Viral hepatitis
Blood Born hepatitis

Dr. MONA BADR

Assistant Professor

College of Medicine & KKUH

Hepatitis = inflammation of liver cells

- Hepatitis feature of many diseases usually as a part of a generalized infection e.g. cytomegalovirus, yellow fever, Epstein-Barr virus.
- However, some viruses primarily targeting the liver to cause viral Hepatitis, viral hepatitis presents more or less similar clinical picture whatever the causative viruses.
- Laboratory tests can differentiate between different

We have to determine the causative virus to know how to treat and to determine the prognosis.

❑ primary viral hepatitis

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 virus.

- ❑ 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 G virus (HGV).**

Characteristics of HBV

- **Family of *hepadnaviridae.***

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

➢ Internal core (nucleo-capsid) composed of hepatitis B core antigen **(HBcAg).**

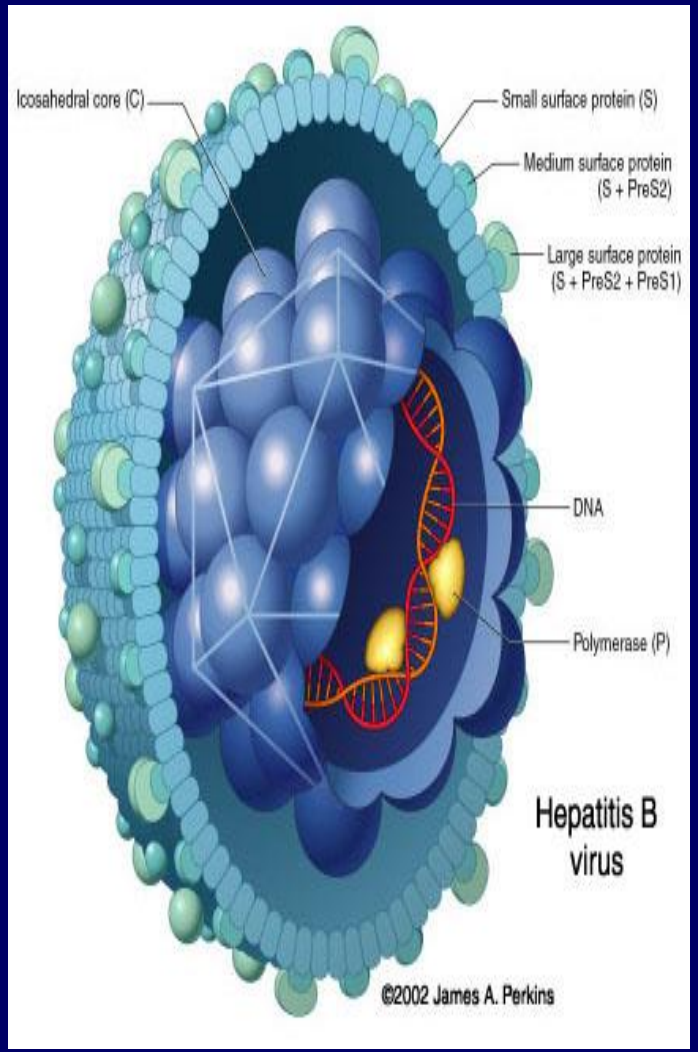
➢ The viral genome which is small partially circular ds-DNA.

➢ The virus contains the enzyme reverse transcriptase.

HBe Ag is a component of core gene product

and *indicate active viral replication.*

Hepatitis B virus, resist low pH and moderate heating.



The size is 42-nm in diameter.

HBV

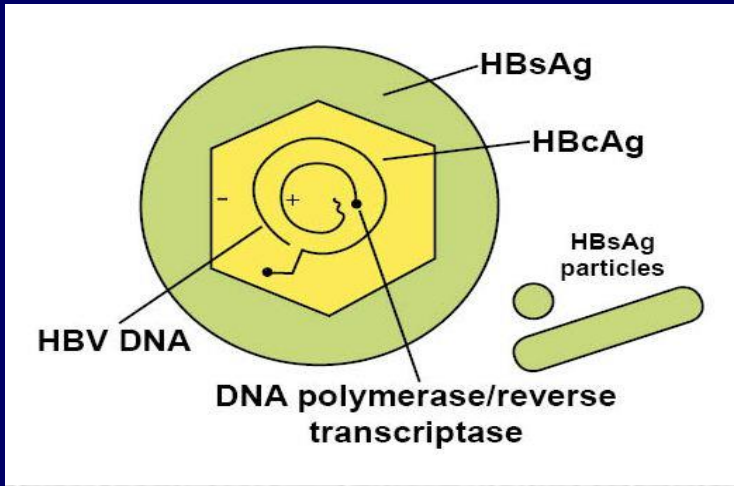
❑ The serum of infected individual contains three types of hepatitis B particles:

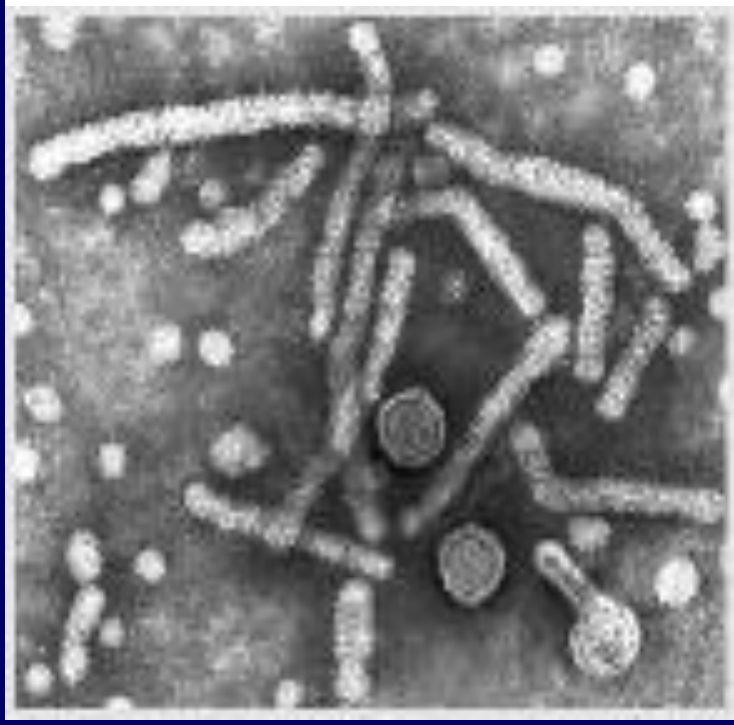
➢ Large number of small spherical free HBsAg particles.

