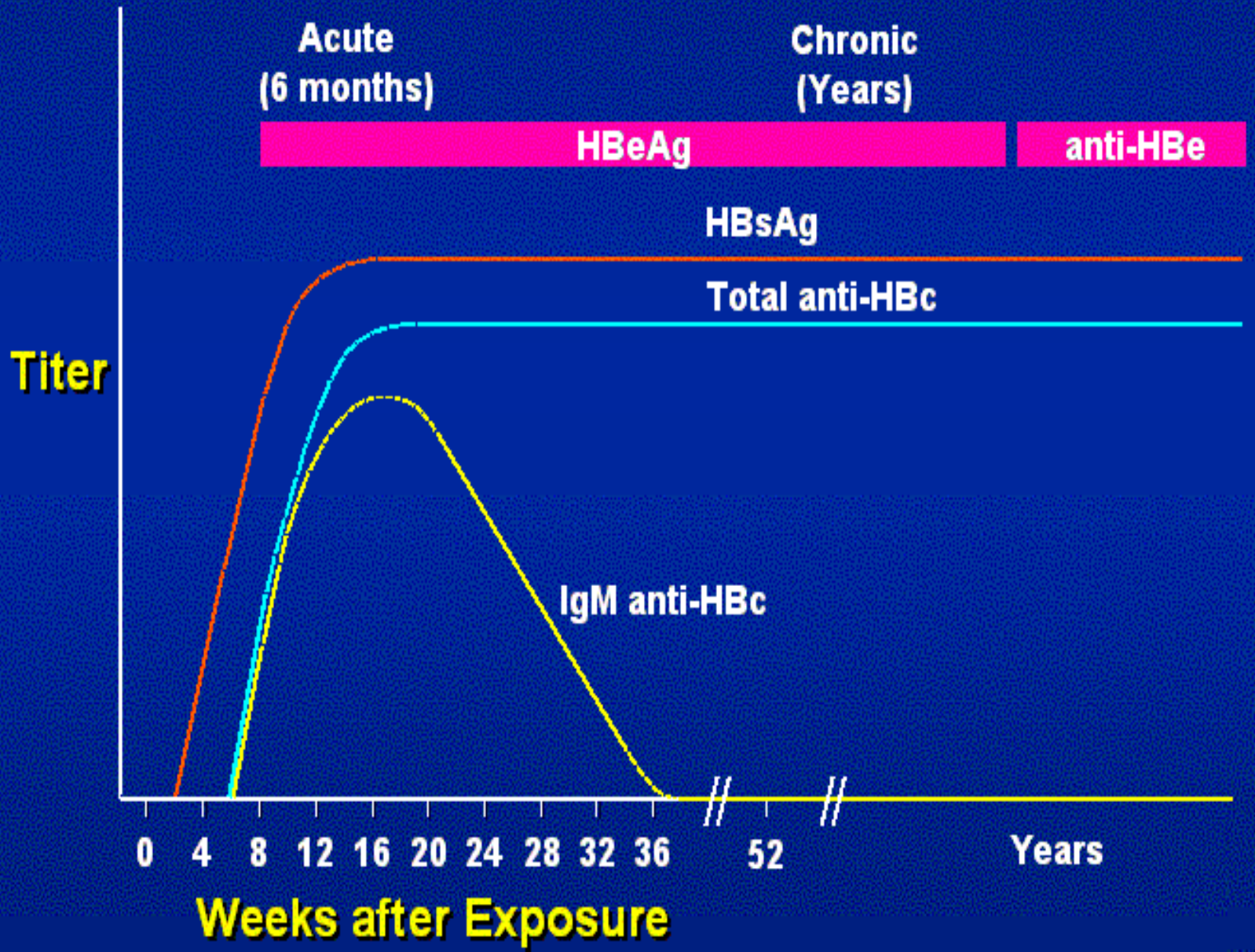
HBsAg window

- **“HBsAg window” -** the period from about 6 to 8 months when neither free HBsAg nor its antibody can be detected.
- Anti-HBsAg are undetectable because they are complexed with the large amount of the antigen that is shed from infected cells.
- The best tool for diagnosis of an acute HBV infection during the window is the presence of anti-HBc IgM



Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course



Laboratory markers for HBV infection and their interpretation

- **HBsAg** – present in acute or chronic infection. It is detectable in the blood from 1 to 6 months after infection.
- **anti-HBs** – marker of recovery and/or immunity to HBV infection (from about 8 months after infection).

- **anti-HBc IgM** - marker of recent acute infection ≥6 months.
- **anti-HBc IgG** - past or chronic infection.

- **HBeAg** - indicates active replication of virus and therefore infectiveness (from 2 to 6 months after infection).
- **anti-HBe** - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV (from about 4 months after infection).

- **DNA** - indicates active replication of virus.

Interpretation of Serological Markers of HBV Infection

SEROLOGICAL REACTIVITY	DISEASE STATE			HEALTHY STATE	
	ACUTE	CHRONIC	LATE ACUTE	RESOLVED	VACCINATED
Anti HBc	−*	+	+/−	+	−
Anti HBe	−	−	+/−	+/−†	−
Anti HBs	−	−	−	+	+
HBeAg	+	+	−	−	−
HBsAg	+	+	+	−	−
Infectious virus	+	+	+	−	−

*Anti-HBc IgM should be present.

†Anti-HBe may be negative after chronic disease.

