Viral hepatitis
Blood Born hepatitis

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Outline

- Introduction to hepatitis
- Characteristics of viral hepatitis
- Mode of transmission
- Markers of hepatitis infections
- Serological profile
- Stages of hepatitis infection
- Lab diagnosis
- Management & treatment

Hepatitis

- Is inflammation of the liver.

Etiology

❑ Primary infection:

- ➢ Hepatitis A virus (HAV)
- ➢ Hepatitis B virus (HBV).
- ➢ Hepatitis C virus (HCV), was known as non-A non-B hepatitis,
- ➢ Hepatitis D virus (HDV) or delta virus.
- ➢ Hepatitis E virus (HEV).
- ➢ Hepatitis F virus (HFV).
- ➢ Hepatitis G virus (HGV).

❑ As part of generalized infection:

- ➢ (CMV, EBV, Yellow fever virus)

Continued ….

- Hepatitis F has been reported in the literature but not confirmed.
- Viral hepatitis is divided into two large groups, based on the mode of transmission:

1– Enterically transmitted hepatitis or water born hepatitis. This group includes hepatitis A and E viruses.

2– Parenterally transmitted hepatitis or blood born hepatitis. This group includes hepatitis B, C, D & G viruses.

Characteristics of HBV

- Family of *hepadnaviridae.*

Virion consists of:

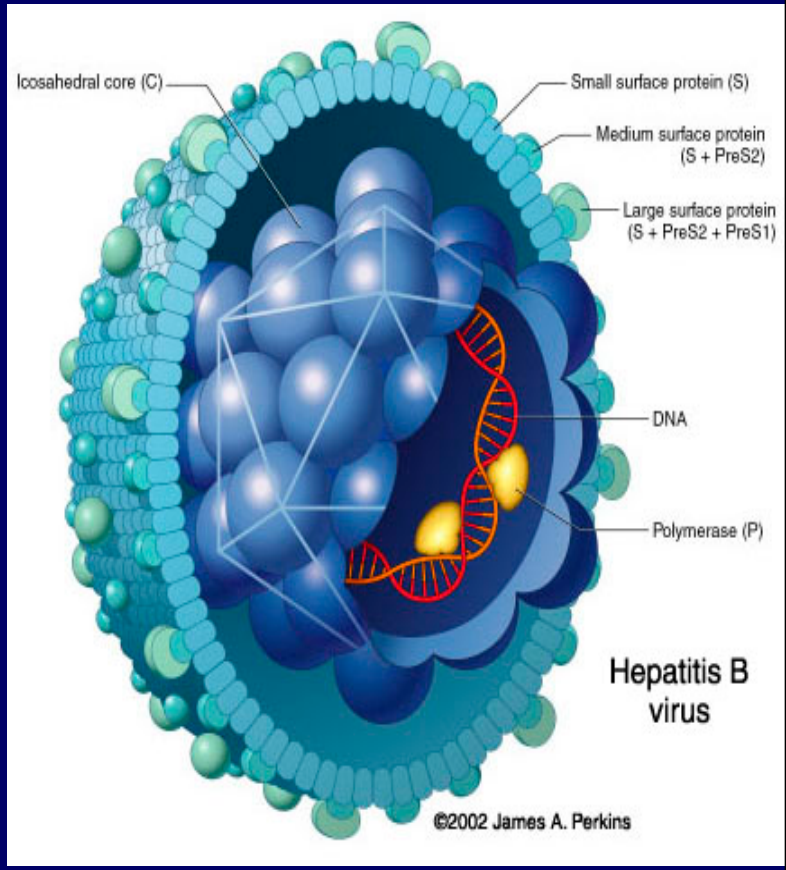
➢ Outer envelope containing hepatitis B surface antigen **(HBsAg).**

➢ Internal core (nucleocapsid) composed of hepatitis B core antigen **(HBcAg**).

➢ The viral genome which is small partially circular ds-DNA.

➢There are 8 genotype (A-H),genotype **D** is dominant in Saudi Arabia.

➢ The virus contains the **2 enzymes reverse transcriptase & protease enzyme**.



The size of the complete virus (DANE) particle is 42-nm in diameter.

Characteristics of HBV

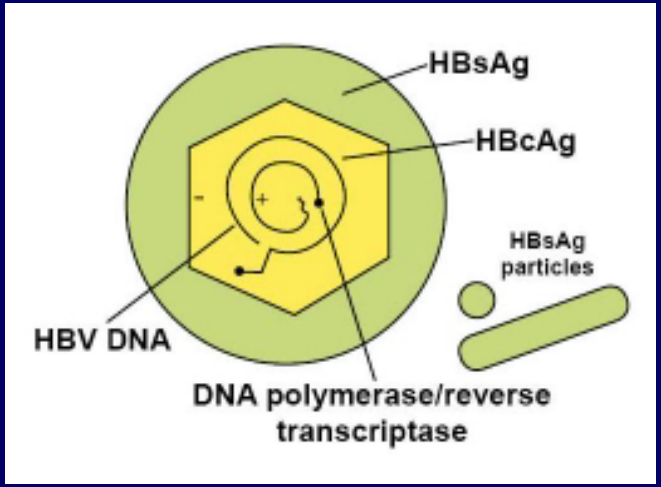
❑ The serum of infected individual contains three types of hepatitis B particles:

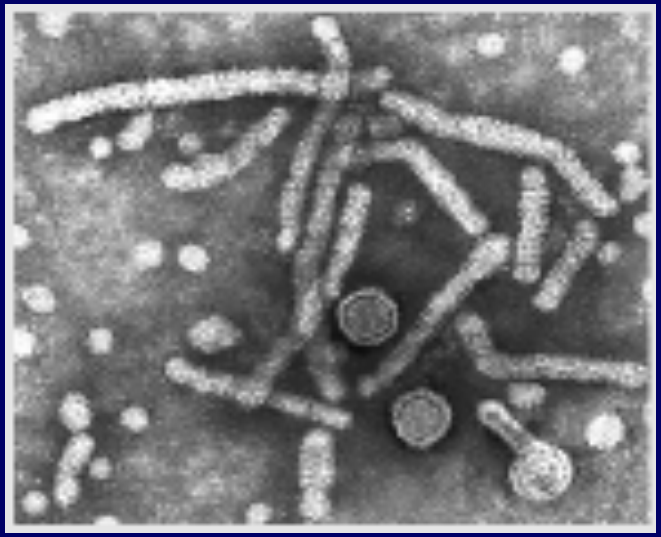
➢ Large number of small spherical free HBsAg particles.

➢ Some of these HBsAg particles are linked together to form filaments.

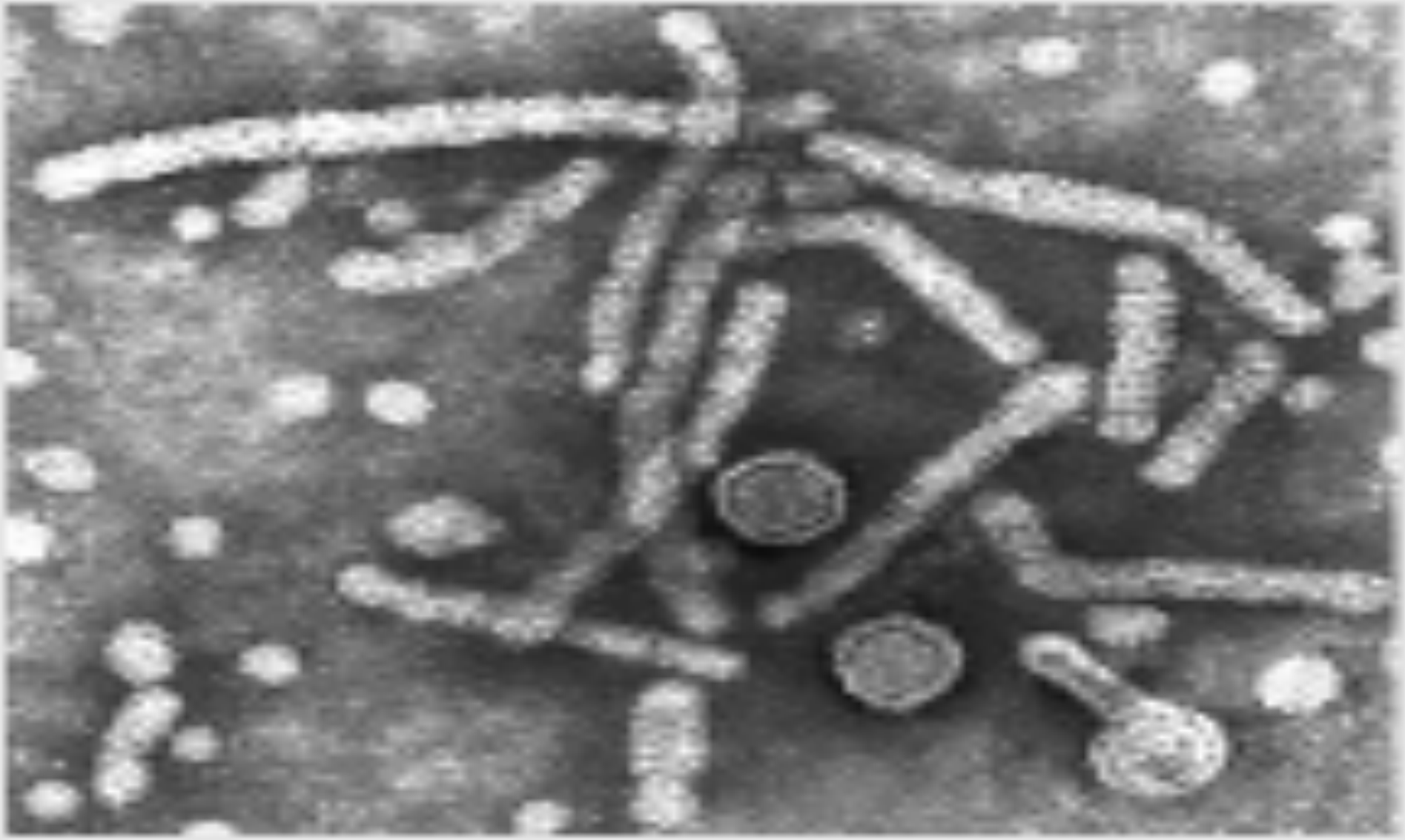
➢ The complete HBV particles (Dane particles).

❑ There are 8 known genotypes (A-H), Genotype D is the dominant in Saudi patients.





Electron micrograph of particles in the blood of a patient infected with HBV



Transmission of HBV

1- Parentally:

- Direct exposure to infected blood or body fluids (e.g. receiving blood from infected donor).
- Using contaminated or not adequately sterilized tools in surgical or cosmetic practice (dental, tattooing, body piercing).
- Sharing contaminated needles, razors, or tooth brushes.

2- Sexually (unprotected sex):

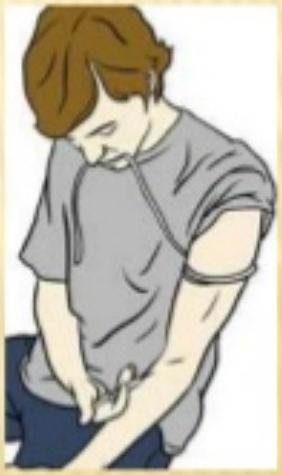
- The virus is present in blood and body fluids. By having sexual contacts with infected person ,virus is present in semen and vaginal secretion ,**HOMOSEUAL .**

3- From mother to the fetus :

- Mostly(**perinatally**) during delivery ,nursing ,breast feeding and less likely through placenta **(vertical transmission)**

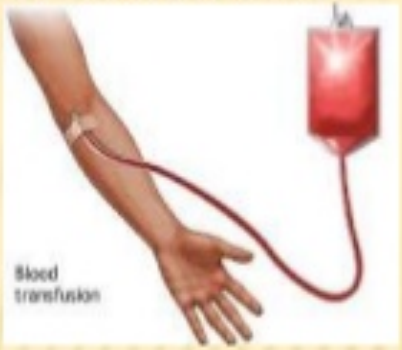
ROUTES OF TRANSMISSION

1) Intravenous drug use:
sharing of needles and syringes
Reuse of contaminated needles



2) Sexual transmission

3) Blood transfusion



5) Needlestick injury

4) Vertical transmission

The following groups are at high risk of acquiring hepatitis B

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors.
- Individuals with multiple sexual partners.
- Recipient of blood transfusion , before 1992.
- Health care workers with frequent blood contact.
- Individuals exposed to risk factors such as tattooing, body piercing and cupping.

Hepatitis B markers

Types	Description
HBV DNA	Marker of infection, contiguous.
Hepatitis B surface antigen (HBsAg)	Marker of infection, contagious .
Hepatitis B e antigen (HBeAg)	Marker of active virus replication, the patient is highly infectious, the virus is present in all body fluids, **highly contiguous.**
Antibody to hepatitis B e antigen (Anti-HBe)	Marker of low infectivity, the patient is less infectious, contiguous.
Antibody to hepatitis B core (Anti-HBc)	Marker of exposure to hepatitis B infection, contiguous.
Antibody to hepatitis B surface antigen (Anti-HBs)	**Marker of immunity .NOT CONTIGOUS.**

Hepatitis B virus

Acute hepatitis B infection;

Incubation period varies from 2 to 4 months.➢

Many HBV infection are asymptomatic.➢

If symptomatic hepatitis as:➢

An-icteric hepatitis: (no jaundice) fever, malaise ➢ , anorexia, rash, nausea, vomiting and high upper quadrant abdominal pain with raised liver enzyme.

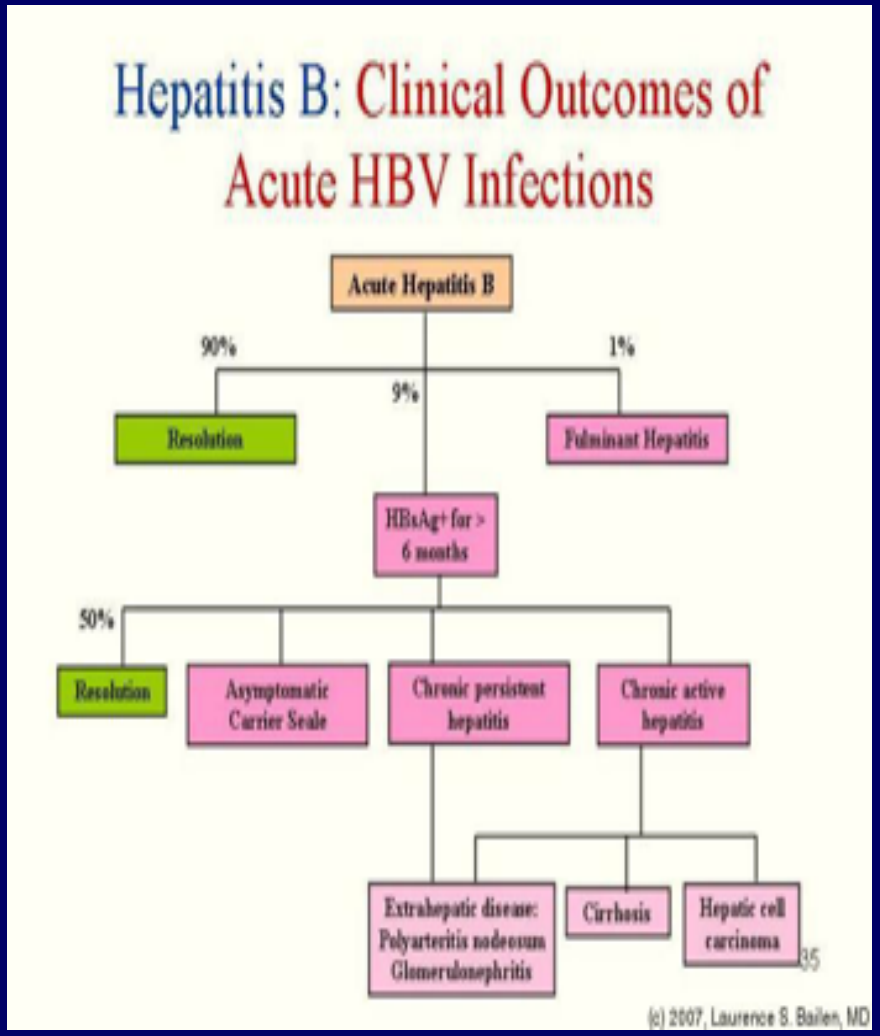
Icteric hepatitis: **(with jaundice)** about 25% of ➢ the patient become icteric Jaundice with raised bilirubin, dark bile containing urine and pale stools .