➢ 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 & Epidemiology

Hepatitis B virus **(HBV)** is transmitted from patients who are infected to those who are not immune . Hepatitis B vaccination has significantly reduced the risk of transmission worldwide**.** The predominant mode of HBV transmission **varies** in different geographical areas.

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): sexual transmission remains as one of the common source of HBV transmission.**

Homosexual men & heterosexual persons who have multiple sex partners are at particularly high risk.

Transmission of HBV

3 -Mother-to-child transmission :

Mother-to-child transmission may occur in utero **(VERTICAL transmission), but more % of transmission are reported at the time of birth, or after birth (perinatal transmission) .**
Passive and active immunization of the newborn within **12 hours** of delivery has reduced the risk of HBV transmission by more than 95%.
However, despite the proper use of prophylaxis, transmission can still occur. The risk appears to be greatest if the mother is positive for **(HBeAg)** and/or has a **high HBV viral load**.

There is no evidence that transmission of HBV occurs during breast feeding.

4- Transplant recipients

Infection can be transmitted from HBsAg-positive donors to HBsAg-negative recipients, with severe clinical consequences when the recipient is nonimmune. Transmission of HBV infection has been reported after hematopoietic stem cell and solid organ transplantation.

➢ High risk groups INCULDES:

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors.
- Individuals with multiple sexual partners & homosexuals.
- Health care workers with frequent blood contact.

Individuals who exposed to tattooing, body piercing or cupping.

Pathogenesis:

HBV infects hepatocytes, and viral antigens are displayed on the surface of hepatocytes cells.

Cytotoxic T cells mediate an immune attack against the viral antigens, causing inflammation and necrosis
(**cell mediated immunity**),
HBV itself does not cause a cytopathic effect.

Acute hepatitis B infection

- **Incubation period varies from 1 to 4 months (10 to 12 weeks).**
- Most of the HBV infections are asymptomatic .
- The clinical appearance of acute hepatitis B is similar to that of hepatitis A .However, with hepatitis B ,symptoms tend to be more severe.