HEPATITIS B VIRUS INFECTION

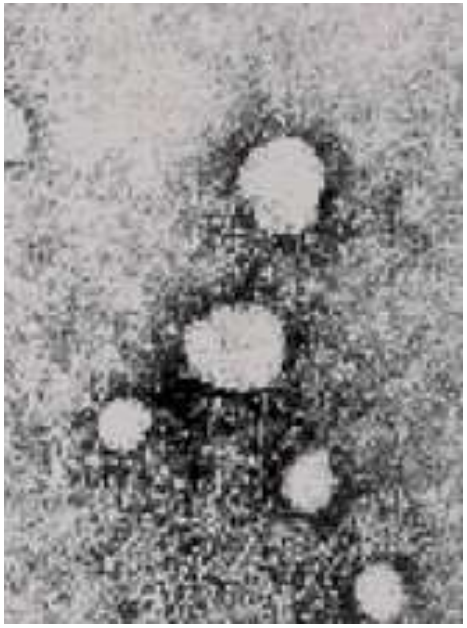
INTERPRETATION OF TEST RESULTS

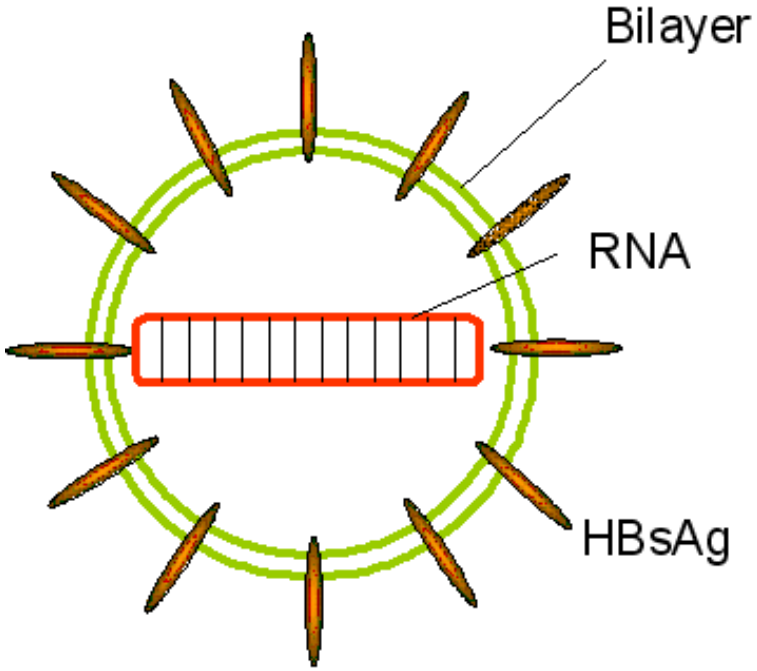
Serologic Test Results	HBsAg	Total anti-HBc	IgM anti-HBc	anti-HBs
DETECTED FOLLOWING VACCINATION OR FOR 3-6 MONTHS FOLLOWING RECEIPT OF HBIG	−	−	−	+
FALSE POSITIVE (SUSCEPTIBLE) / PAST INFECTION (RESOLVED) / "LOW LEVEL" CHRONIC INFECTION (UNLIKELY TO BE INFECTIOUS)	−	+	−	−
CHRONIC INFECTION	+	+	−	−
PAST INFECTION, WITH RECOVERY, IMMUNITY TO NEW INFECTION	−	+	−	+
ACUTE INFECTION	−	+	+	−
EARLY ACUTE INFECTION / OR RECEIPT OF THE VACCINE WITHIN SEVERAL WEEKS	+	−	−	−
NEVER INFECTED / SUSCEPTIBLE	−	−	−	−

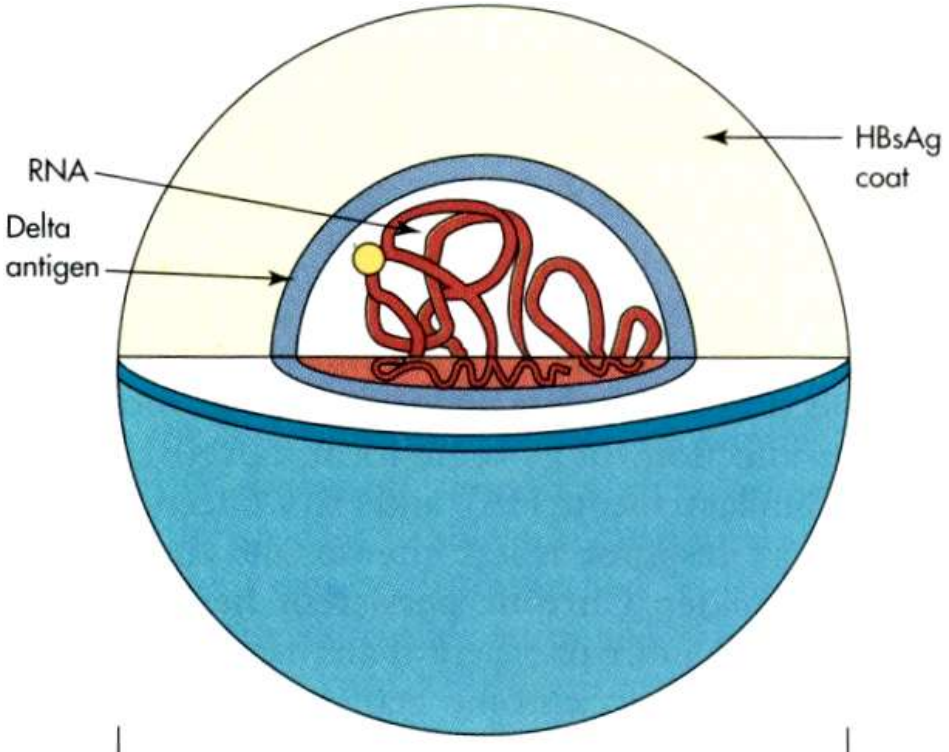
Hepatitis D virus (HDV) - delta agent

ss, circular (-) RNA virus similar to certain plant viroids. It has delta antigen.

- HDV is coated with HBsAg which is needed for release from the host hepatocyte and for entry in the next round of infection.
- 3 genotypes.







Epidemiology of HDV infection

- HDV infects children and adults with underlying HBV infection.
- **Transmission:**

  - parenterally and sexually;