The clinical outcome of HBV infection

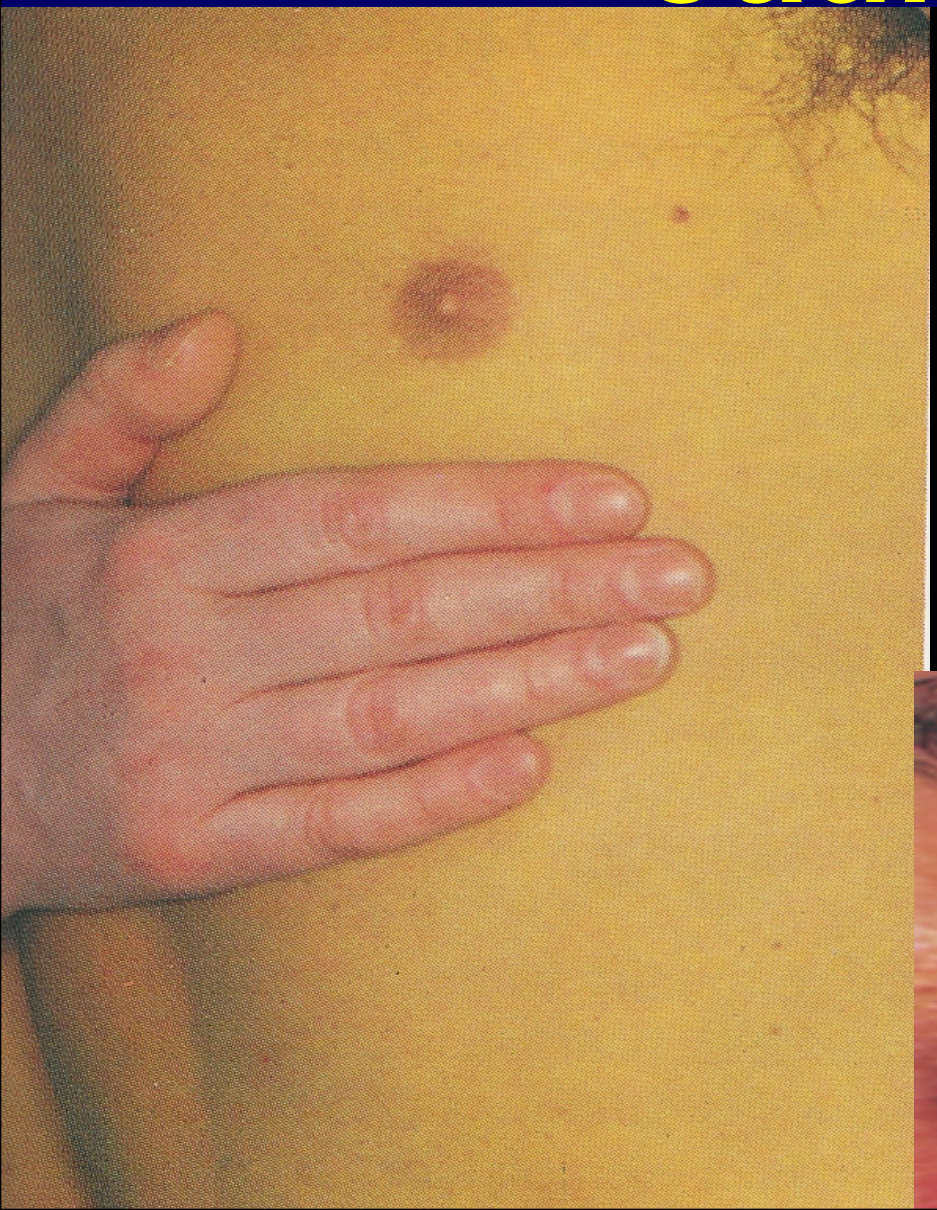
- **About 90 % of infected adults** will develop acute hepatitis B infection and **recover completely.**

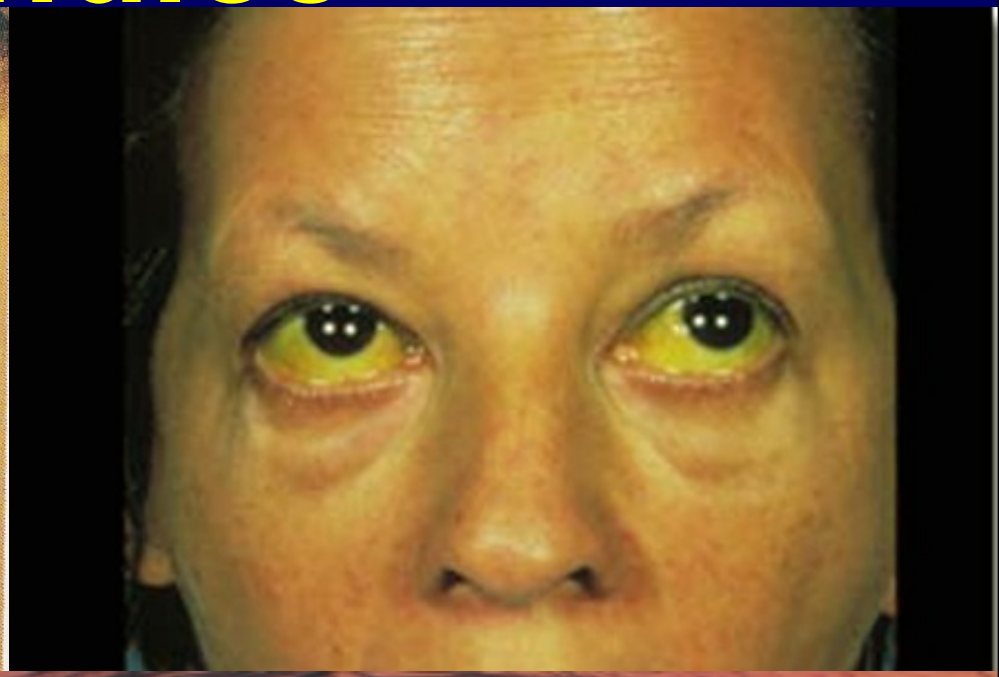
- **< 9 % of the infected adult 90% of infected infants** and **20% of infected children** may progress to chronic hepatitis B.

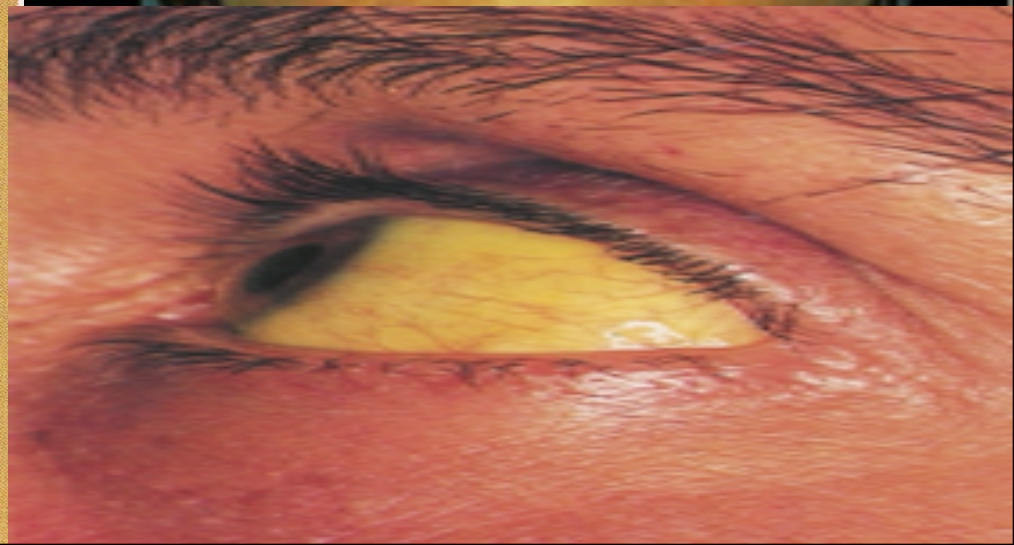
- < 1 % may develop fulminant hepatitis B, characterized by massive liver necrosis, liver failure and death.