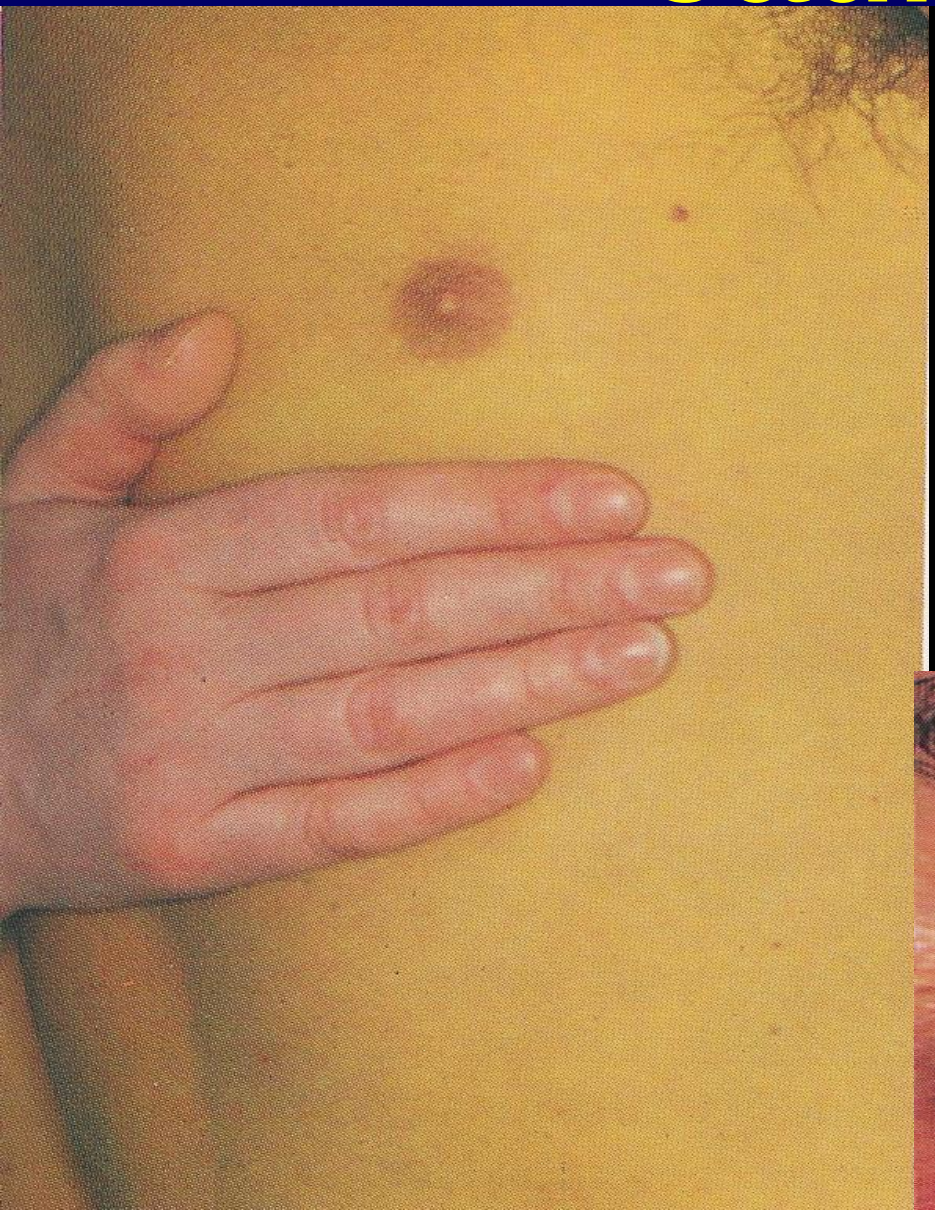
➢ 1- *Anicteric phase:*

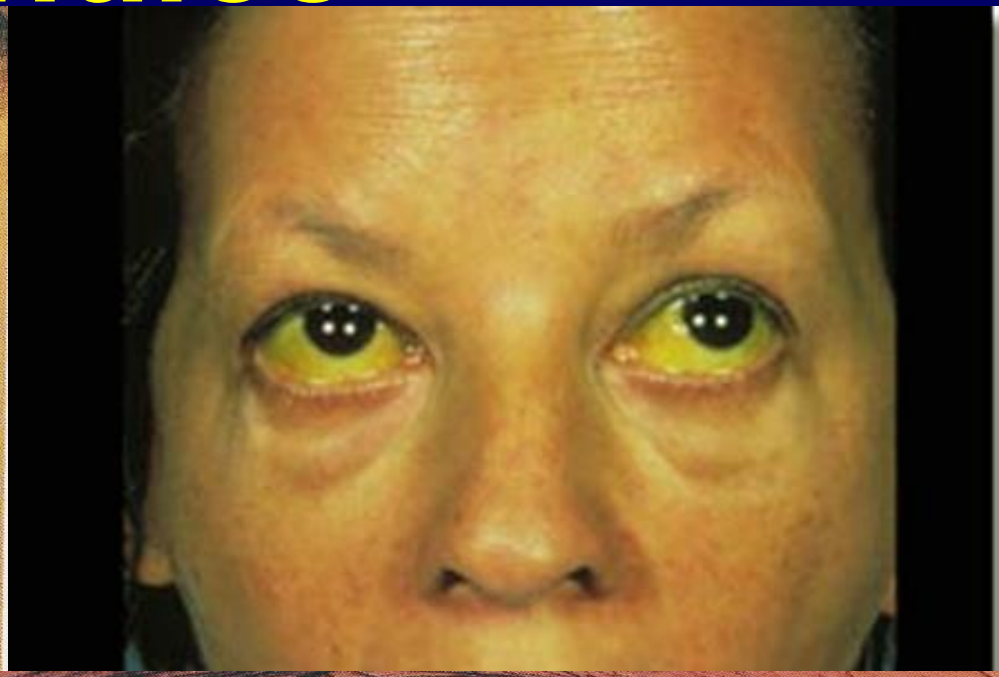
❖ **Low grade fever, anorexia, malaise, nausea, vomiting and pain at the right upper quadrant of the abdomen, raised liver enzyme.**

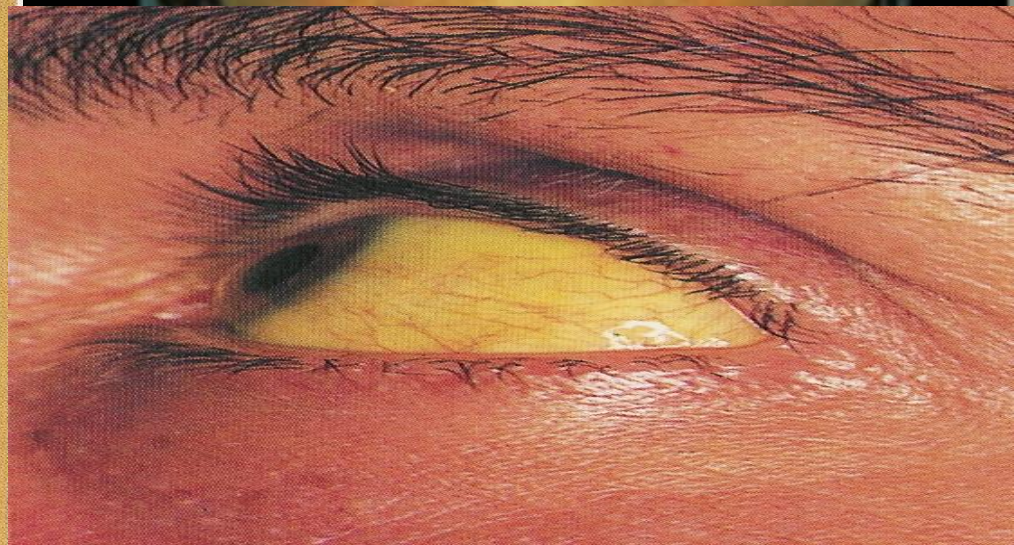
➢ 2- *Icteric phase (25%):*

which is characterized by jaundice ,raised bilirubin leading , dark urine and pale stool.

Jaundice







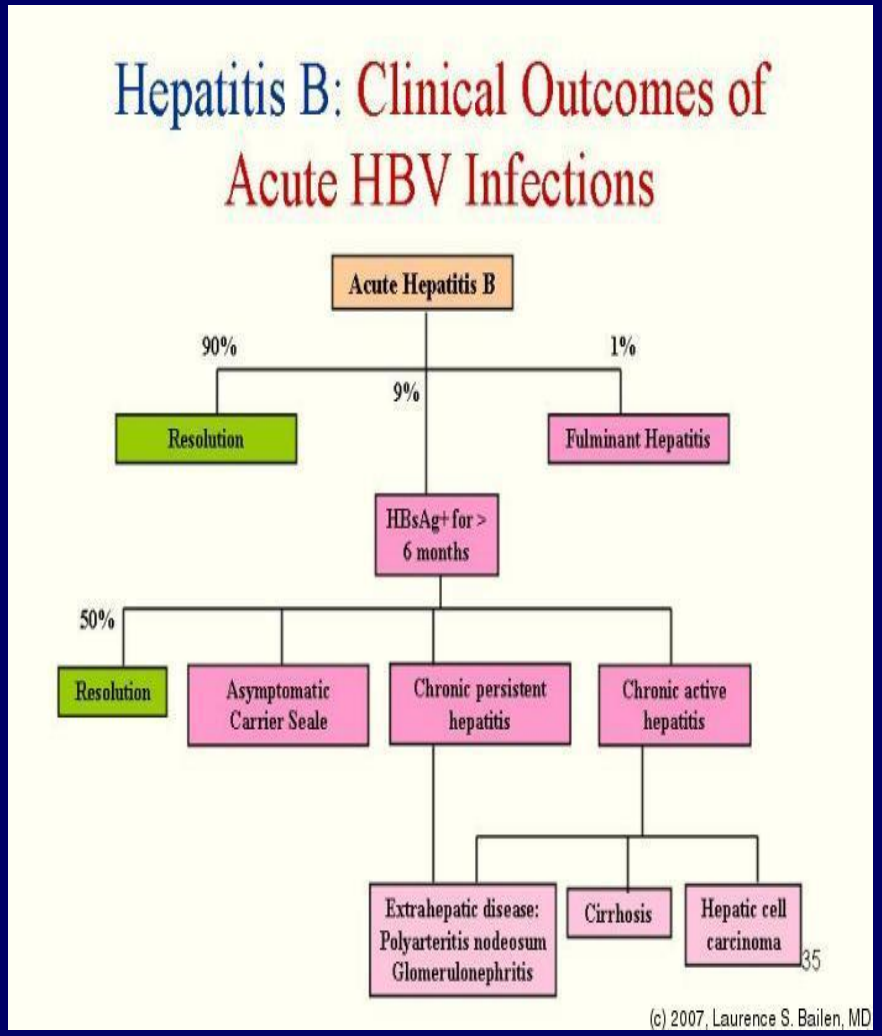
The clinical outcome of HBV infection*****

- **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%-50% of infected children age 1 to 5 years** may progress to chronic hepatitis B********

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

. Fulminant hepatitis B is believed to be due to massive immune-mediated lysis of infected hepatocytes.