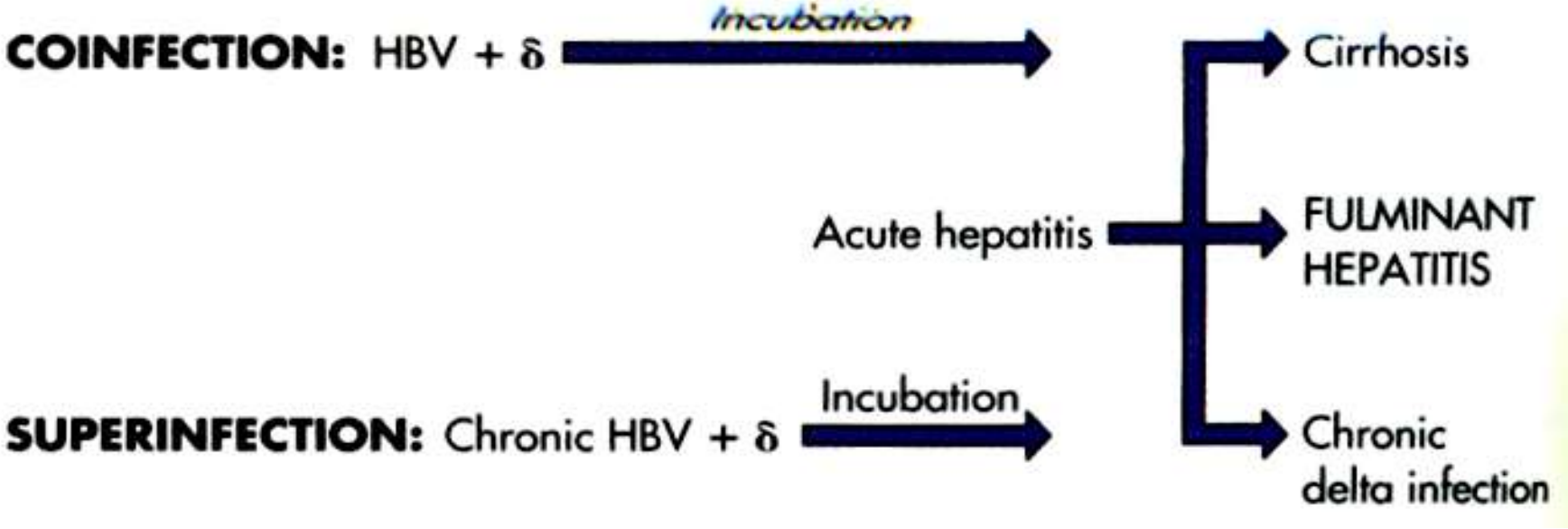
  - vertically (rarely).

  - In blood, semen, and vaginal secretions;

  - Unsterilized equipment and infusion.

  Intravenous drug abusers, transfusion and organ recipients, and hemophiliacs are at highest risk for infection.

Consequences of delta virus infection



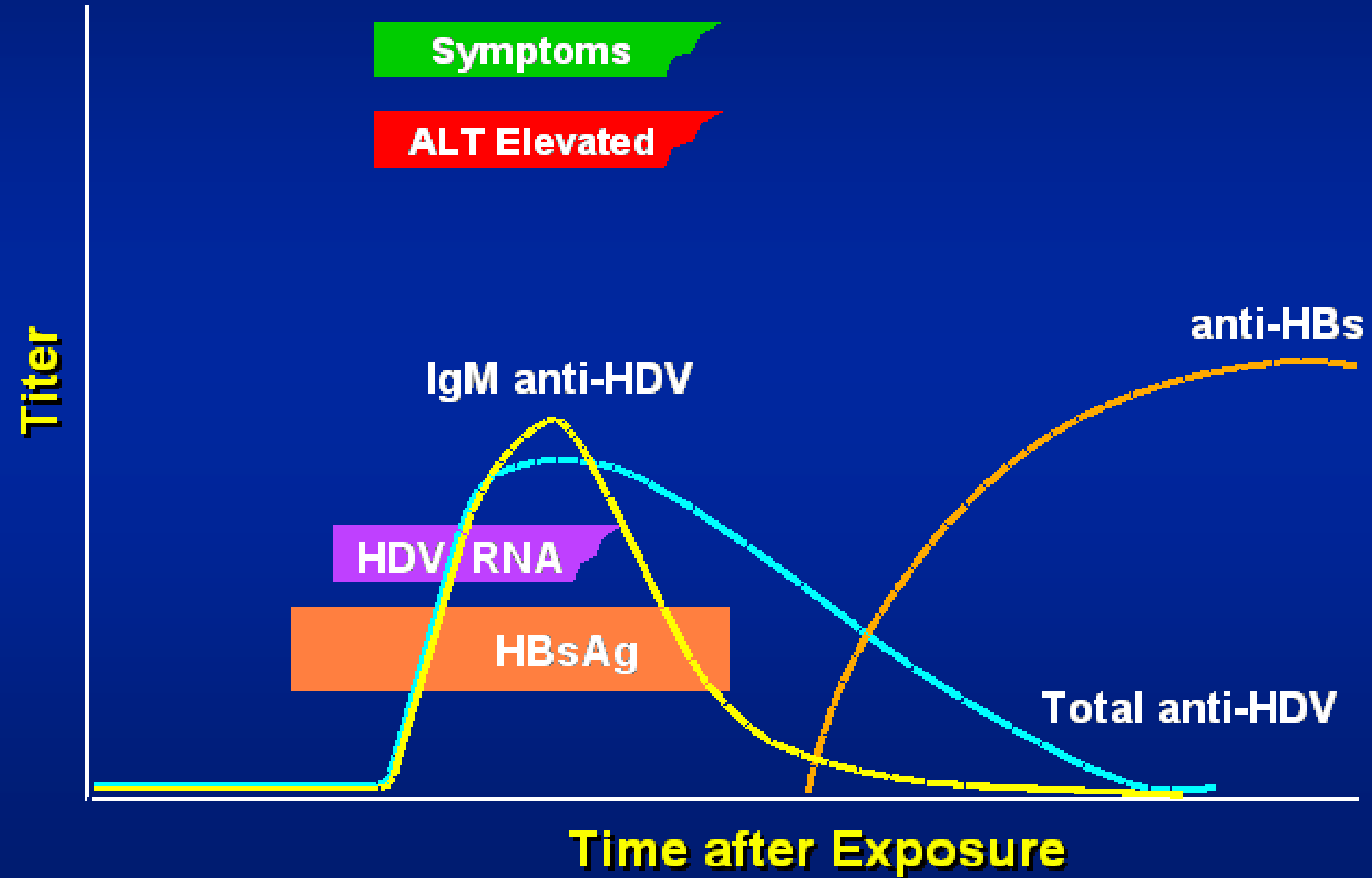
- **Co-infection** by HDV and HBV exacerbates the acute disease (90%) and fulminant hepatitis (2-4%) is more likely than with HBV alone.
- **Superinfection** of a person already infected with HBV causes a more rapid, severe progression than co-infection because super-infection requires HBV replication before HDV replication can occur.
  - about half of the patients exhibit acute hepatitis that resolves
  - about 10-40% get chronic persistent hepatitis
  - 7-10% get fulminant hepatitis.