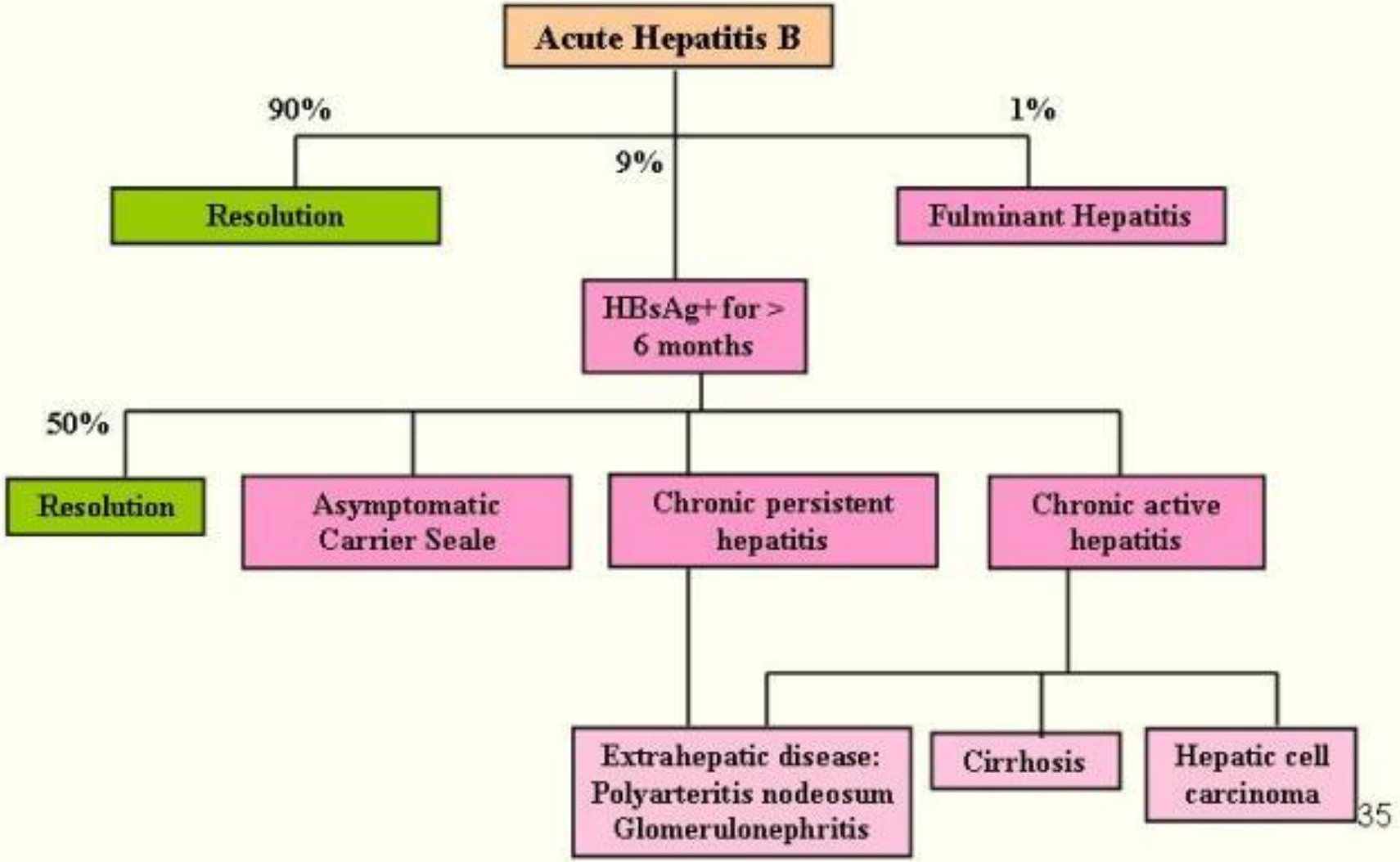
Jaundice







Hepatitis B: Clinical Outcomes of Acute HBV Infections

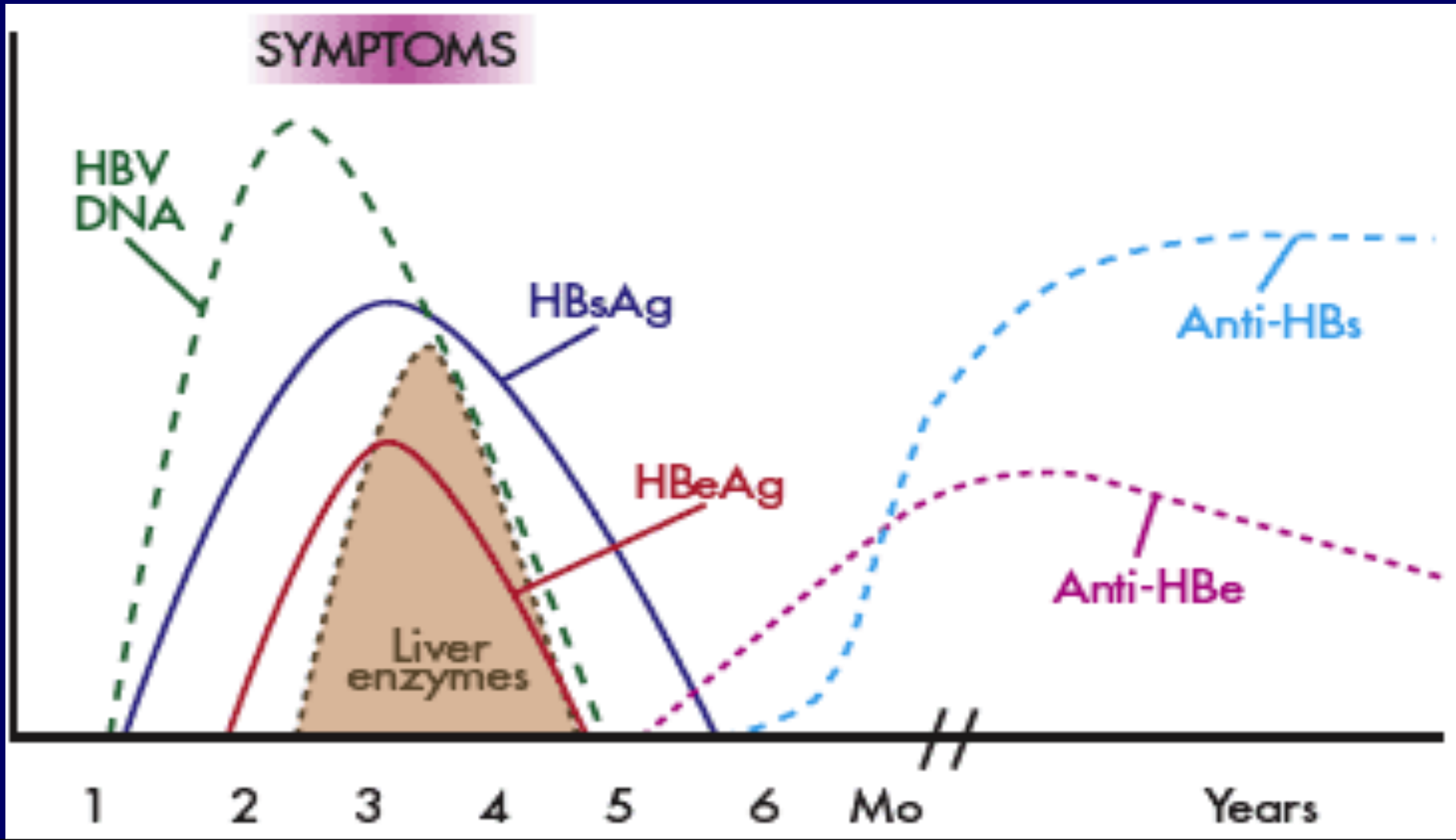


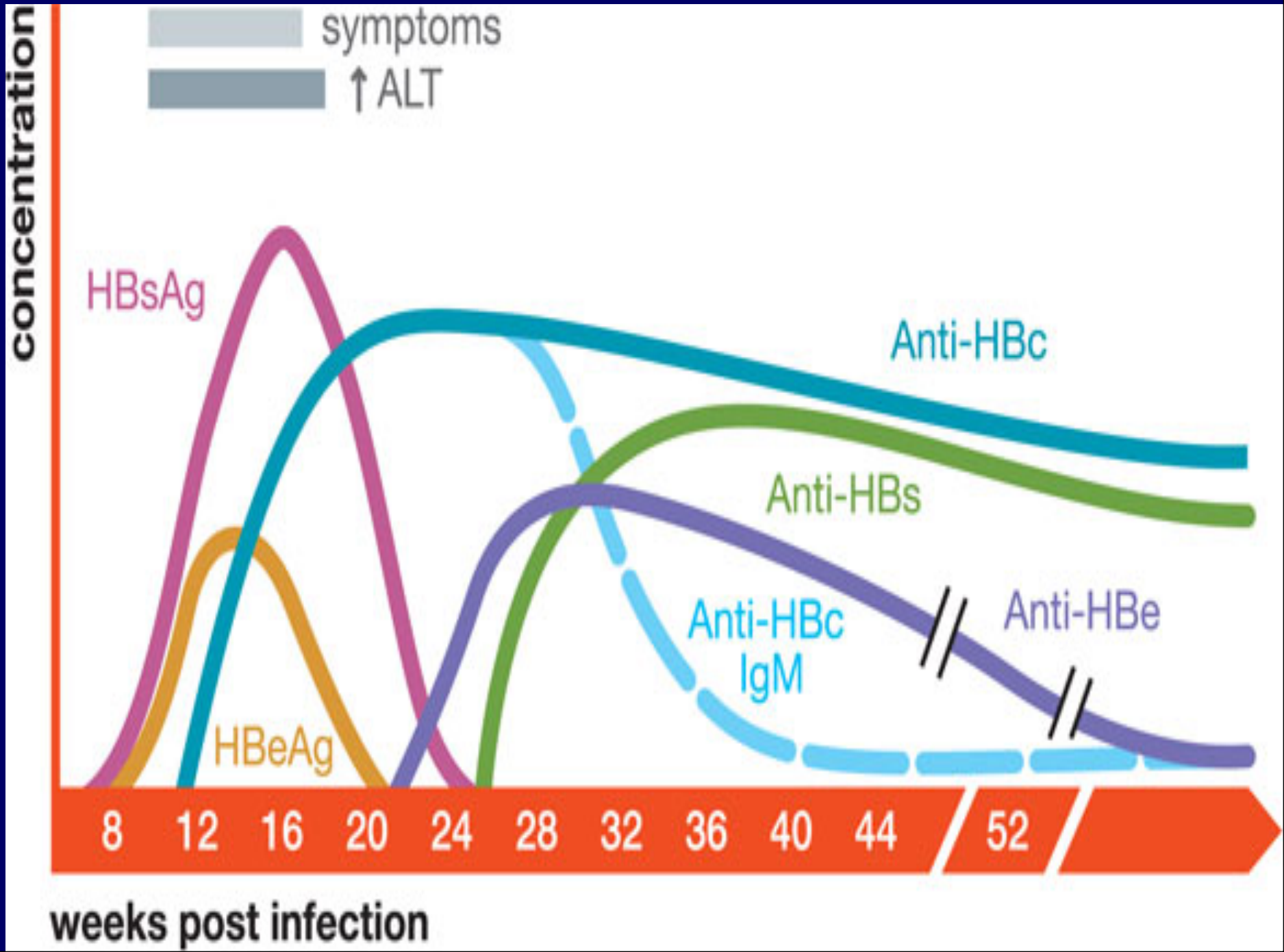
Serological profile of acute HBV infection

- Hepatitis **B DNA** is the 1st marker that appears in circulation, 3-4 weeks after infection.
- **HBsAg** is the 2nd marker that appears in the blood and persists for < 6 months, then disappears.
- **HBeAg** is the 3rd maker that appears in circulation and disappears before HBsAg, it indicate active viral replication.
- **Anti-HBc Ab** is the 1st antibody that appears in the blood and usually persists for several years.
- with the disappearance of **HBeAg** and appearance of **anti-HBe Ab** whish usually persists for several weeks to several months.
- **Anti-HBs Ab** is the last marker that appears in the blood, It appears few weeks after disappearance of HBsAg and persists for several years,

It is the marker of immunity to hepatitis B infection.

Serological profile of acute HBV infection



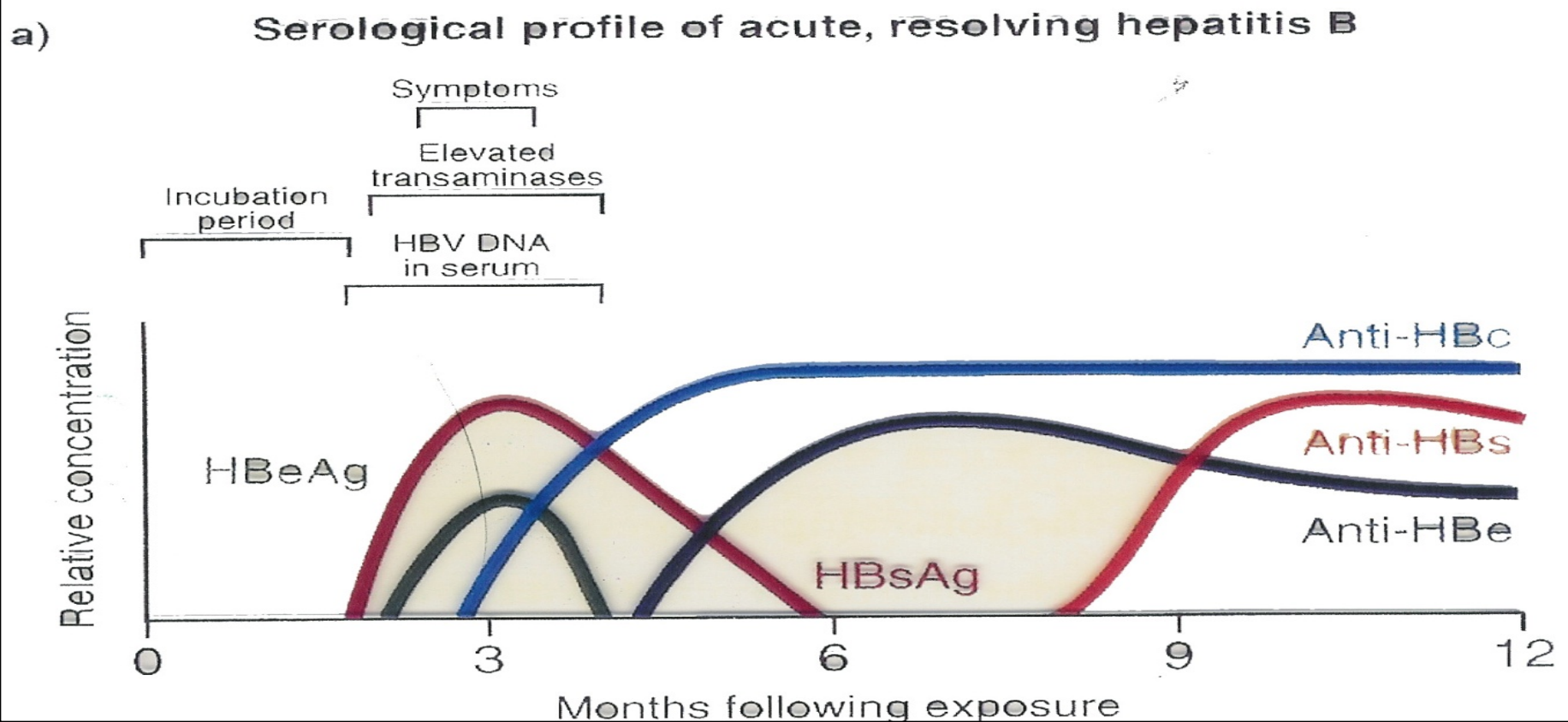

concentration
symptoms
↑ ALT
HBsAg
Anti-HBc
Anti-HBs
Anti-HBc IgM
Anti-HBe
HBeAg
8 12 16 20 24 28 32 36 40 44 52
weeks post infection

Important information

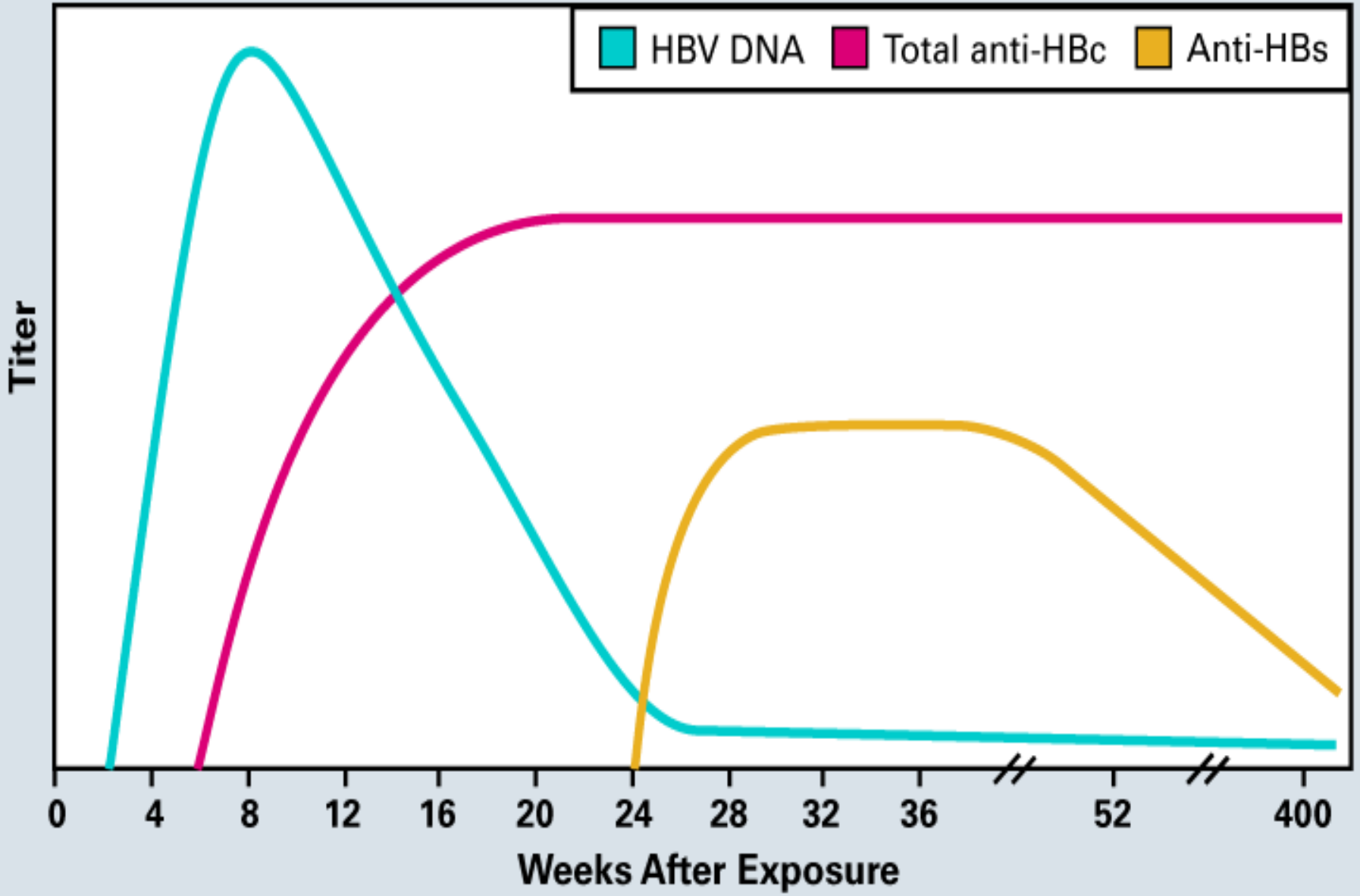
Notice here the **Anti –HB cAg IgM** is found before any ANTI BODIES either **Anti -HBsAg** or **Anti –HB eAg.**

This antibodies (Anti-HBcAg) indicate viral infection in the past if we detected in immune patient = having both(Anti –HB SAg + Anti-HBc Ag)

Vaccinated patients= having only Anti- HB sAg.