Serologic markers

Hepatitis B surface antigen and antibody : HBsAg

(HBsAg) is the serologic hallmark of HBV infection. It can be detected using an (EIA) ,,HBsAg appears in serum 1 to 12 weeks(I.P) after an acute exposure to HBV prior to the onset of hepatitis symptoms or elevation of serum alanine aminotransferase (ALT).

Hepatitis B core antibody - HBcAb

Anti-HBc can be detected throughout the course of HBV infection..

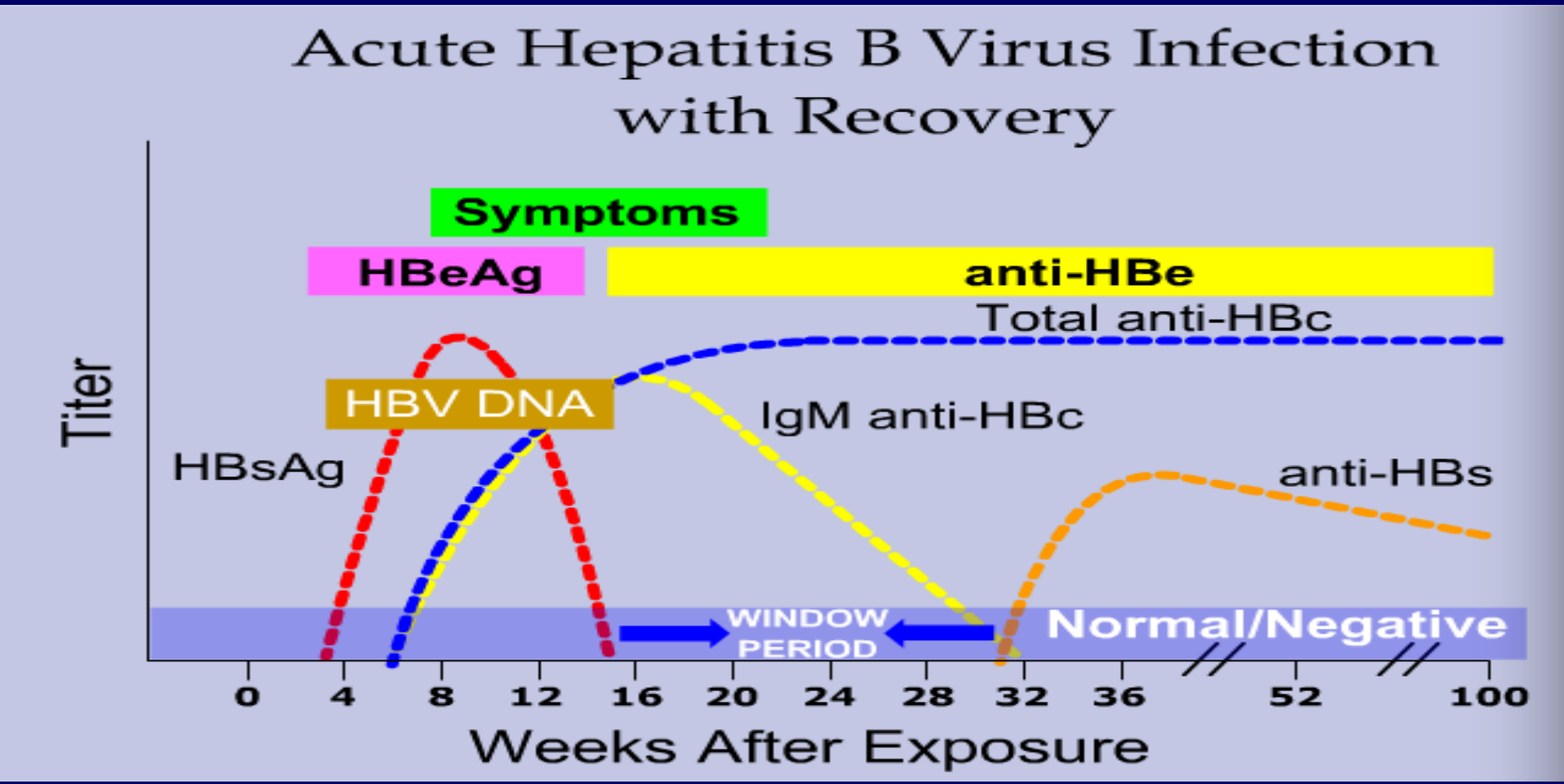
IgM anti-HBc is the **sole** marker of HBV infection during **the window period** (the period in infection when neither hepatitis B surface antigen(HBsAg) nor its antibodies(anti-HBsAge) can be detected in the serum of the patient).

Anti-HBc IgG persists along with anti-HBsAg in patients who recover from acute hepatitis B (immune) ,It also persists in association with HBsAg in those who progress to chronic HBV infection and it indicate natural infection .

Hepatitis B markers

HBV DNA	Marker of infection*******
Hepatitis B surface antigen (HBsAg)	Marker of infection *****
Hepatitis B e antigen (HBeAg)	Marker of active virus replication, the patient is **highly infectious**, the virus is present in all body fluids.**********
Antibody to hepatitis B e antigen (Anti-HBe)	Marker of low infectivity, the patient is less infectious.***Not immune***
Antibody to hepatitis B core (Anti-HBc)	Marker of exposure to hepatitis B infection. Not found in vaccinated person only if exposed to natural infection .**Not immune**
Antibody to hepatitis B surface antigen (Anti-HBs)	The only **marker of immunity.*********

Window phase: there is a period of several weeks when HBsAg has disappeared but HBsgAb is not yet detectable ,at that time ,HBcAb (IgM) is always positive and can be used to make the diagnosis.



Hepatitis B e antigen and antibody (HBeAg) is a secretory protein that is processed from the pre-core protein. It is generally **considered to be a marker of HBV replication and infectivity.** The presence of **HBeAg** is usually associated with high levels of HBV DNA in serum and higher rates of transmission of HBV infection from carrier mothers to their babies and from patients to another person. .

HBeAg to anti-HBeAg seroconversion occurs early in patients with acute infection, However, HBeAg seroconversion may be delayed for years to decades in patients with **chronic HBV infection.** In such patients, the presence of HBeAg is usually associated with the detection of high levels of HBV DNA in serum and active liver disease.