Laboratory markers for HDV infection

- **In an HBV-HDV co-infection:**
  - HDV antigen is detected in about ¼ of patients. HDV antigen disappears when HBsAg appears,
  - anti-HDV IgG and IgM are usually seen,
  - anti-HDV decline as the symptoms resolve and, unlike anti-HBs, there are no antibodies to show that the patient was once HDV-infected,
  - anti-HBs IgG rises.
- **In a super-infection by HDV:**
  - HBsAg and HDV RNA remain because super-infection usually leads to chronic infection.
  - anti-HDV IgG rises.

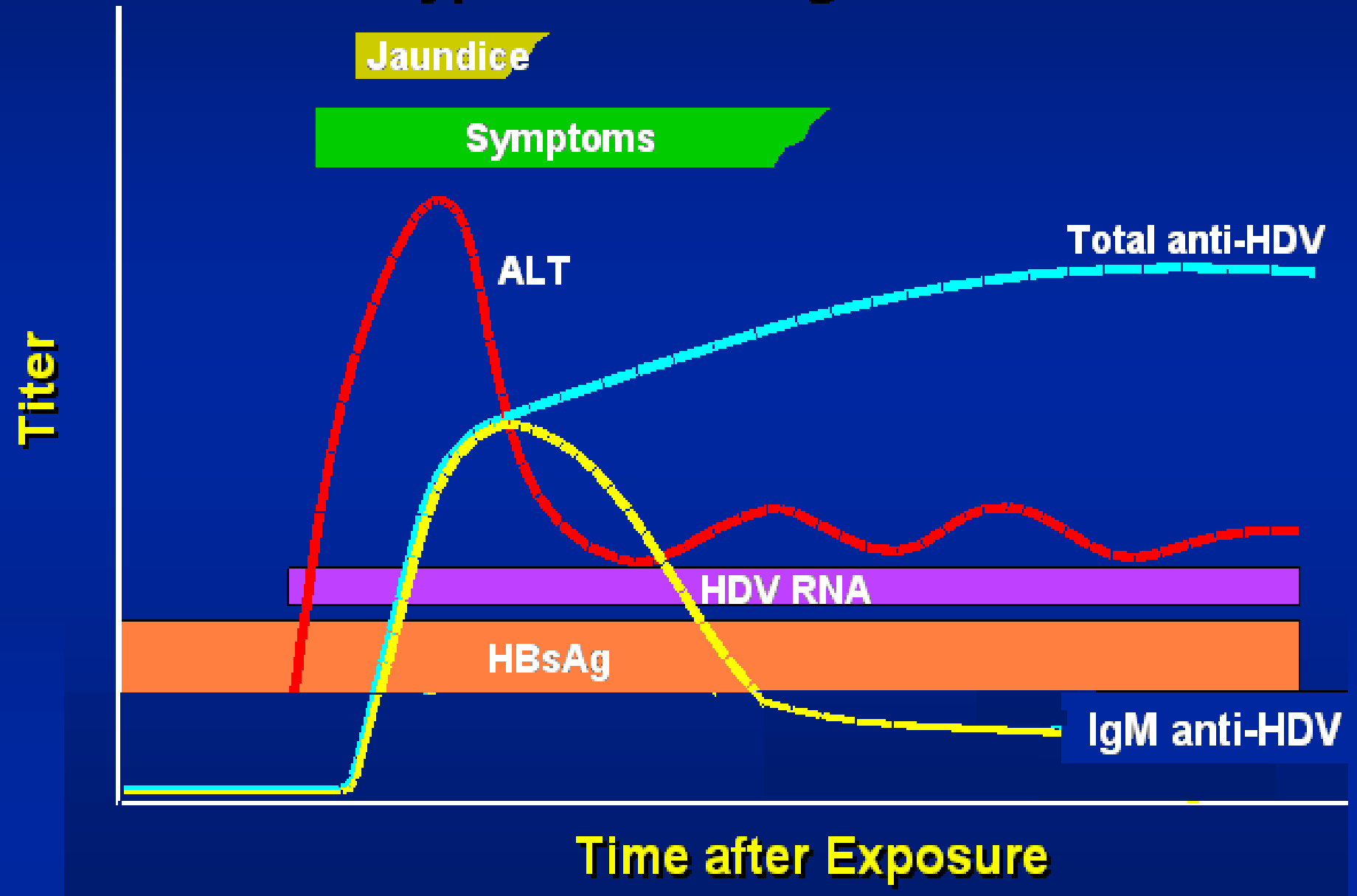
HBV - HDV Coinfection