Resolved HBV Infection with Waning Anti-HBs



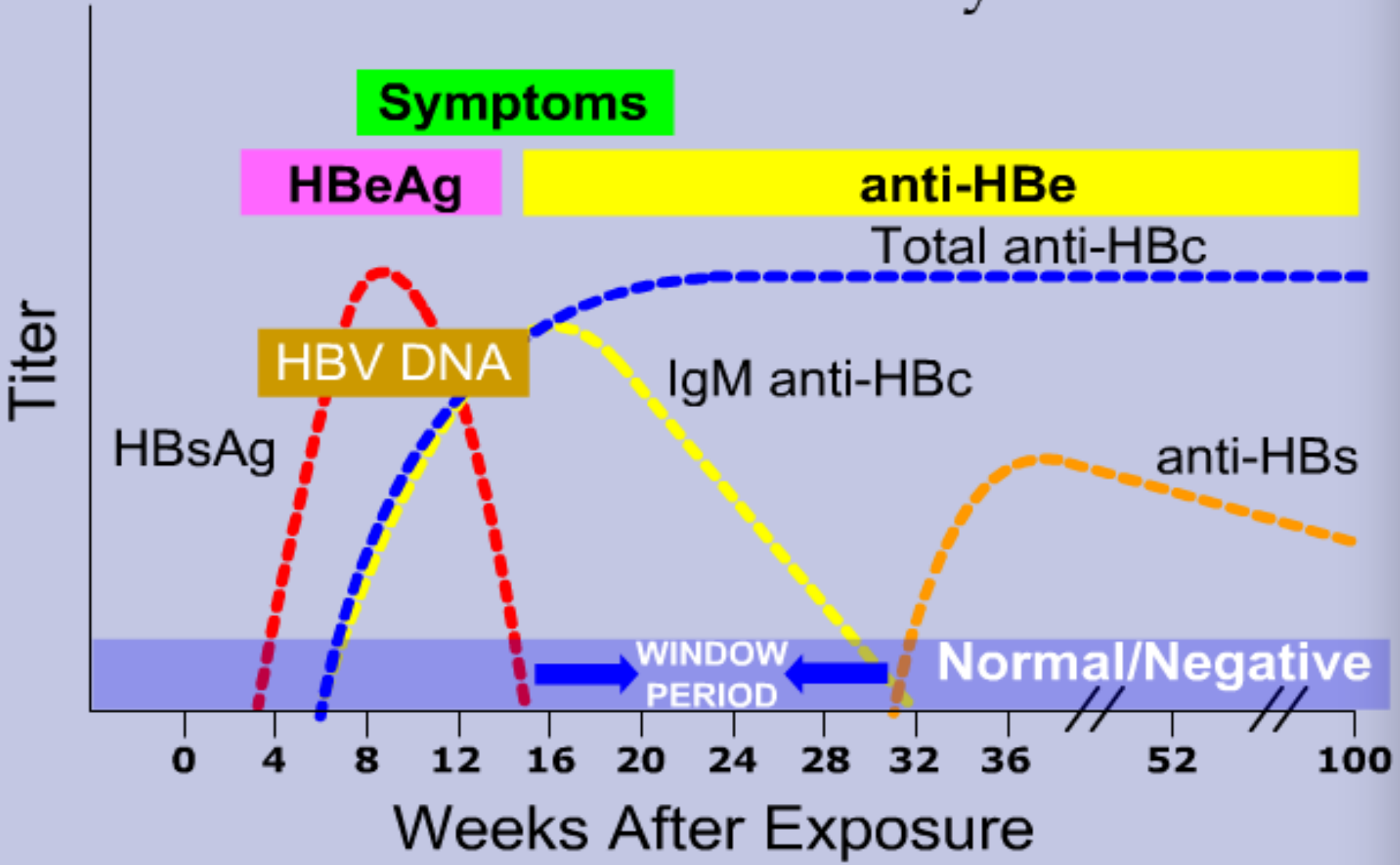
Chronic hepatitis infection

- Chronic hepatitis B means persistent detection of HBsAge and HB-DNA in the serum for more than 6 months.
- The majority of patients with chronic hepatitis B are asymptomatic or have mild fatigue only.
- Symptoms include right upper quadrant abdominal pain, enlarged liver & spleen. Jaundice may or may not developed, fatigue.

Chronic asymptomatic hepatitis B infection

- **Chronic hepatitis B** is defined by the presence of HBsAg or HBV-DNA in the blood for more than> 6 months.
- The majority of patients with chronic hepatitis B are **asymptomatic** may only be detected by elevated liver enzyme on a routine blood chemistry profile , some have mild fatigue, RT upper quadrant abdominal pain or enlarged liver &spleen

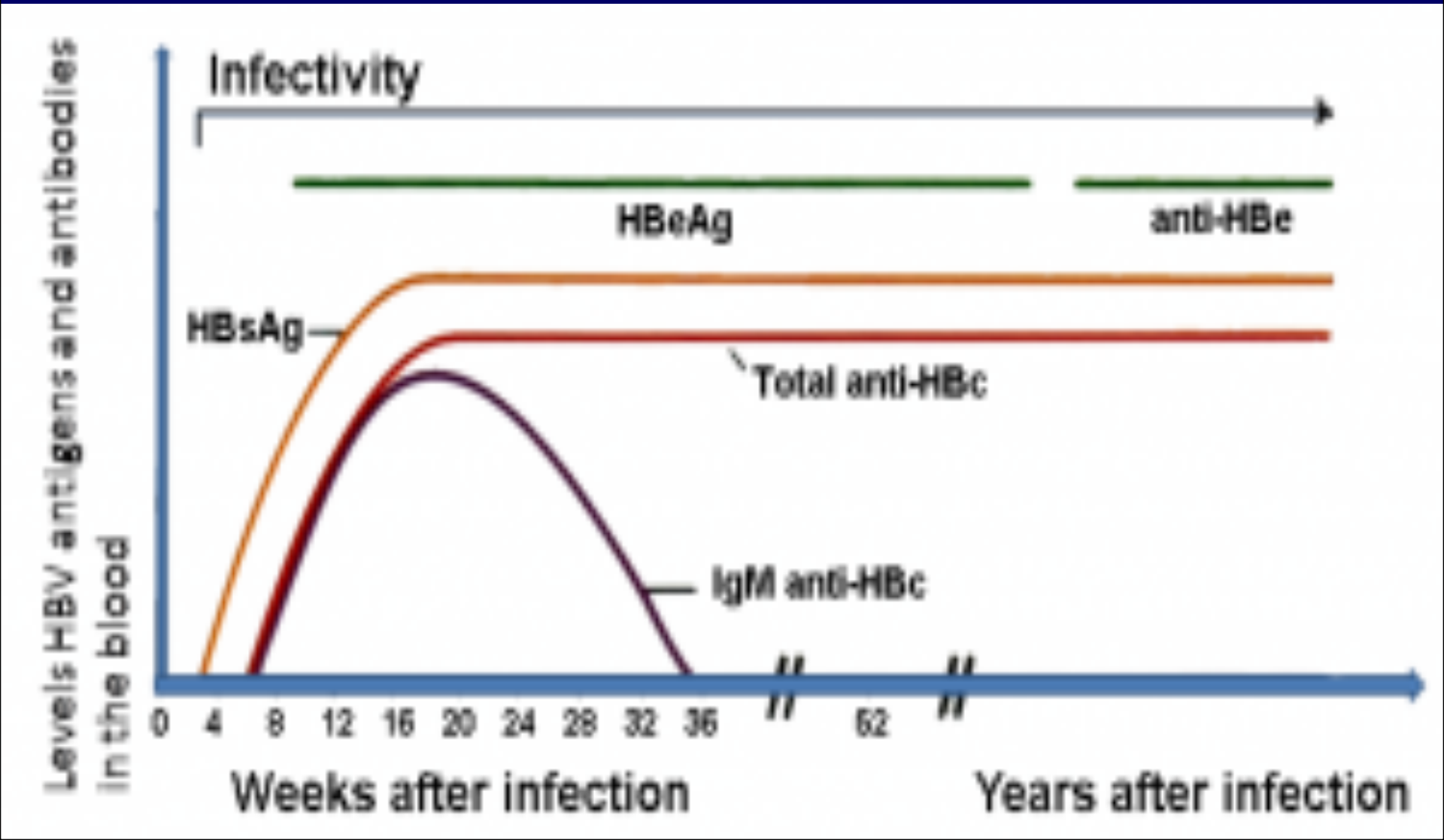
Acute Hepatitis B Virus Infection with Recovery

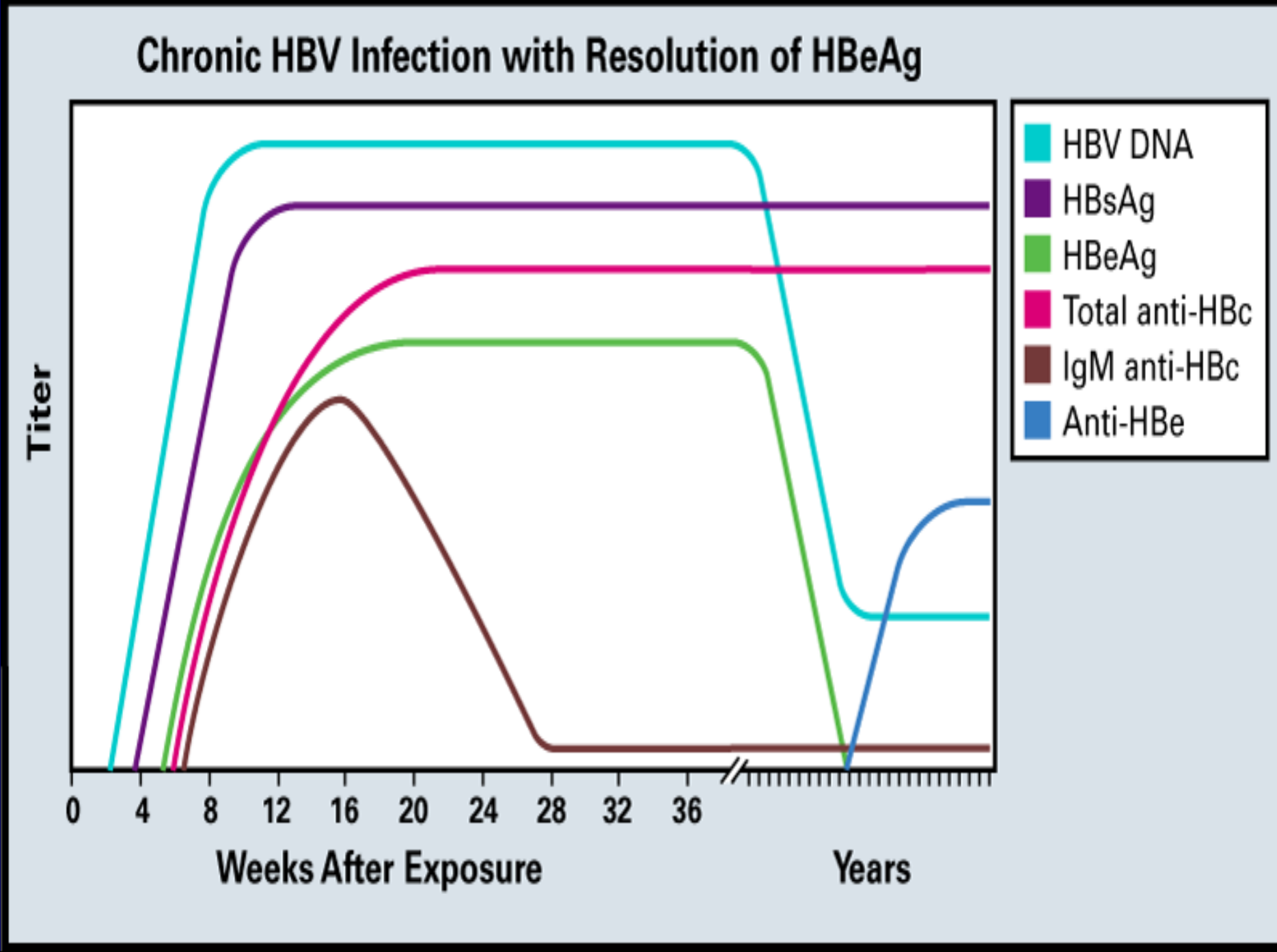


Serological profile of chronic HBV infection

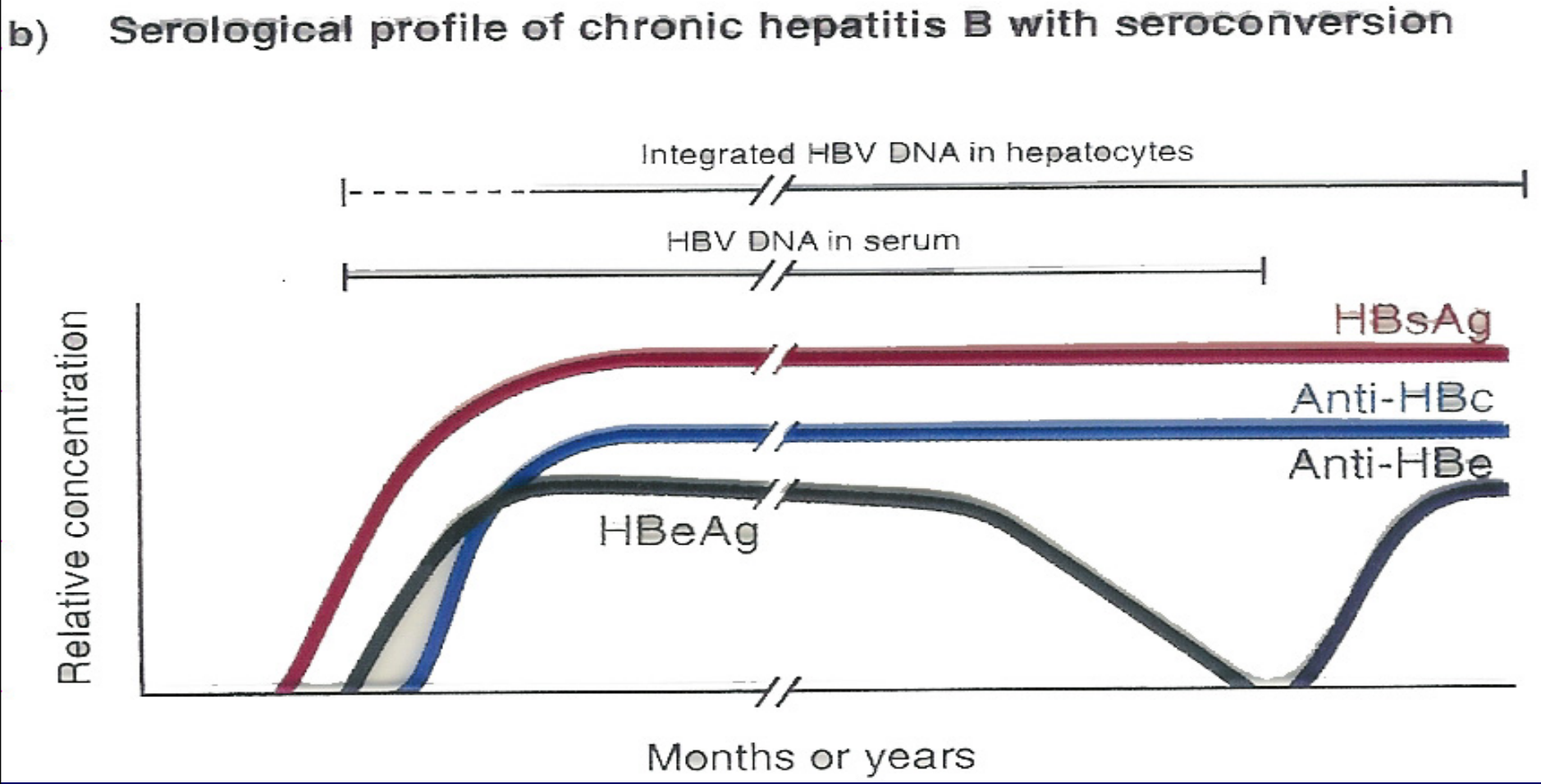
- Chronic hepatitis B infection is defined by the presence of HBV-DNA and HBsAg in the blood for > 6 months.
- **HBsAg** may persist in the blood for life OR
- Some patients will become immune after years and the **HBsAg** disappeared and **anti-HBs Ab** detected in the serum and persists for life.

Serological profile of chronic HBV infection




Chronic HBV Infection with Resolution of HBeAg
Titer
HBV DNA
HBsAg
HBeAg
Total anti-HBc
IgM anti-HBc
Anti-HBe
0
4
8
12
16
20
24
28
32
36
Weeks After Exposure
Years

Notice the Anti- HB cAg founded in the chronic HBV infected patient

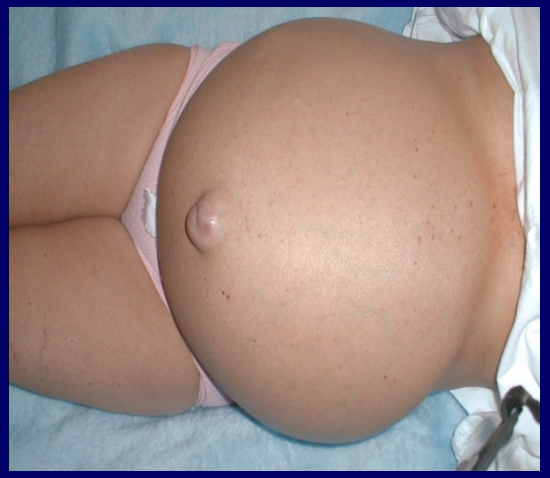


Chronic active hepatitis

- The major long term risk of chronic HBV infection are cirrhosis with hepatic failure and hepatocellular carcinoma ,when HBV genome integrates into hepatocytes DNA.