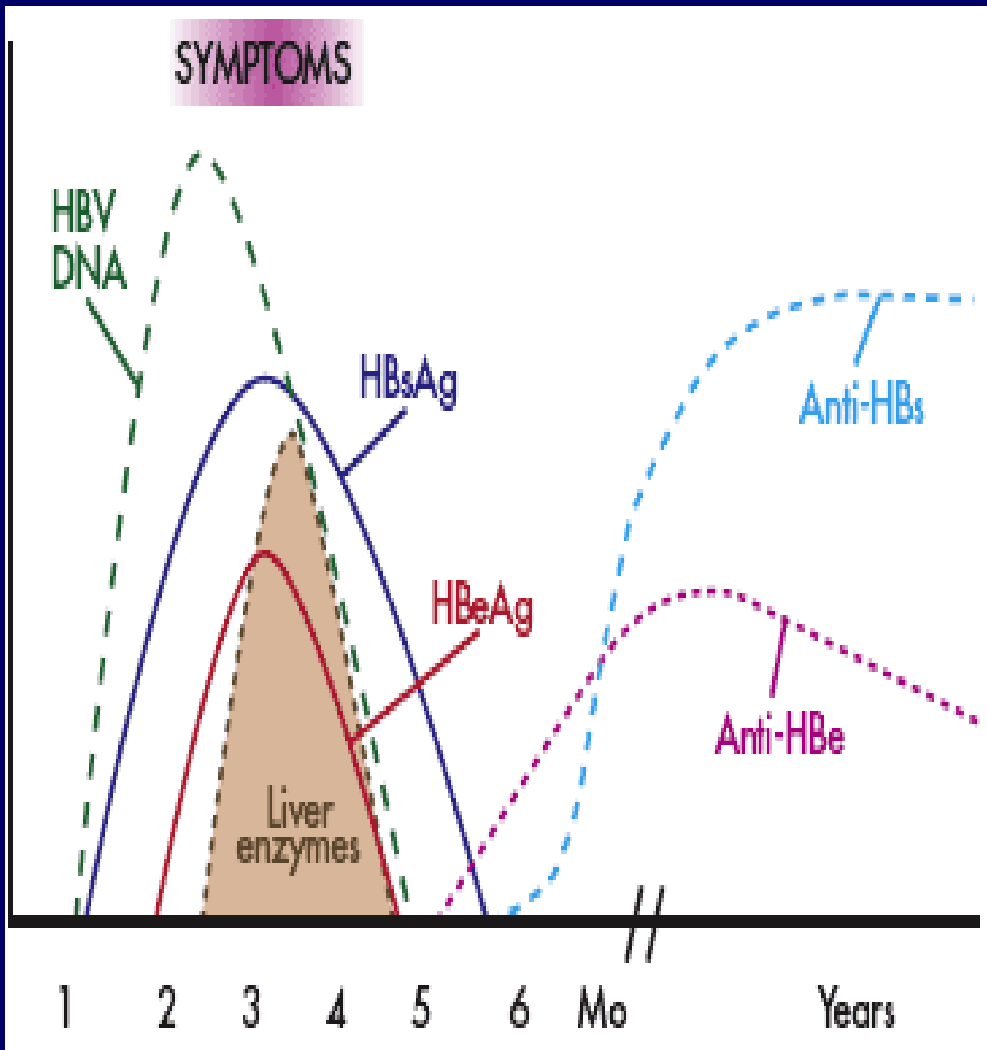
Serum HBV DNA assays — Qualitative and quantitative tests for HBV DNA in serum have been developed to assess HBV replication. Currently, most HBV DNA assays use **real-time PCR techniques**, report results in international units/mL, Recovery from acute hepatitis B is usually accompanied by the disappearance of HBV DNA in serum.

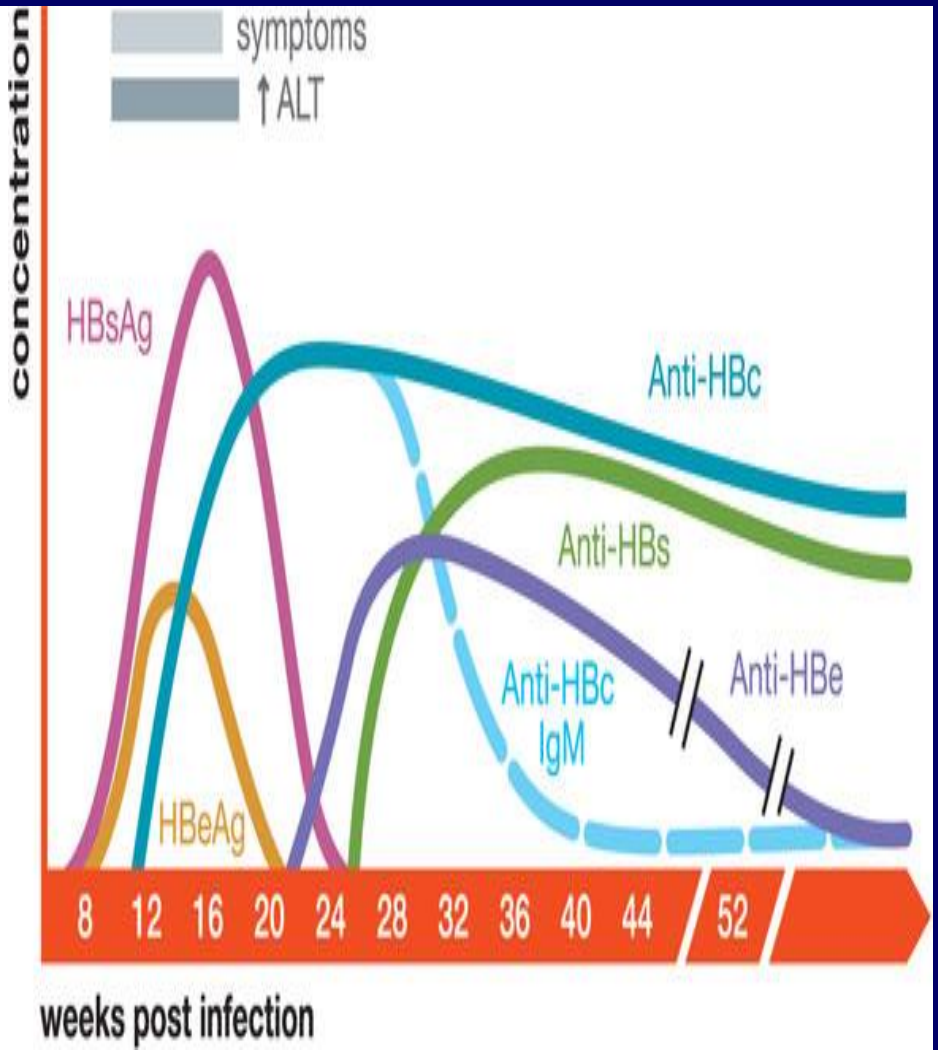
Serological profile of acute HBV infection

- **HBV- 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 if patient not become chronic.
- **HBeAg** is the 3rd maker that appears in circulation and disappears before HBsAg, it indicate active viral replication.
- **Anti-HBc Ab IgM** is the 1st antibody that appears in the blood and usually persists for 2 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





Very important*******

Serologic markers for the different phases of acute and chronic hepatitis B virus infection

HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA	Interpretation
Acute HBV infection							
+	+	+				+++	Early phase
		+				+	Window phase
			+	+	+	±	Recovery phase
Chronic HBV infection							
+	+		+		-	+++	HBeAg+ high replicative phase (immune tolerance or immune clearance)
+	-		+		+	±	HBeAg- low replicative or inactive phase
+	±	±	+			+	Flare of chronic HBV
+	-		+		+	++	HBeAg- replicative phase (HBeAg-chronic hepatitis, precore/core promoter variants)
-	-		± (generally +)	±	±	+	Occult HBV

Anti-HBc: antibody to hepatitis B core antigen; anti-HBe: antibody to hepatitis B e antigen; anti-HBs: antibody to hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

Chronic hepatitis B infection

- **Chronic hepatitis B is defined by 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 tests, although some of them have mild fatigue, RT upper quadrant abdominal pain or enlarged liver & spleen. some of these chronic patient will become immune after years and they develop anti-HBs Ab in the serum with disappearance of HBeAg .**
- **Some other chronic patient will develop active hepatitis ,which can lead to cirrhosis and death.**

Factors predictive of disease progression

Both virologic and non-virologic factors influence disease progression and survival in patients with chronic HBV infection

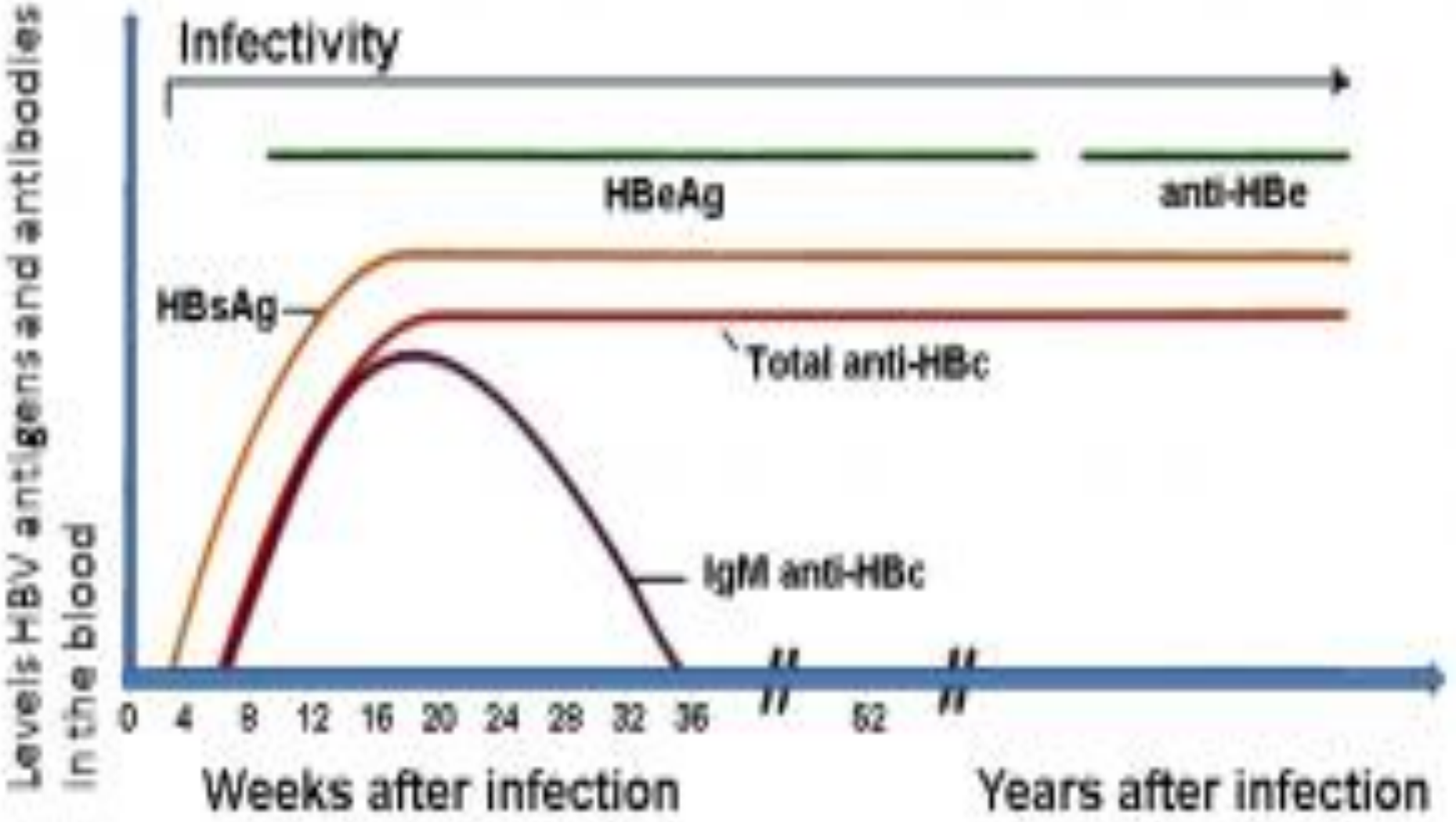
- **HBeAg** :Patients with a prolonged replication phase (ie, HBeAg positive) have a worse prognosis, mostly due to the development of cirrhosis and hepatocellular carcinoma.

HBV DNA : High HBV DNA levels are associated with an increased incidence of cirrhosis, hepatocellular carcinoma, and liver-related mortality.

- **HBsAg levels** :In patients with HBeAg negative chronic HBV with a low viral load, HBsAg levels >1000 IU/mL have been associated with an increased risk of disease progression and hepatocellular carcinoma .

Host related factors as (gender, age, diabetes) and environment (alcohol, smoking, carcinogens) as well as coinfection with other viruses (eg, HCV, HDV, HIV) can play a role in prognosis.

Serological profile of chronic HBV infection

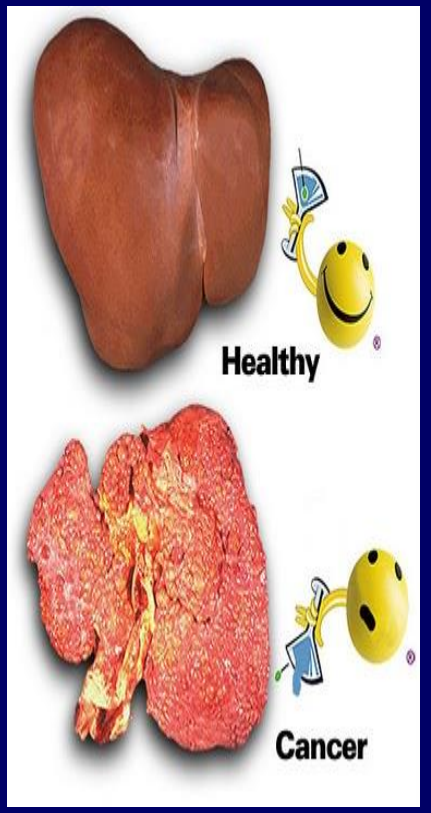


Cirrhosis

- Is a chronic diffuse liver disease.
- Characterized by fibrosis and nodular formation.
- Results from liver cel 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



- 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.