Typical Serologic Course



HBV - HDV Superinfection

Typical Serologic Course

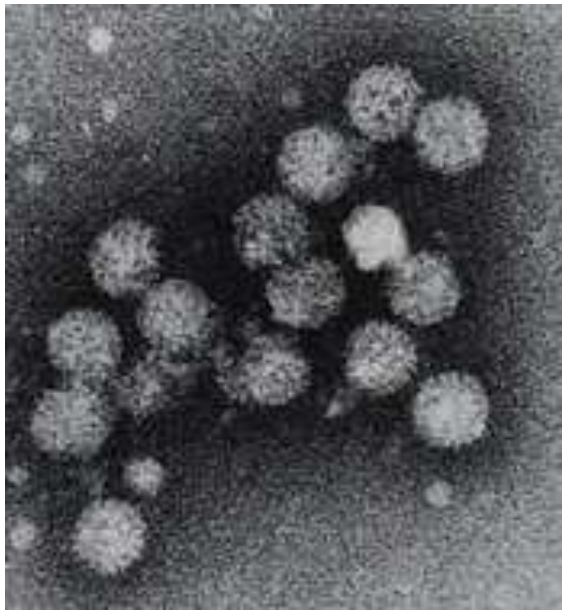


Family Flaviviridae.
Hepatitis C and G viruses

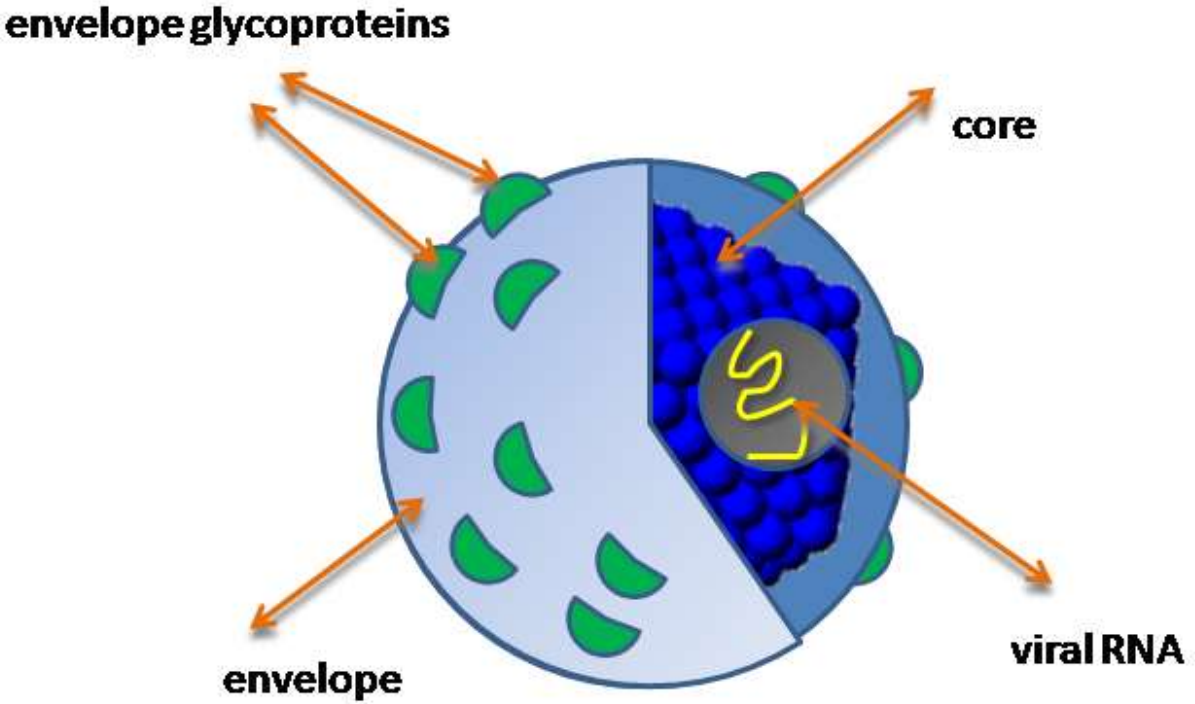
Enveloped ss+RNA viruses, 55-65 nm diameter.

14 genotypes of HCV.

5 genotypes of HGV.

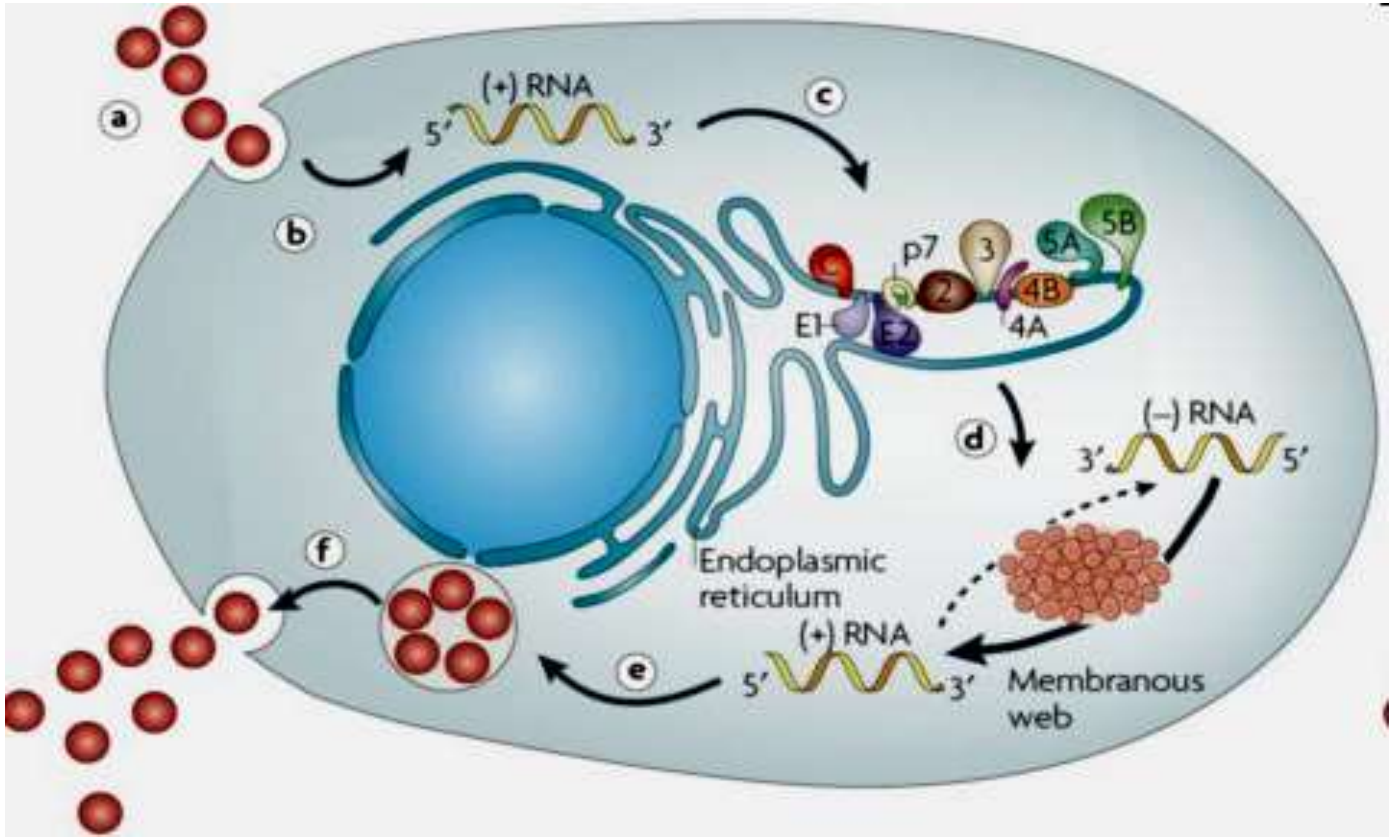


Electron micrograph of the hepatitis C viruses



HCV life cycle

- a) Virus binding and internalization,
- b) cytoplasmic release and uncoating,
- c) translation,
- d) RNA replication,
- e) packaging and assembly,
- f) virion maturation and release.