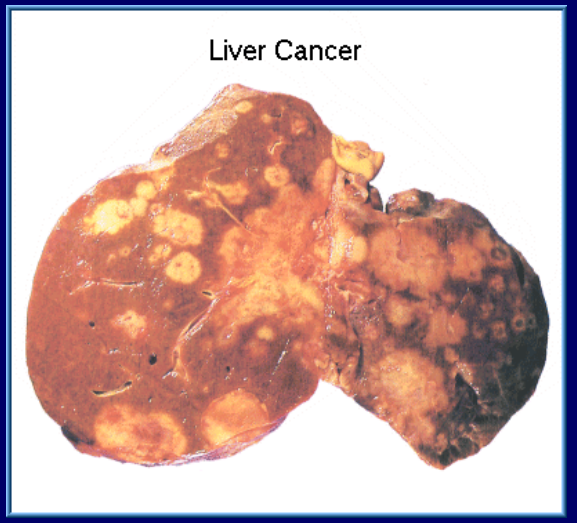
Cirrhosis

- Characterized by fibrosis and nodular formation.
- Results from liver cell necrosis and the collapse of hepatic lobules.
- Symptoms includes: ascites, coagulopathy (bleeding disorder), portal hypertension, hepatic encephalopathy, vomiting blood, weakness, weight loss.



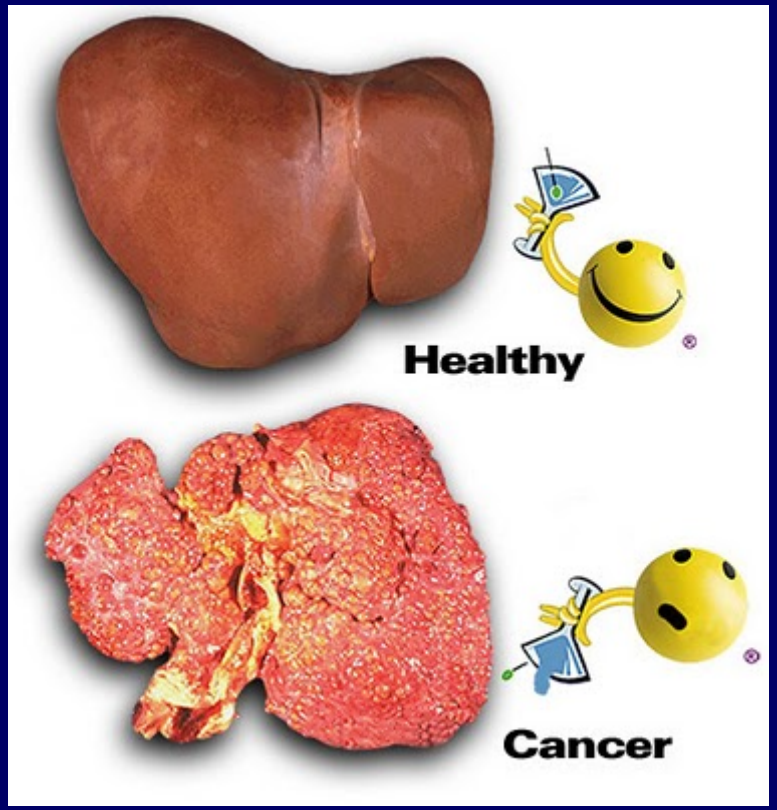
Hepatocellular carcinoma (HCC)

- One of the most common cancer in the world. Also, one of the most deadly cancer if not treated.
- Hepatitis B and C viruses are the leading cause of chronic liver diseases.
- Symptoms include: abdominal pain, abdominal swelling, weight loss, anorexia, vomiting, jaundice.
- Physical examination reveals hepatomegaly, splenomegaly and ascites.



Hepatocellular carcinoma

- Prognosis: without liver transplantation, the prognosis is poor and one year survival is rare.
- Diagnosis: alpha-fetoprotein measurement with multiple CT-abdominal scan are the most sensitive method for diagnosis of HCC.
- Treatment: surgical resection and liver transplant.



Lab diagnosis of hepatitis B infection

- Hepatitis B infection is diagnosed by detection of HBsAg in the blood.

➢ **Positive results must be repeated in duplicate.**

➢ Repeatedly reactive results must be confirmed by **neutralization test**.

➢ Detection of HB-DNA by PCR.

- Additional lab investigations:

1- Liver function tests (LFT).

2- Ultrasound of the liver.

3- Liver biopsy to determine the severity of the diseases.

Hepatitis B vaccine

- **It contains highly purified preparation of HBsAg particles , produced by genetic engineering in yeast.**
- **It is not live attenuated nor killed vaccine**
- The vaccine is administered in three doses
- **IM injection at 0 &1 & 6 months**
- **Booster doses may be reacquired after 3-5 years.**
- **It is safe and give excellent protection**

Hepatitis B virus

Prevention and Control:

Pre-exposure prophylaxis:

Active vaccination given to all newborn, children or adult.

Recombinant hepatitis B vaccine:

It is prepared by cloning HBsAg in yeast cells. The vaccine is given in 3 IM injection at 0-1-6 months and booster dose after 5 years.

Post exposure prophylaxis:

Persons exposed to needle prick or infant born to +ve HBsAg mother should immediately receive both:

Active vaccine and hepatitis B specific immunoglobulin.

Treatment of hepatitis B infection

- There are several approved antiviral drugs:

1- **Pegylated alpha interferon**, one injection per week, for 6- 12 months.

2- **Lamivudine**, antiviral drug, nucleoside analogue. One tablet a day for at least one year.

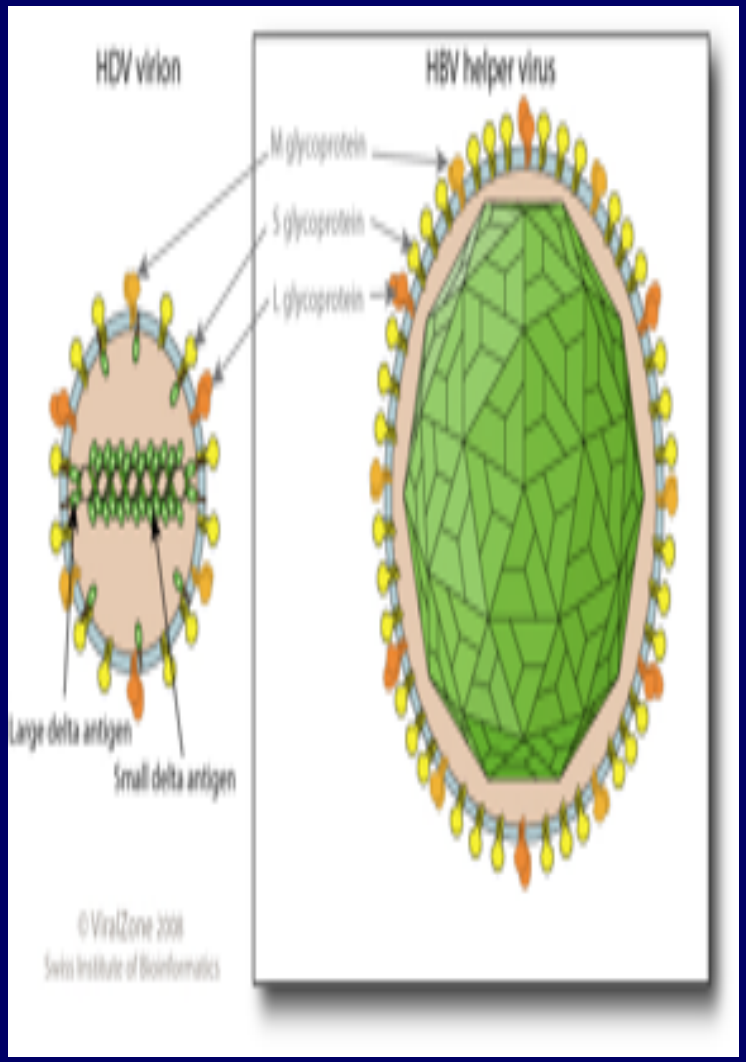
3- **Adefovir**, antiviral drug, nucleoside analogue. One tablet a day for at least one year.

- Treatment is limited to patients having chronic hepatitis B based on liver biopsy.

- Criteria for treatment:
- Positive for HBsAg
- Positive for HBV-DNA > 20,000 IU/ml.
- ALT > twice the upper normal limit .
- Moderate liver damage.
- Age > 18 years.

Hepatitis D virus (delta virus): Structure

- It is a defective virus, that cannot replicates by its own.
- It requires a helper virus.
- The helper virus is HBV.
- HBV provides the free HBsAg particles to be used as an envelope.
- HDV is small 30-40 nm in diameter.
- Composed of small ss-RNA genome, surrounded by delta antigen that form the nucleocapsid.



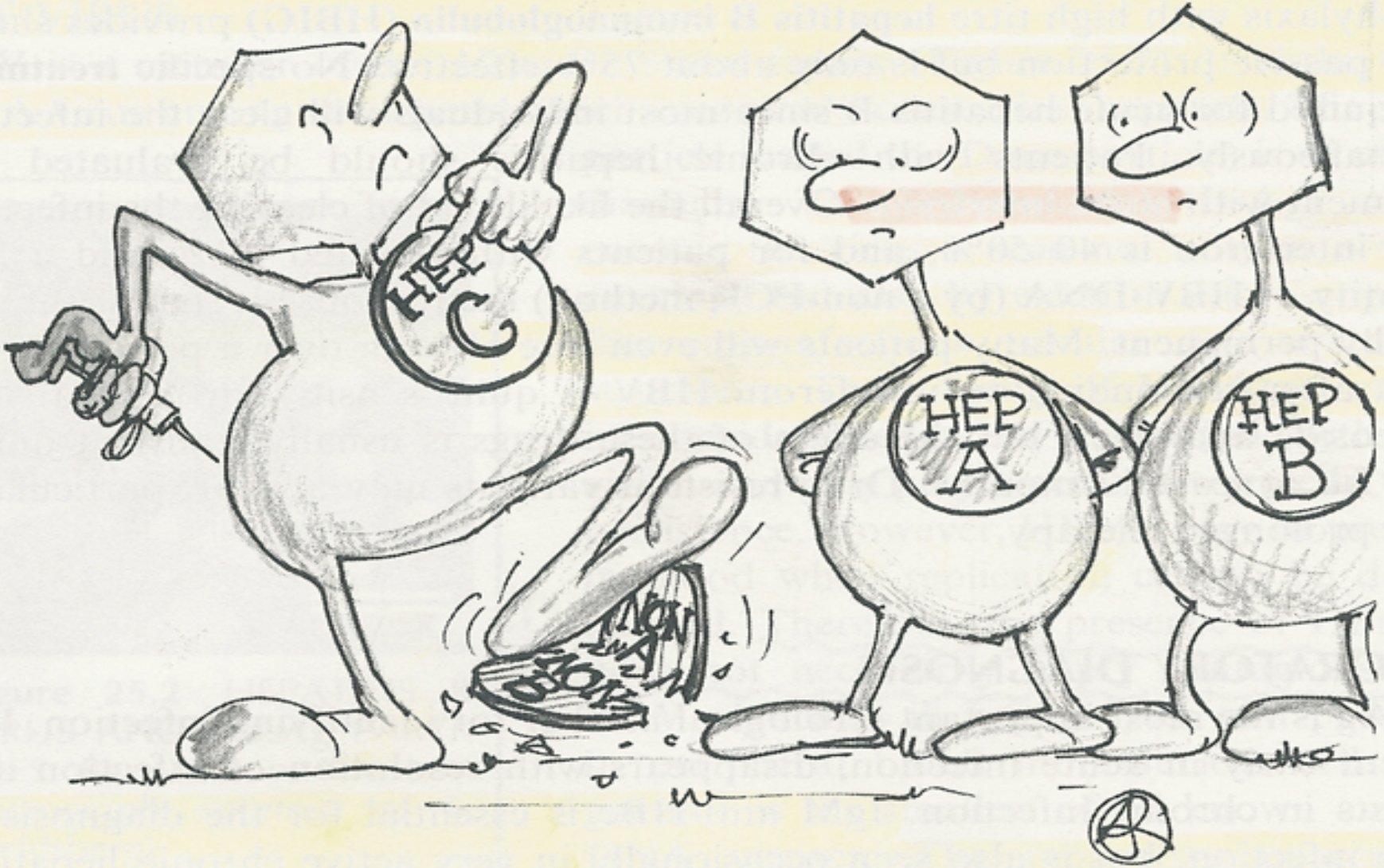
Types of HDV infections

➢ *1- Co-infection:*

- ❖ The patient is infected with HBV and HDV at the same time leading to severe acute hepatitis .
- ❖ Prognosis: recovery is usual.

➢ *2- Super infection:*

- ❖ In this case, delta virus infects those who are already have chronic hepatitis B leading to severe chronic hepatitis.



FINALLY NAMED, SEE?!

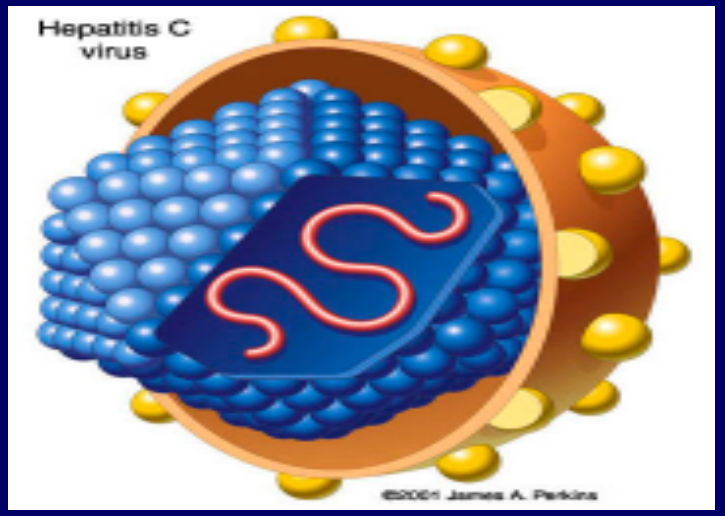
Hepatitis C virus: Classification & structure

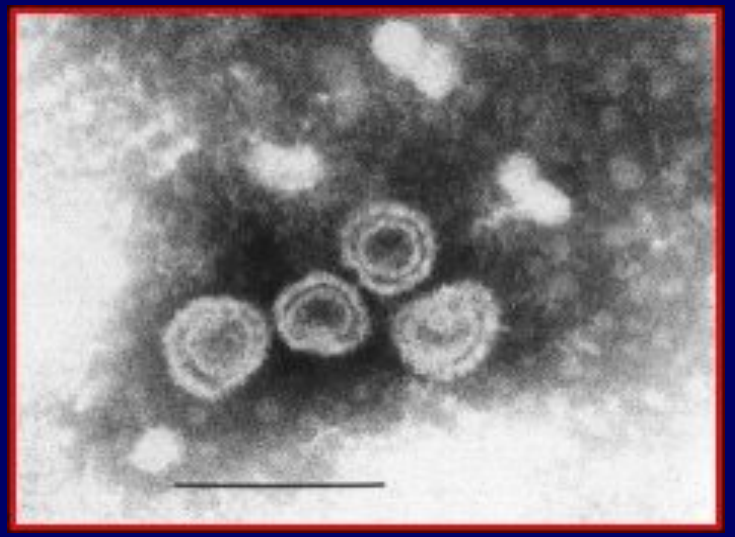
- Family: *Flaviviridae.*
- Genus: *hepacivirus.*

- The virus is small, 60 – 80 nm in diameter.