Glossary of clinical terms used in HBV infection

Definitions
Chronic hepatitis B
Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B.
Inactive HBsAg carrier state
Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.
Resolved hepatitis B
Previous HBV infection without further virological, biochemical, or histological evidence of active virus infection or disease.
Acute exacerbation or flare of hepatitis B
Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.
HBeAg clearance
Loss of HBeAg in a person who was previously HBeAg positive.
HBeAg seroconversion
Loss of HBeAg and detection of anti-HBe.

HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; anti-HBe: hepatitis B e antibody.

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**.

- Additional lab investigations:

1- Liver function tests (LFT).

2- Ultrasound of the liver.

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

Prevention

Prevention involve the use of either the vaccine or hyper immune globulin or both.

1-HBV-Vaccine

Vaccine is not live attenuated nor killed vaccine, It contains highly purified preparation of HBsAg particles , produced by genetic engineering in yeast.

The vaccine is highly effective and has few side effect..

The vaccine is administered in three doses **IM injection at 0 &1 & 6 months. the seroconversion rate is about 95% in healthy adults.It is indicated for people who are frequently exposed to blood or blood products and to travelers who plan to visit endemic area, in our region it is given to all newborn. If antibody titers have declined in immunized patients who are at high risk, such as dialysis patients ,then a booster dose should be considered .**

Prevention

2- Hepatitis B immuno-globulin(HBIG)

- It contain high titer of HBsAb , it is used to provide immediate ,passive protection to individuals known to be exposed to HBsAg positive blood (after accidental needle-stick injury). .Both the vaccine and HBIG should also be given to them and to a new born whose mother is HBsAg –positive, this regimen is very effective in reducing the infection rate of newborns whose mothers are chronic carriers.

Prevention of HBV

Pre-exposure prophylaxis:

- **Vaccine is prepared by cloning HBsAg in yeast cells. Universal vaccination of newborns is recommended in most countries. Vaccination should also be provided to individuals who are not immune to HBV and are at high risk of exposure (eg, healthcare personnel, injection drug users, household contacts of hepatitis B surface antigen [HBsAg]-positive patients, men who have sex with men, human immunodeficiency virus [HIV]-infected patients, hepatitis C virus [HCV]-infected patients)**

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 immunoglobulins

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.

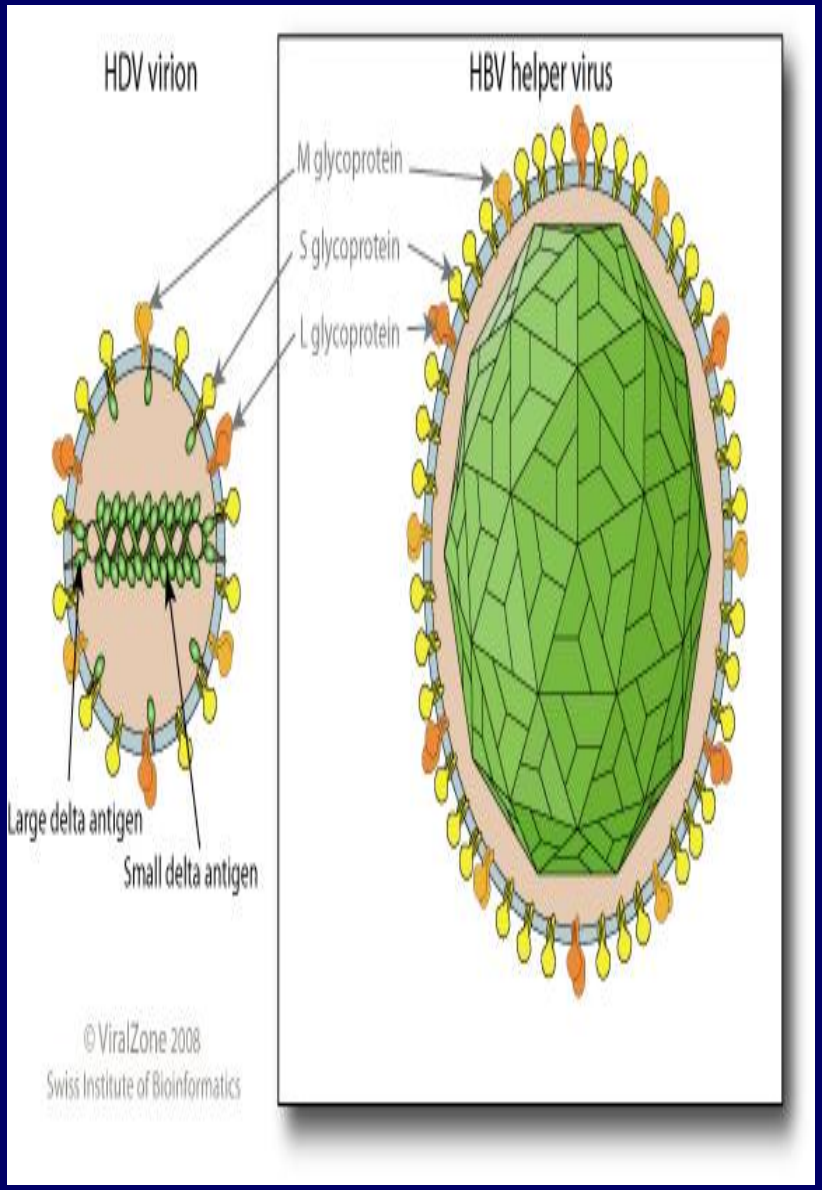
3- Adefovir, antiviral drug, nucleoside analogue. One tablet a day for at least one year.

- 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



Transmission & Epidemiology

- HDV is transmitted by the same means as HBV.
- HDV infections occur worldwide, with a similar distribution to that of HVB.

Pathogenesis & Immunity

- Same like pathogenicity of HBV , but there is some evidence that delta antigen is cytopathic for hepatocytes.