Epidemiology of HCV and HGV infection

- 85-90% patients will develop chronic disease.
- About 50% of chronic carriers of HCV progress to cirrhosis or liver cancer in 10-40 years.
- **Transmission:**

- parenterally (through sharing drug-injection equipment or from transfusion of unscreened blood or untreated clotting factors),

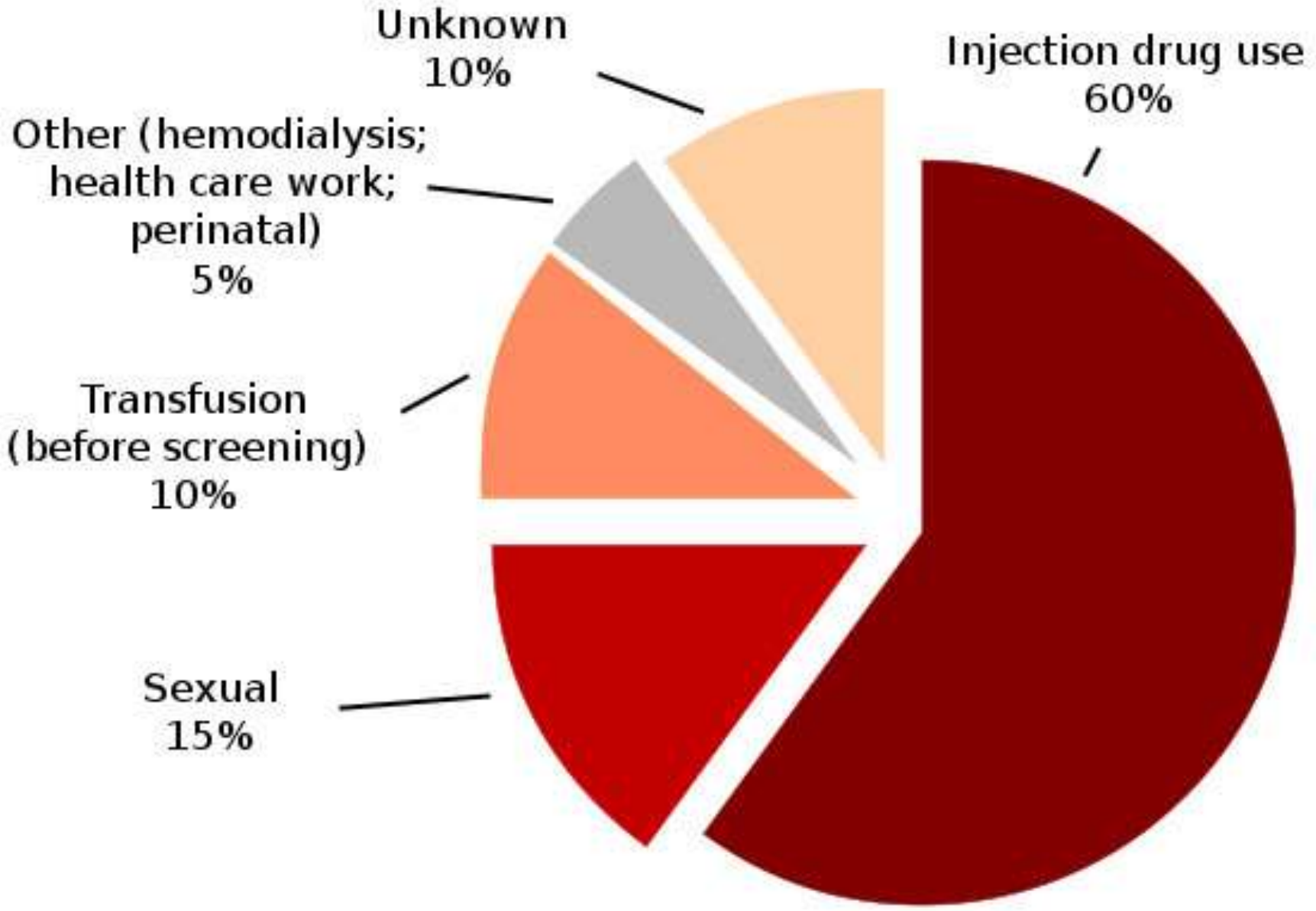
- sexually,

- perinatally.

- In blood, semen, and vaginal secretions.

- Contagious period extends 2-3 weeks before and 10 weeks after onset of symptoms.