- Consists of an outer envelope, icosahedral core and linear positive polarity ss-RNA gemone.

- There are 6 major genotypes (1 – 6), genotype 4 is the dominant in Saudi patients.





Transmission of HCV

Similar to HBV:

1- Parenterally:

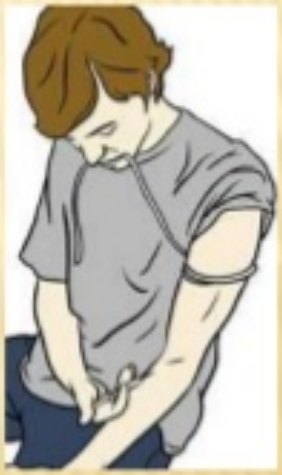
- Direct exposure to infected blood.
- Using contaminate needles, surgical instruments.
- Using contaminate instruments in the practice of tattooing, ear piercing & cupping.
- Sharing contaminated razors 7 tooth brushes.

2- Sexually.

3- From mother to child perinatally.

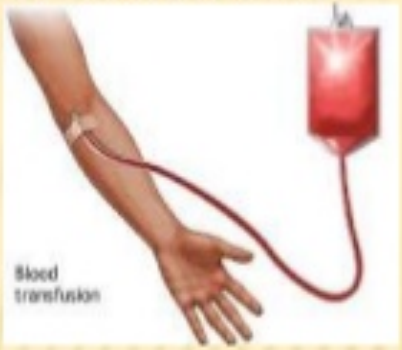
ROUTES OF TRANSMISSION

1) Intravenous drug use:
sharing of needles and syringes
Reuse of contaminated needles



2) Sexual transmission

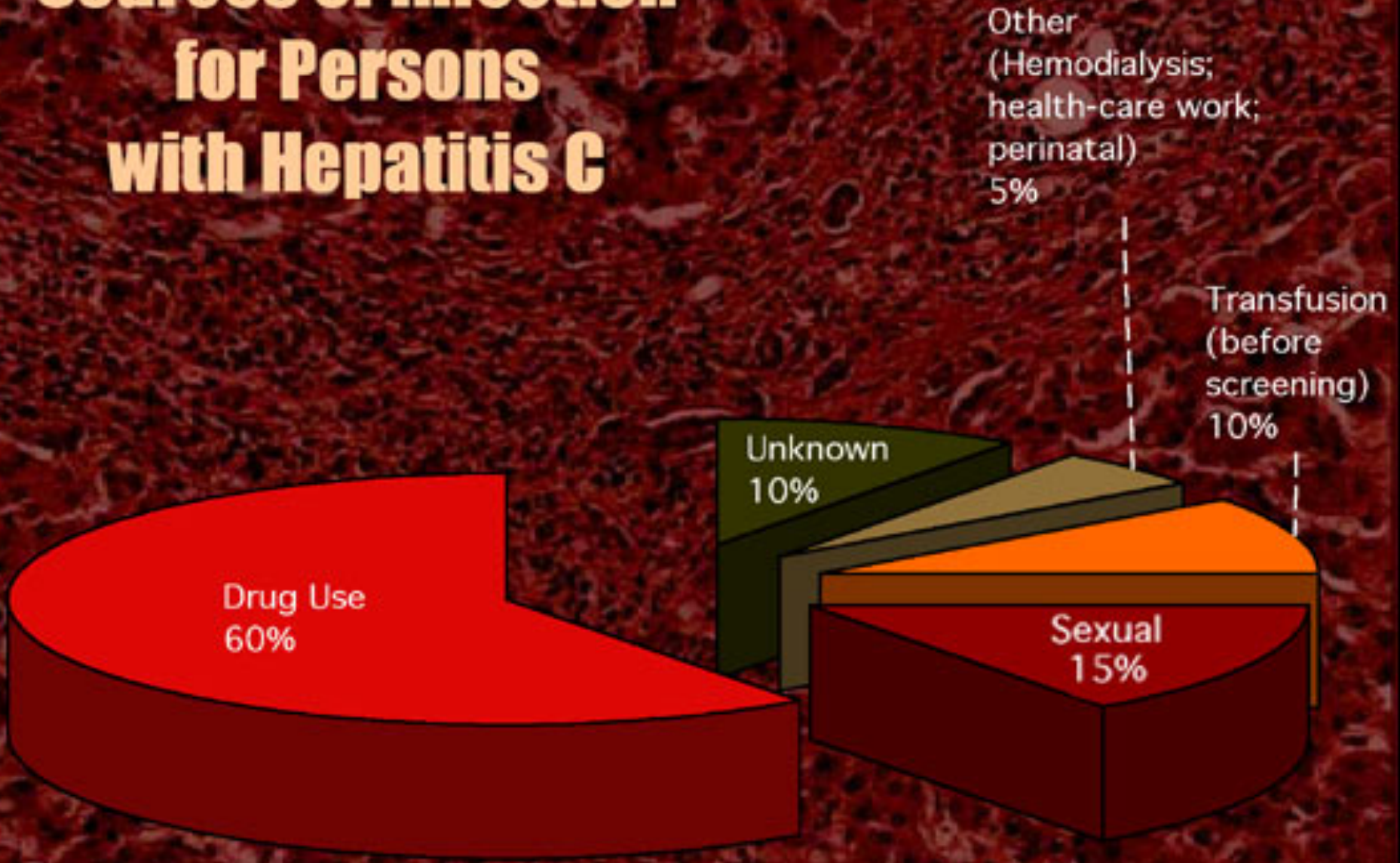
3) Blood transfusion



5) Needlestick injury

4) Vertical transmission

Sources of Infection for Persons with Hepatitis C



The following groups are at high risk of acquiring hepatitis C

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors.
- Individuals with multiple sexual partners.
- Recipient of blood transfusion ,
- Health care workers with frequent blood contact.
- Individuals exposed to risk factors such as tattooing, body piercing and cupping.

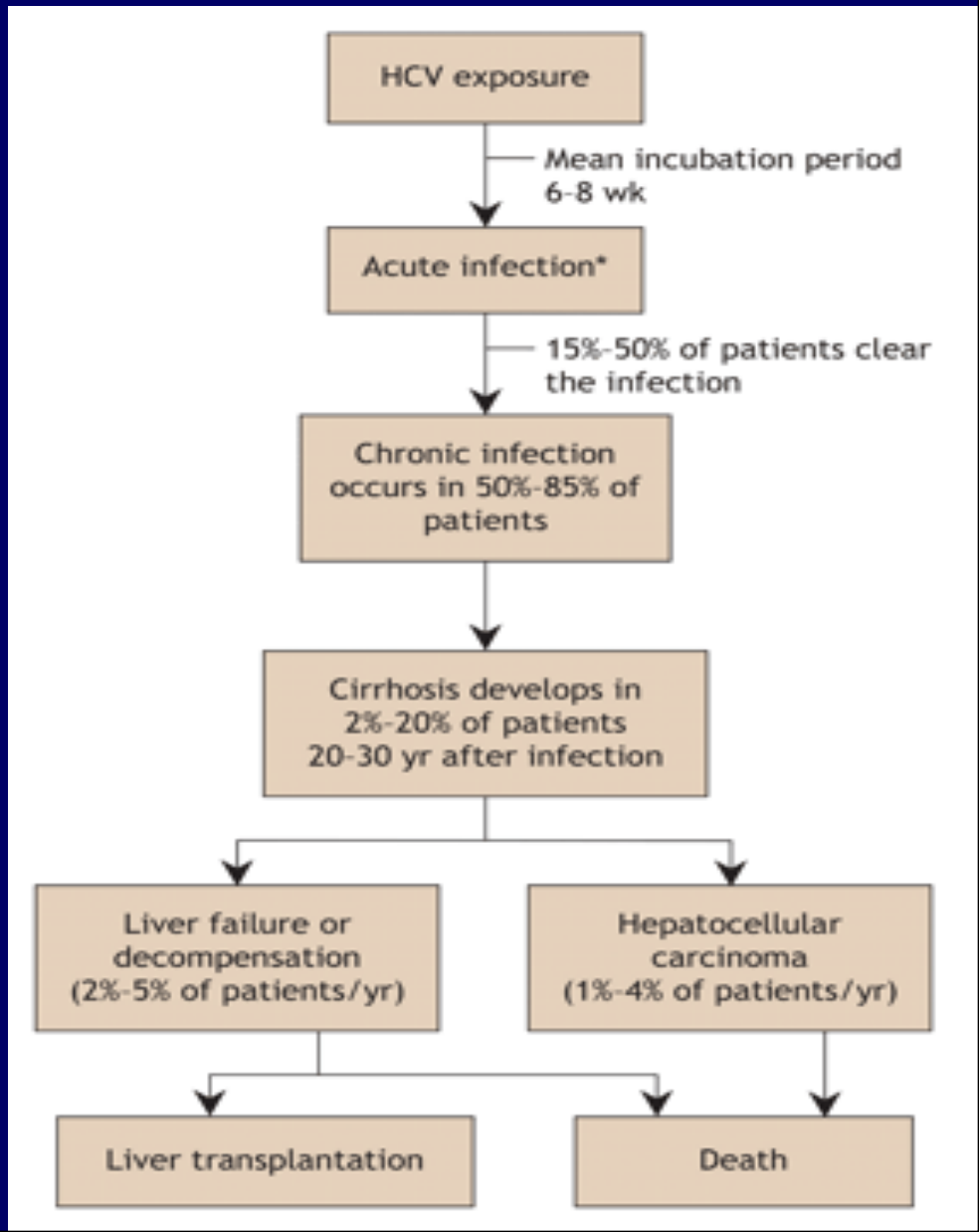
The clinical picture of HCV

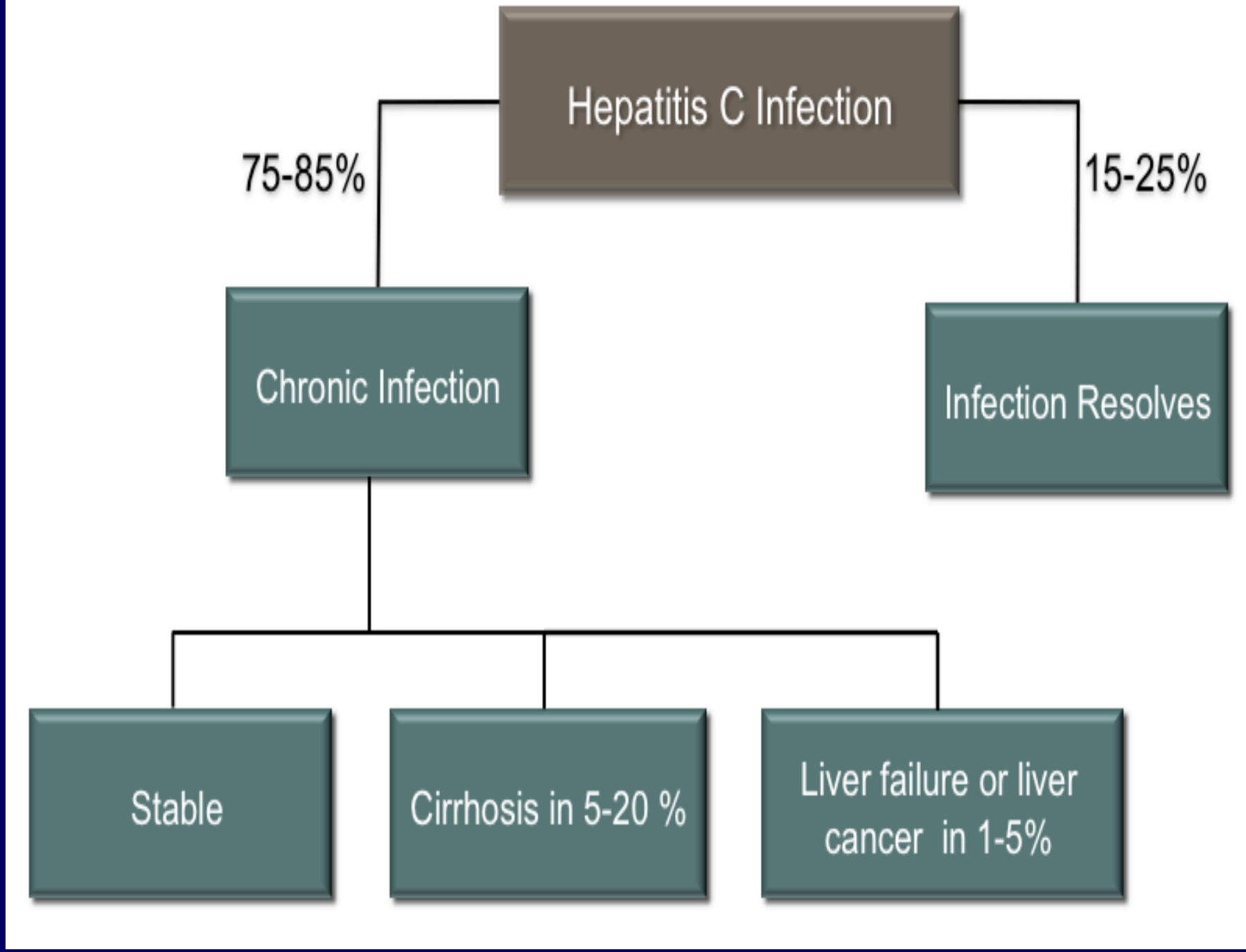
- Incubation period from 2 to 7 weeks.
- Clinically ,the acute infection with HCV is milder than infection with HBV.
- Fever ,anorexia, nausea, vomiting , and jaundice are common.
- Dark urine ,pale feces , and elevated liver enzyme (transaminase) are seen.