Routes of transmission of HCV

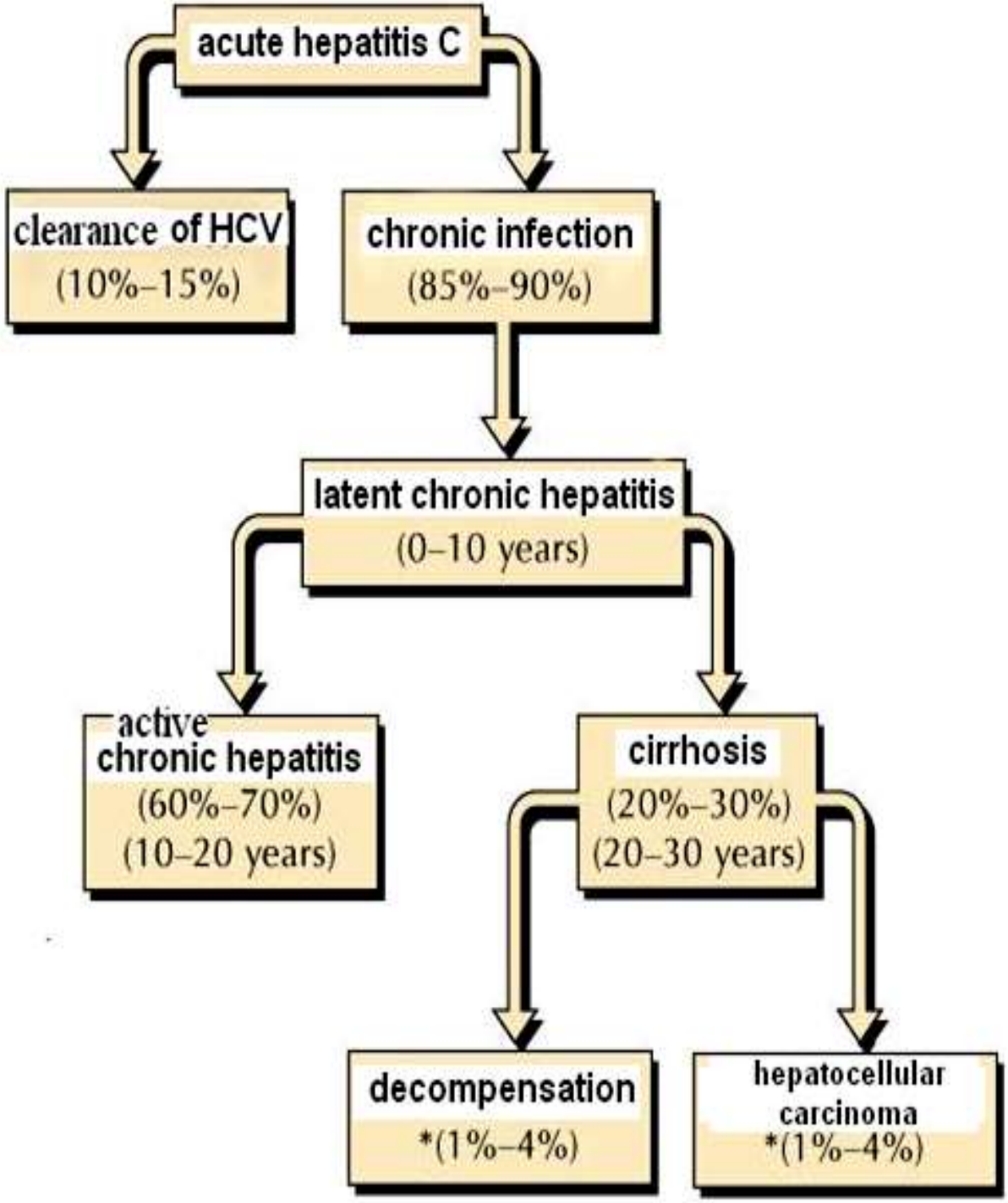


Risk factors of hepatitis C

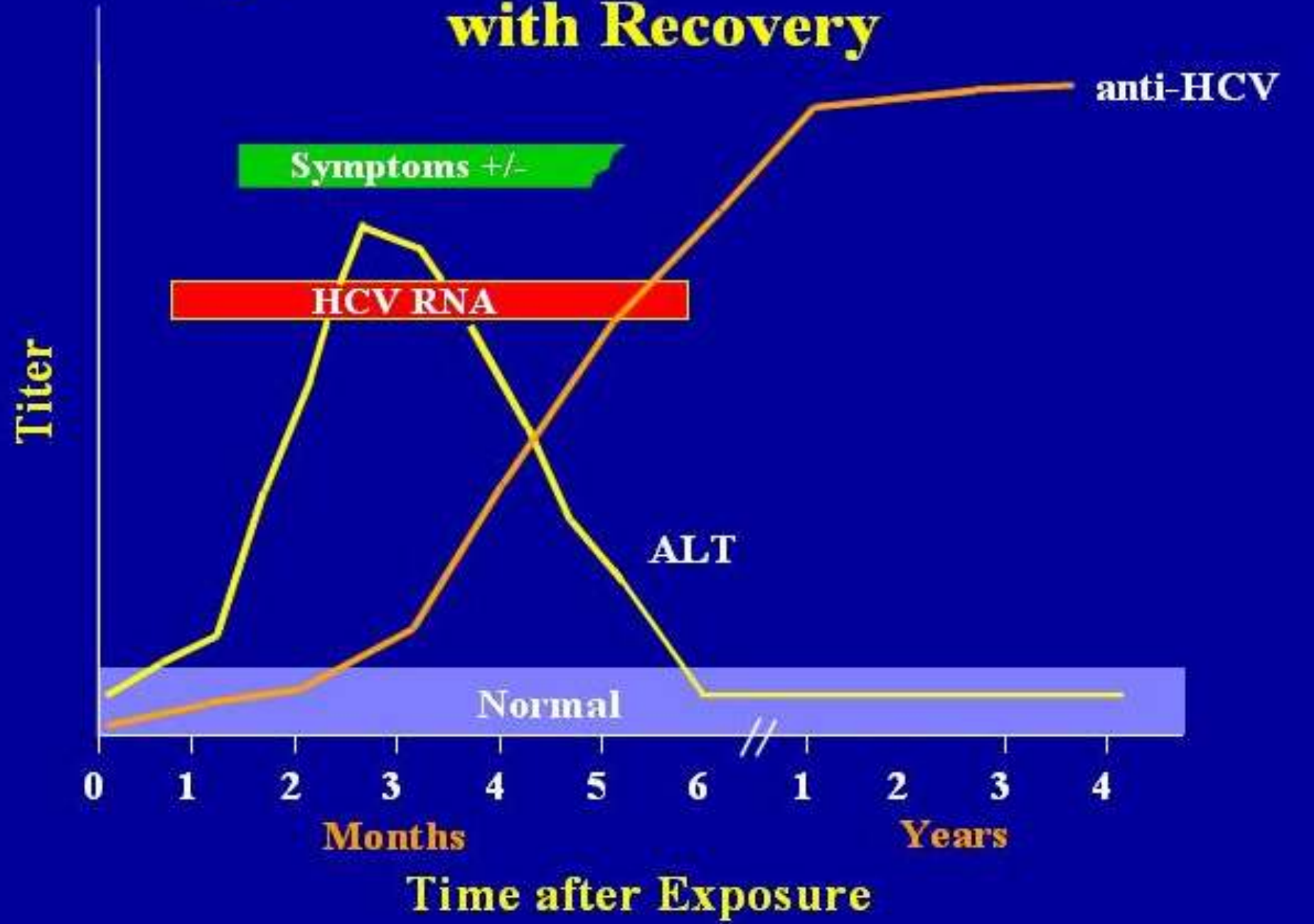
- **Blood-to-blood contact (mainly transfusion):**it is estimated that 90 %of persons with chronic HCV infection were infected through **transfusion** of unscreened blood or blood products.
- **Unsterilized injection equipment and infusion:** considered to be the primary sources of HCV infection.
- **Sexual intercourse** tneserp osla si VIH nehw srucco ylno yllausu dna ,erar si siht hguohtla : .ylekil erom tcatnoc doolb sekam dna
- **Dental equipment:** People can be exposed to HCV via inadequately or improperly sterilized medical or dental equipment including needles or syringes, oral hygiene instruments, and jet air guns, etc.
- **Hemodialysis:**.dewollof ton era sdohtem noitazilirets reporp taht si melborp cisab ehT
- **Occupational exposure to blood:** Medical and dental personnel, first responders (e.g. surgeons, nurses and emergency medical technicians) can be exposed to HCV through needle sticks or blood spatter to the eyes or open wounds.
- **Tattoos:** Tattooing dyes, ink pots, piercing implements can transmit HCV-infected blood from one person to another if proper sterilization techniques are not followed.
- **Shared personal care items:** Such as razors, toothbrushes, cuticle scissors, and other manicuring or pedicure equipment can easily be contaminated with blood carrying the virus, and take care that HCV can live on dried blood for 15days.
- **Vertical transmission:** refers to the transmission of a communicable disease from an infected mother to her child during delivery .