The clinical outcome of HCV infection

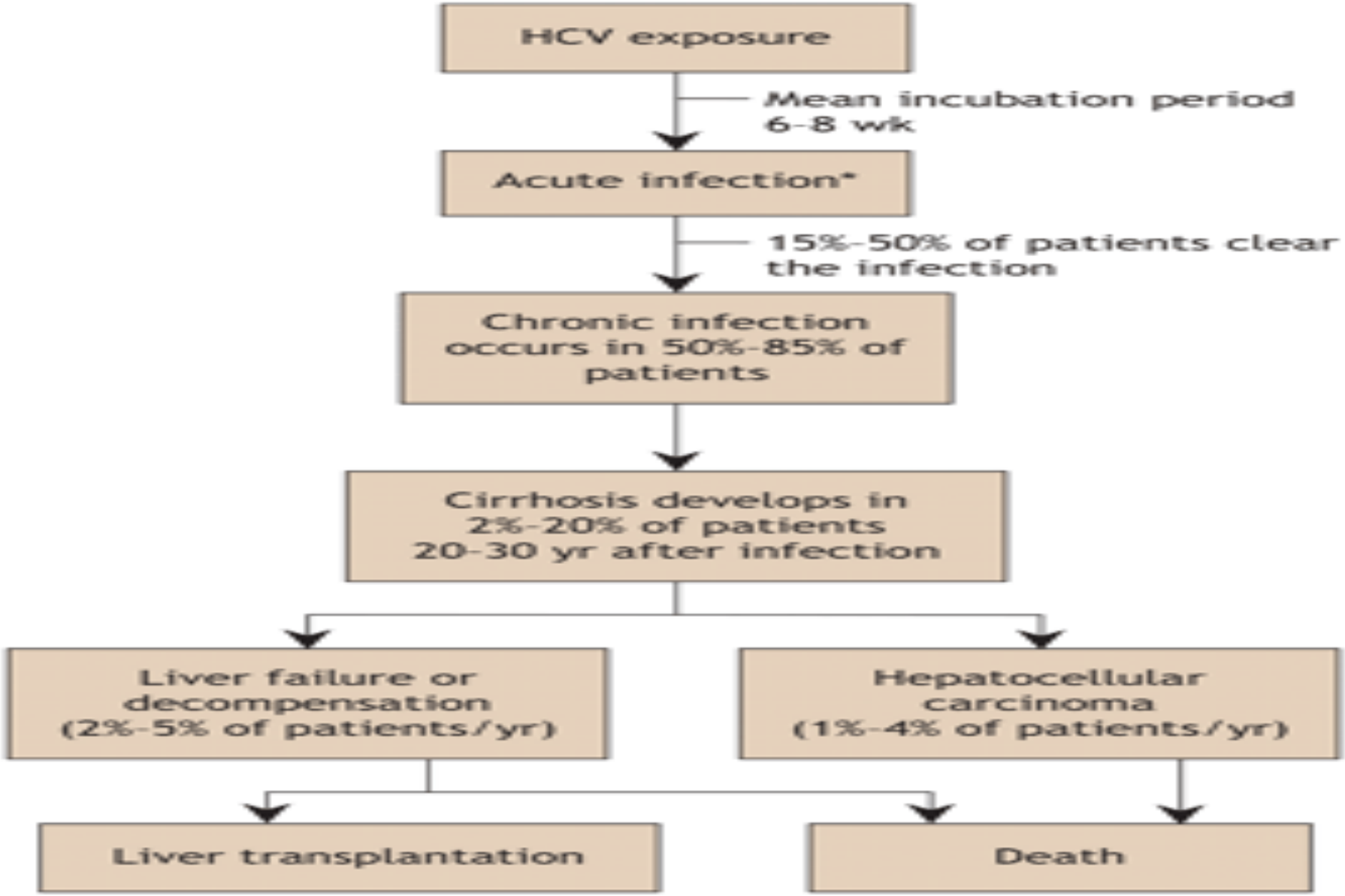
- **About 20 % of the infected individuals will develop self-limiting acute hepatitis C and recover completely.**

- **About 80 % of the infected will progress to chronic hepatitis C.** *about 10%-30% of them can develop cirrhosis within 30 years and liver cancer.* Less than 1 % will develop acute fulminant hepatitis C , liver failure and death.




Hepatitis C Infection
75-85%
15-25%
Chronic Infection
Infection Resolves
Stable
Cirrhosis in 5-20 %
Liver failure or liver cancer in 1-5%

Out come of HCV

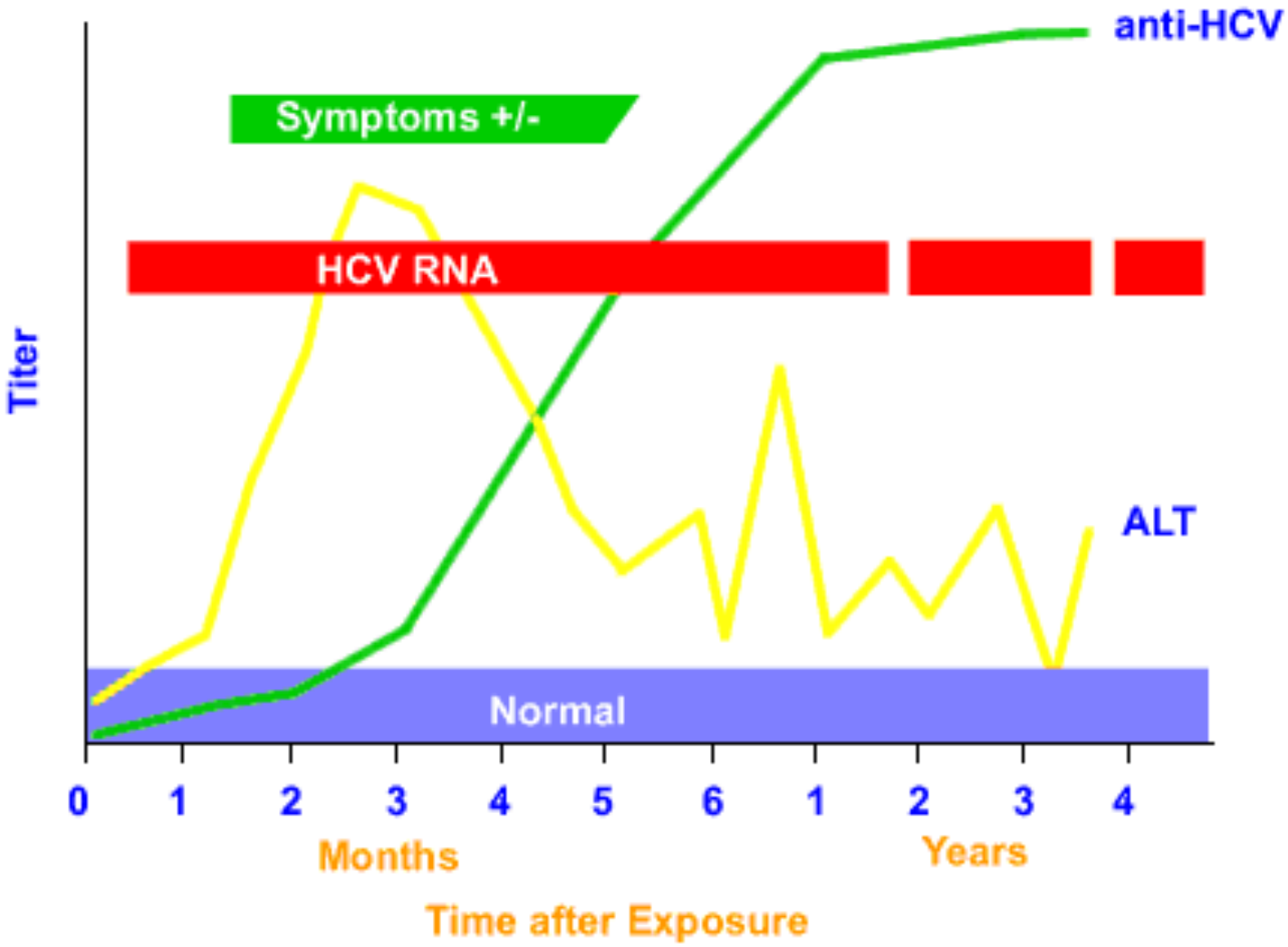


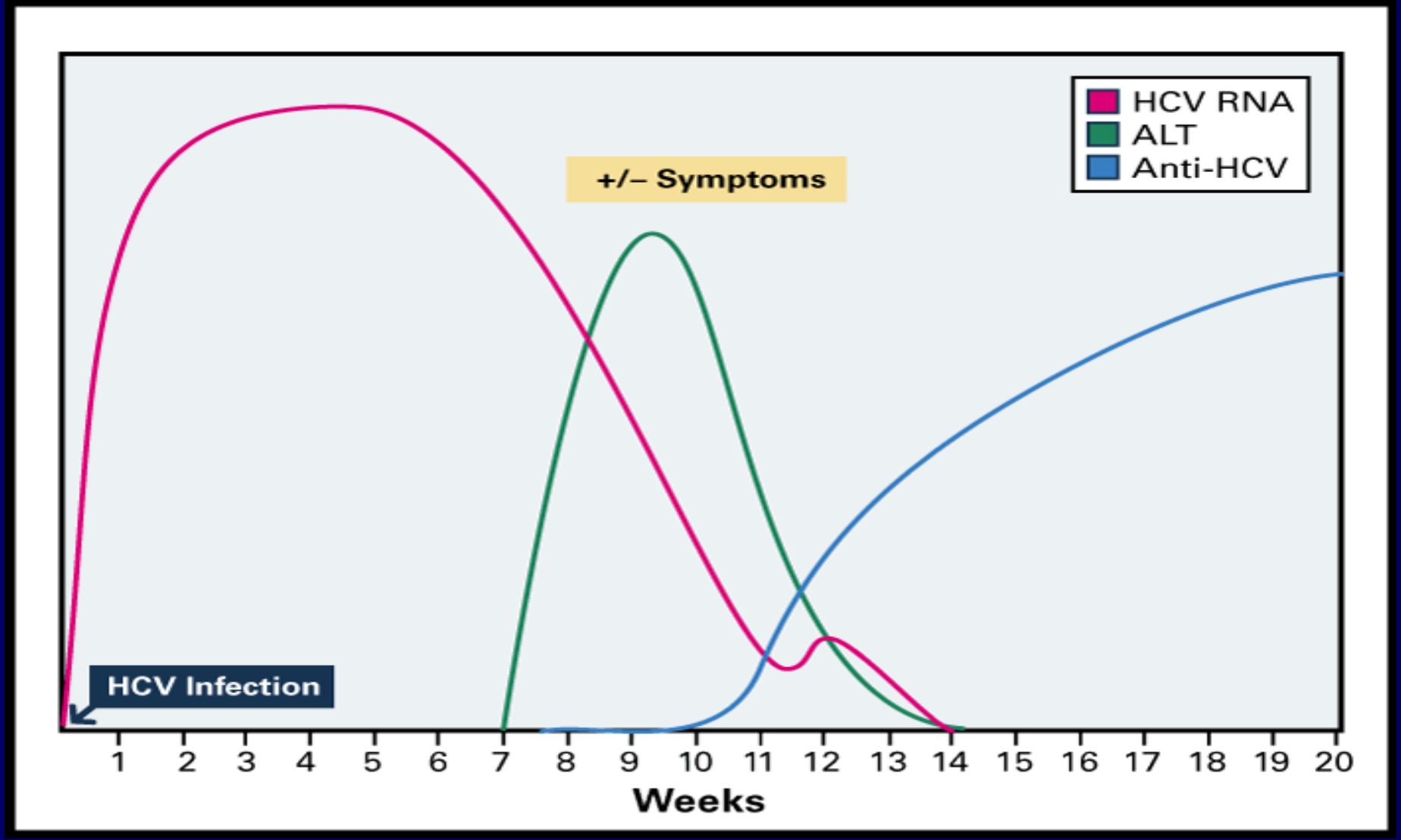
Hepatitis C markers

- ***1- hepatitis C virus RNA.***
  - Is the 1st marker that appears in circulation, it appears as early as 2-3 weeks after exposure. It is a *marker of infection.*
- .

- ***2- HC Ab antibody to hepatitis C.***
  - **Antibodies to hepatitis C virus is the second marker that appears in the blood, usually appear 50 days after exposure (long window period), it is not marker of immunity, can be detected in completely recovered patient and chronic and acute.**

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection





Serological pattern of acute Hepatitis C infection not progress to chronic and patient become cured(infection resolved).

ACUTE HEPATITIS

- Symptom: jaundice, fatigue & nausea.
- Elevated serum ALT (usually greater than 10 folds).
- Presence of anti-HCV (-ve in 30-40%) in early stages of disease.
- HCV-RNA is +ve even before the onset of symptoms.

CHRONIC HEPATITS

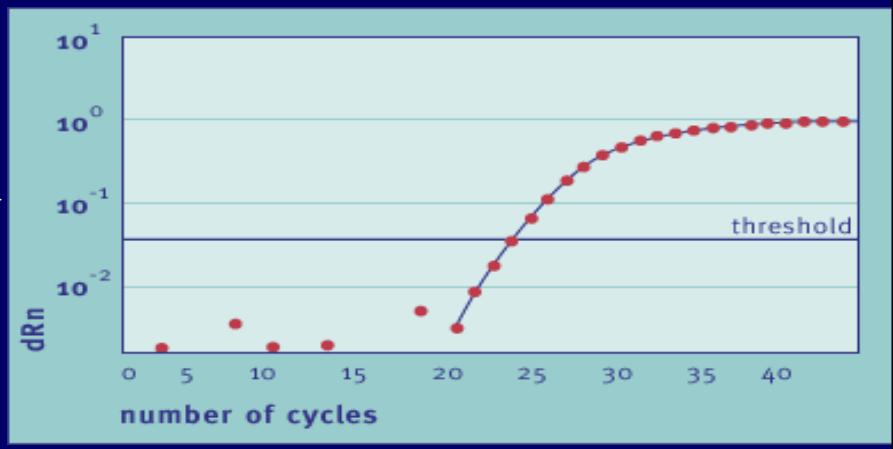
- Defined as the presence of anti-HCV & elevated serum level of ALT for >6 ms.
- Almost all patients with chronic hepatitis C have the genome HC RNA in serum.
- Usually asymptomatic, but if symptom present it's usually mild, non-specific & intermittent.
- Lab finding:
  - Elevated ALT & AST ranging from 3-20 times
  - ALT >AST.

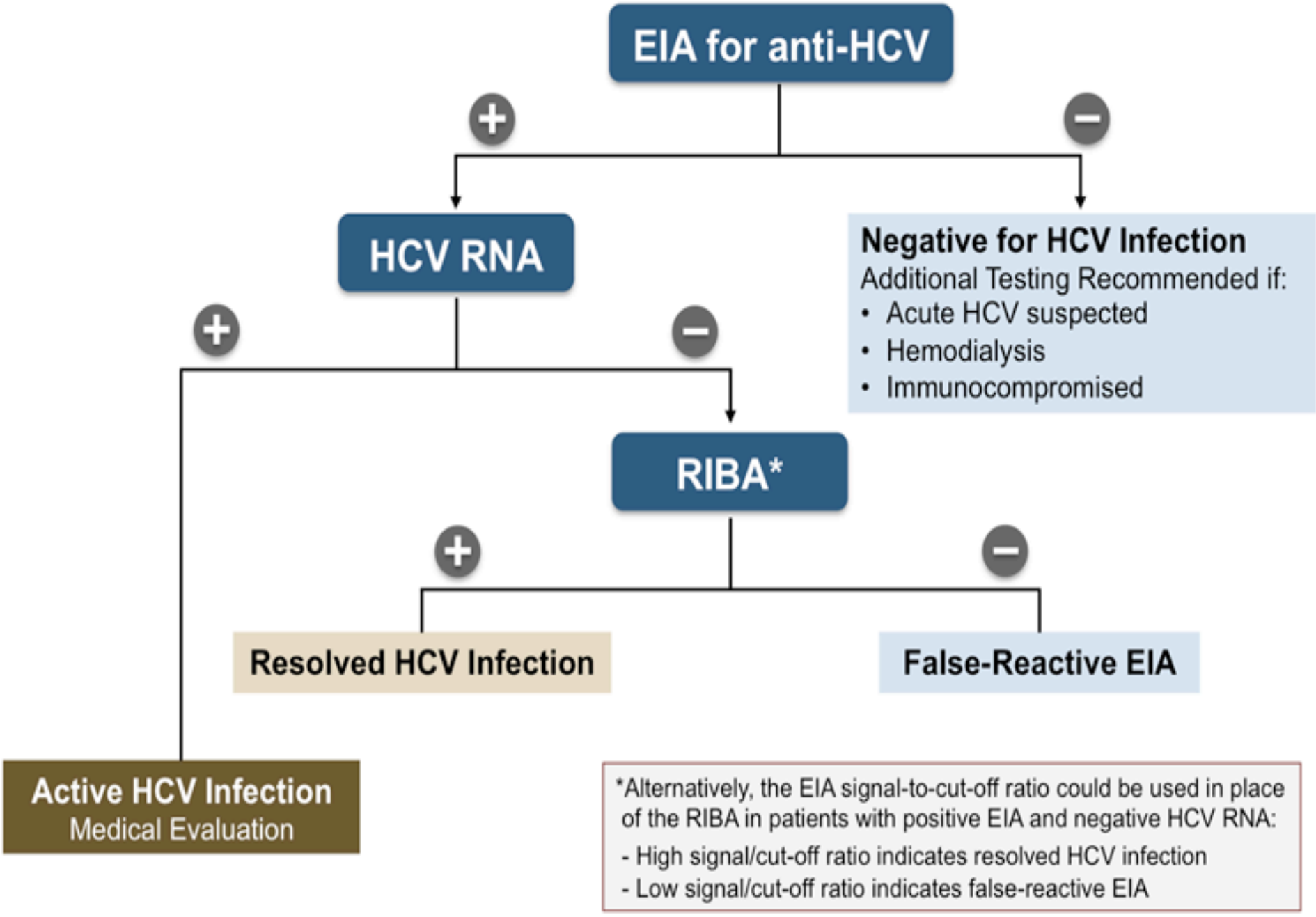
Lab diagnosis of hepatitis C infection

- **By detection of both:**

1- **Antibody to HCV in the blood by ELISA, if positive the result must be confirmed by RIBA or PCR.**

2- HCV-RNA in the blood using PCR.