Pathogenesis of HCV infection

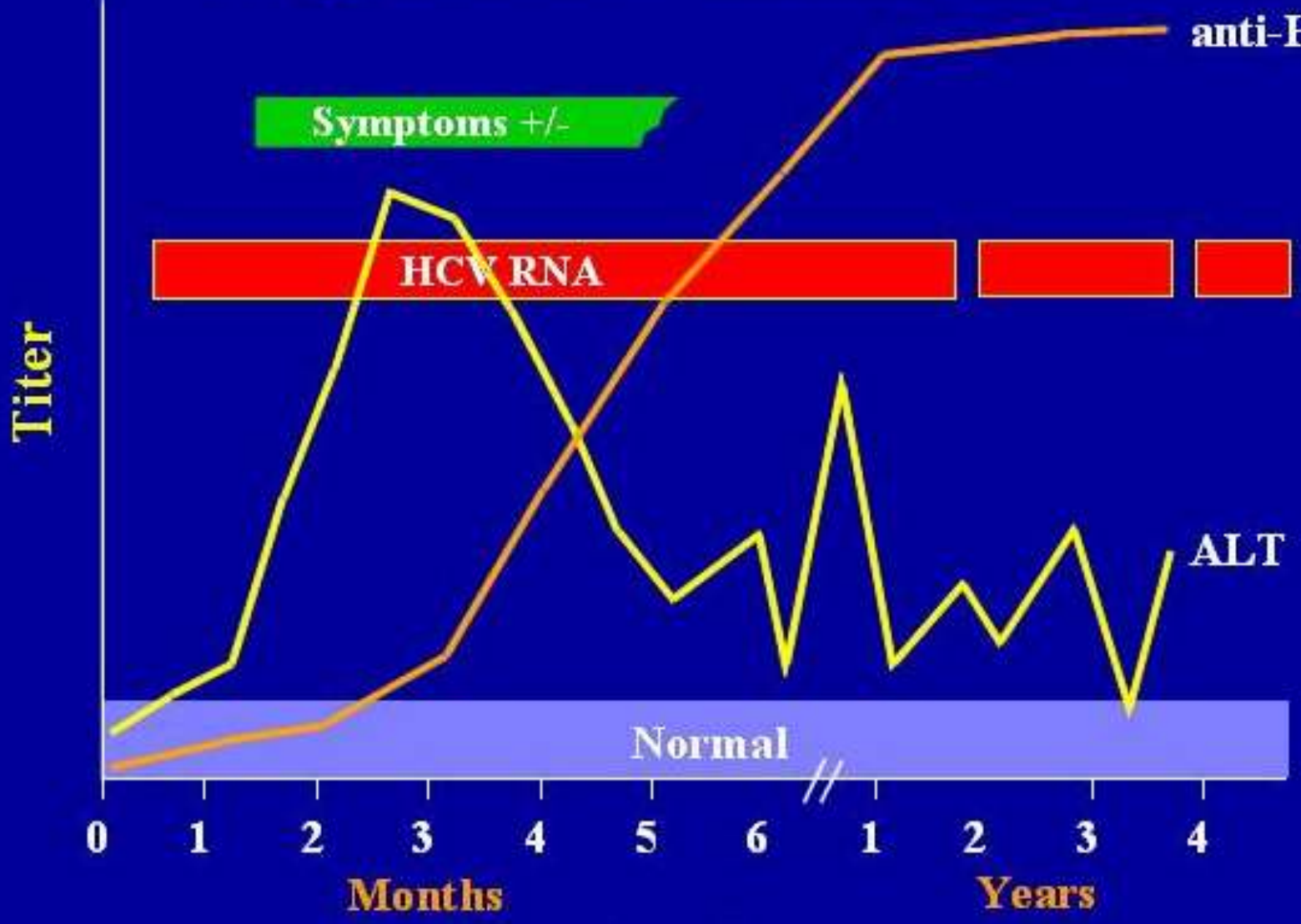
- Hepatocytes are target cells for HCV.
- CPE – lysis of hepatocytes.
- Sensitive cells: monocytes, macrophages, B-lymphocytes, neutrophiles, cells of bone marrow.
- HCV can reproduce in cells of pancreas, adrenal glands, thyroid glands, spleen.
- Immunomediated extrahepatic manifestations:
  - vasculitis (malaise, arthralgia, purpura);
  - glomerulonephritis;
  - altered nervous system (peripheral nerves, brain).


acute hepatitis C
clearance of HCV
(10%–15%)
chronic infection
(85%–90%)
latent chronic hepatitis
(0–10 years)
active
chronic hepatitis
(60%–70%)
(10–20 years)
cirrhosis
(20%–30%)
(20–30 years)
decompensation
*(1%–4%)
hepatocellular
carcinoma
*(1%–4%)

Serologic Pattern of Acute HCV Infection with Recovery



Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Laboratory diagnosis of viral hepatitis

- **Biochemical methods:** Detection of the level of bilirubin and enzymes **ALT, AST** in serum.
- **Serology:**

  ELISA - Detection of the Ag and antibodies

- **Detection of a viral genome:** PCR
- **Rapid immunochromatographic test**

Vaccines

- **Against Hepatitis A**

  Havrix (inactivated)

- **Against Hepatitis B (recombinant)**

  - Monovaccines (HBsAg – genetic engineering):

    Engerix B

    H-B-Vax

    Recombivax B

  - Divaccines:

    Twinrix (inactivated HAV + HBsAg)

Treatment

- **Hepatitis B:**
- Anti-HBV immunoglobuline
- Alpha-interferon
- Lamivudine
- Adefovir
- **Hepatitis C:**
- Alpha-interferon + Ribavirine


The End