EIA for anti-HCV
+
−
HCV RNA
Negative for HCV Infection
Additional Testing Recommended if:
• Acute HCV suspected
• Hemodialysis
• Immunocompromised
+
−
RIBA*
+
−
Resolved HCV Infection
False-Reactive EIA
Active HCV Infection
Medical Evaluation
*Alternatively, the EIA signal-to-cut-off ratio could be used in place of the RIBA in patients with positive EIA and negative HCV RNA:
- High signal/cut-off ratio indicates resolved HCV infection
- Low signal/cut-off ratio indicates false-reactive EIA

MOLECULAR

Qualitative Assay: ➢

- It's the most specific test for indicating ongoing infection & almost +ve in chronic hepatitis.
- it's usually –ve after recovery & effective treatment.
- It's the best method for diagnosis of early sages of acute hepatitis & HCV in immunocompromise patient.
- PCR & TMA(transcription mediated amplification) can detect low level of virus (50-100 copies/ml # 25-50 IU).

MOLECULAR CONT,

Quantitative Assay: ➢

- It gives indirect assessment of viral load by measuring the concentration or level of virus in serum.
- Methods includes quantitative PCR & branched DNA test.
- Most patient have viral load between 100.000-10.000.000 copies/ml # 50.000-500.000 IU.
- It correlate with the likelihood response to therapy.
- Response is higher with low level vireamia <2million copies/ml # one million IU.

Treatment of hepatitis C infection & vaccine

- **The currently used treatment is the combined therapy using both :**
  Pegylated alpha interferon & ribavirin.***

- **Criteria for treatment:**
  - **Positive for HCV-RNA.**
  - **Positive for anti-HCV.**
  - **Known HCV genotype.**
  - **ALT > twice the upper normal limit.**
  - **Moderate liver damage based on liver biopsy.**

there is no vaccine available to hepatitis C.

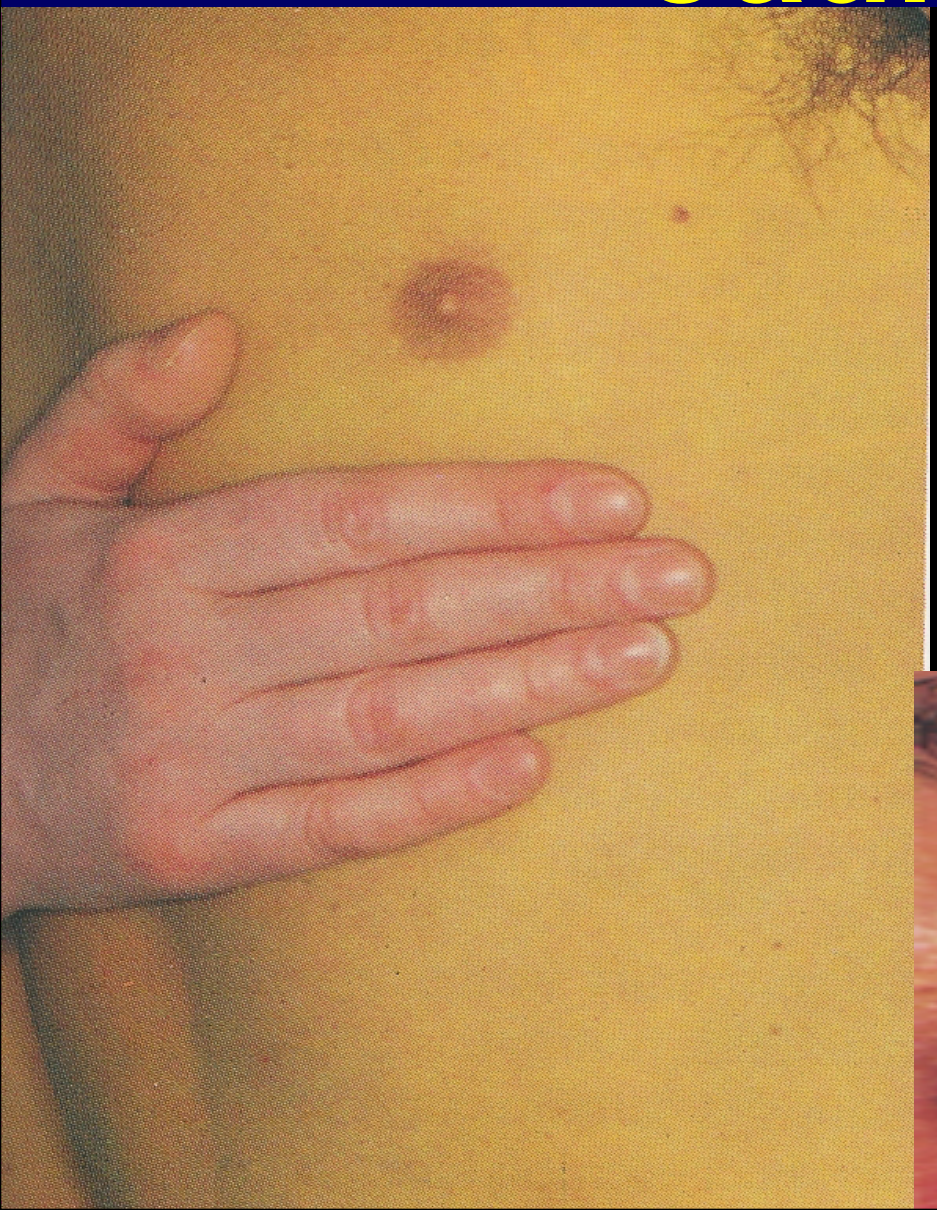
New Drugs

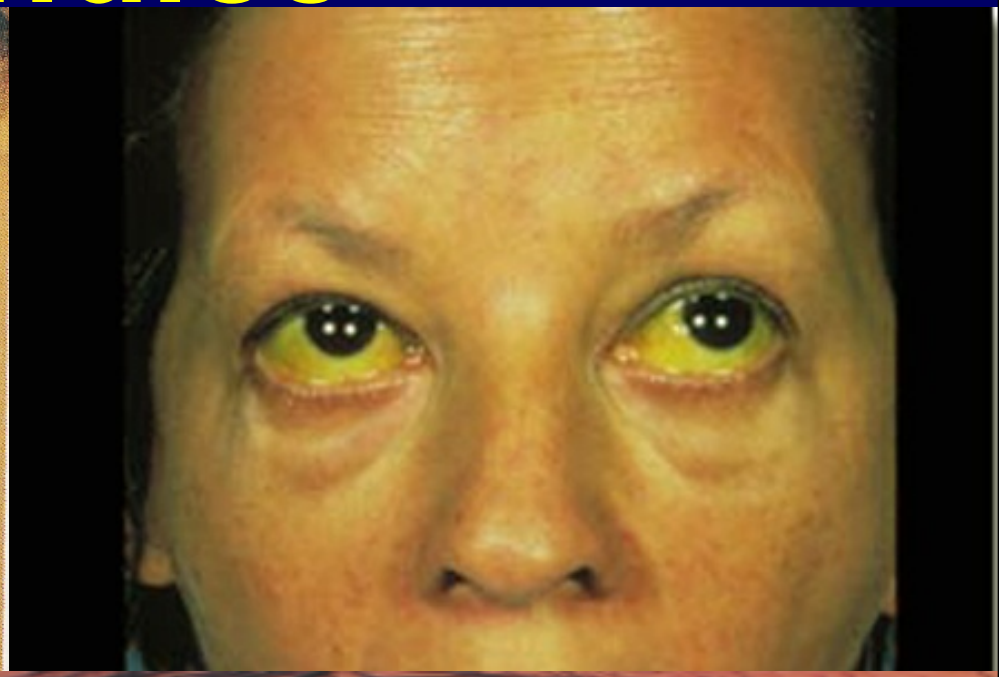
- There are number of approved therapies as SOVALDI may be given together with or without RIBAVIRIN &PEGINTERFERON , When hepatitis C treatment is working , the virus will become undetectable within 4 to 12 weeks and will remain that way throughout treatment .patients consider cured when virus remain undetectable for 12 to 24 weeks after completing therapy.

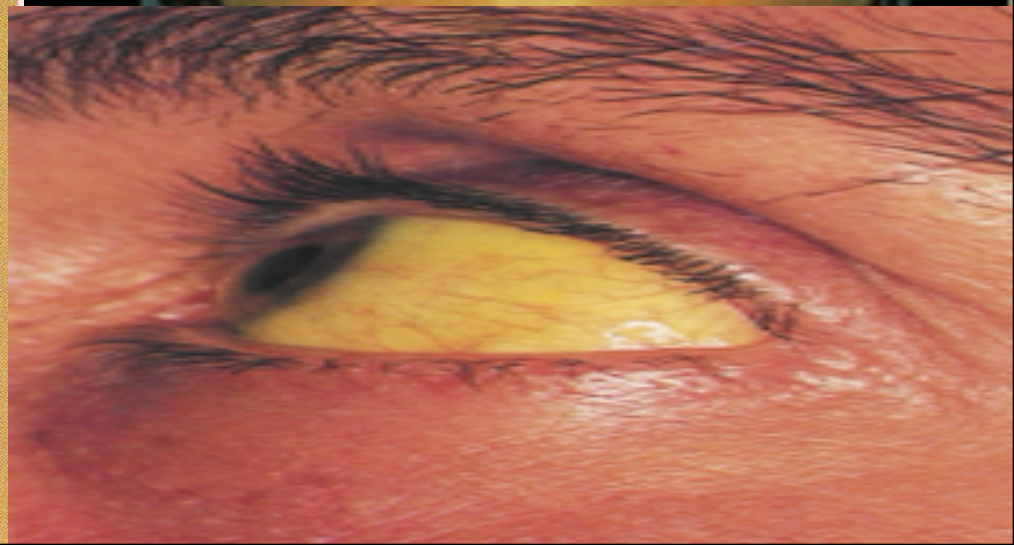
Hepatitis G virus

- Hepatitis G virus or GB-virus was discovered in 1995.
- Share about 80% sequence homology with HCV.
- Family: *Flaviviridae*, genus: *Hepacivirus.*
- Enveloped, ss-RNA with positive polarity.
- Parenterally, sexual and from mother to child transmission have been reported.
- Causes mild acute and chronic hepatitis infection.
- Usually occurs as co-infection with HCV, HBV and HIV.

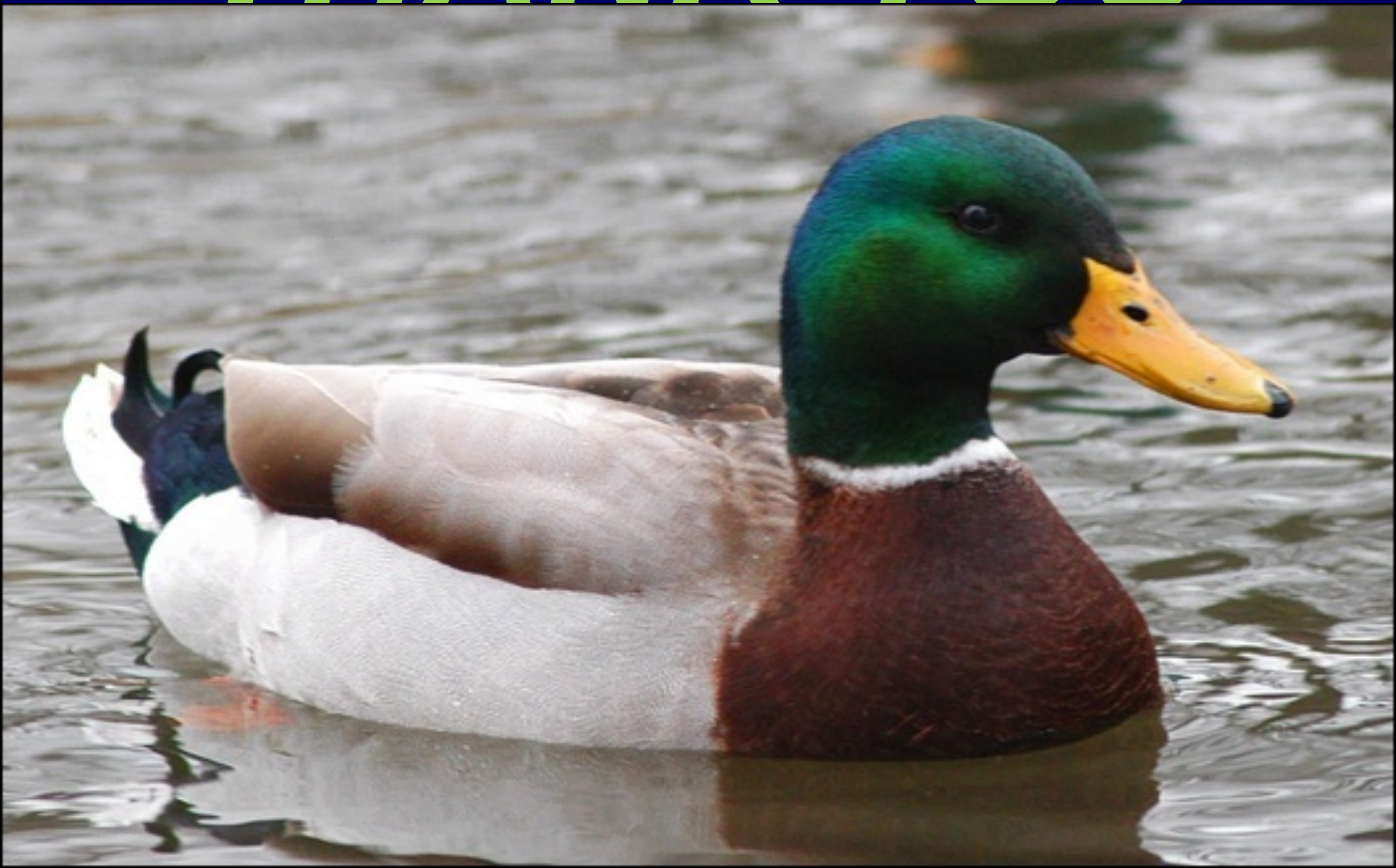
Jaundice







THANK YOU



Thank you for your attention !

THANK YOU