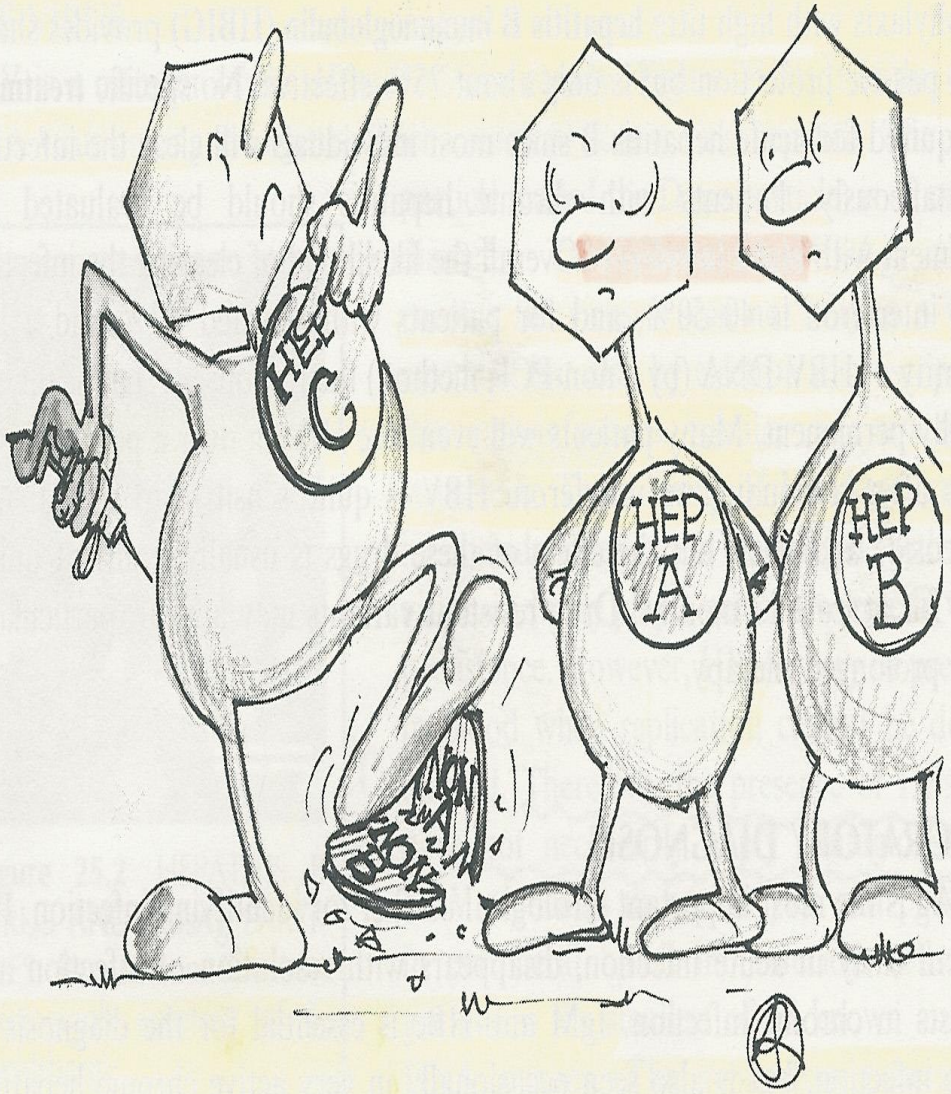
➢ Clinical findings

1- Co-infection: **The patient is infected with HBV and HDV at the same time leading to severe acute hepatitis .**

2- ***Super infection:*** **In this case, delta virus infects those who are already have chronic hepatitis B leading to severe chronic hepatitis , the incidence of fulminant ,life threatening hepatitis and liver failure is significantly higher.**

Diagnosis detecting either delta antigen or IgM Ab to delta antigen .

الحمد لله



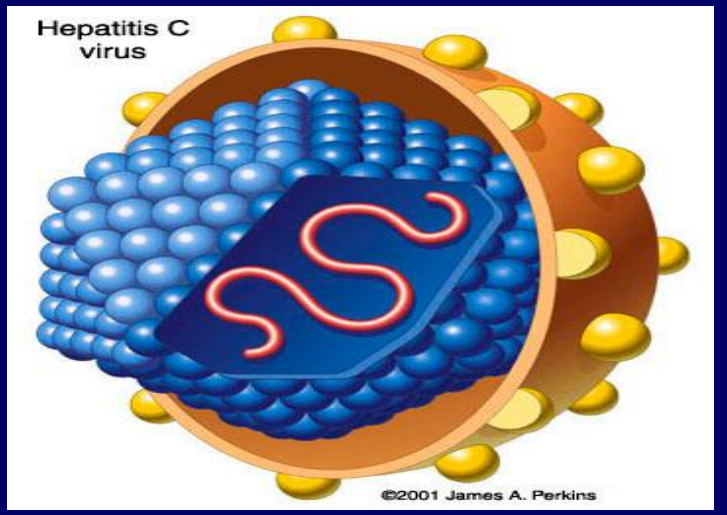
FINALLY NAMED, SEE?!

Hepatitis C virus: Classification & structure

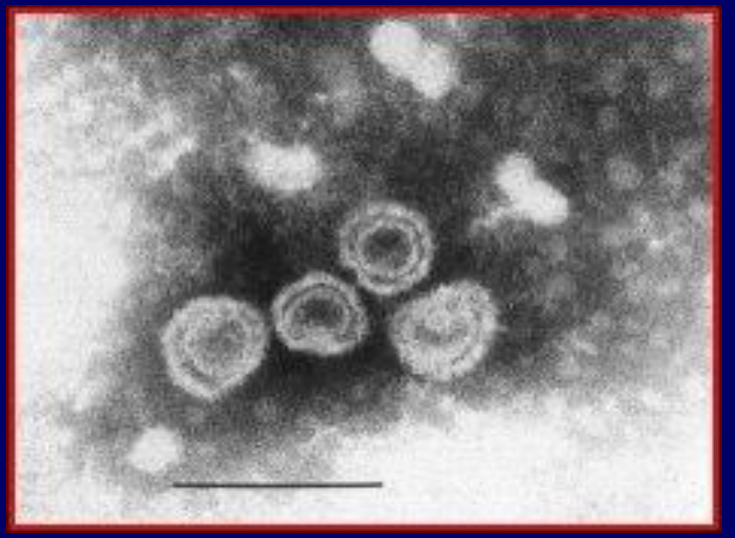
- **Family: *Flaviviridae.***
- The virus is small, 60 – 80 nm in diameter.

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

- It has no polymerase.



- **There are 6 major genotypes (1 – 6), genotype 4 is the dominant in Saudi patients.** This genetic variation results in high mutation rate in the envelope gene , as a result multiple subspecies often occur in the blood of an infected individual at the same time.



Transmission of HCV

1- Parenterally: MAINLY

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

2- **Sexually.**

Is uncommon , controversial .

3- **From mother to child transmission**

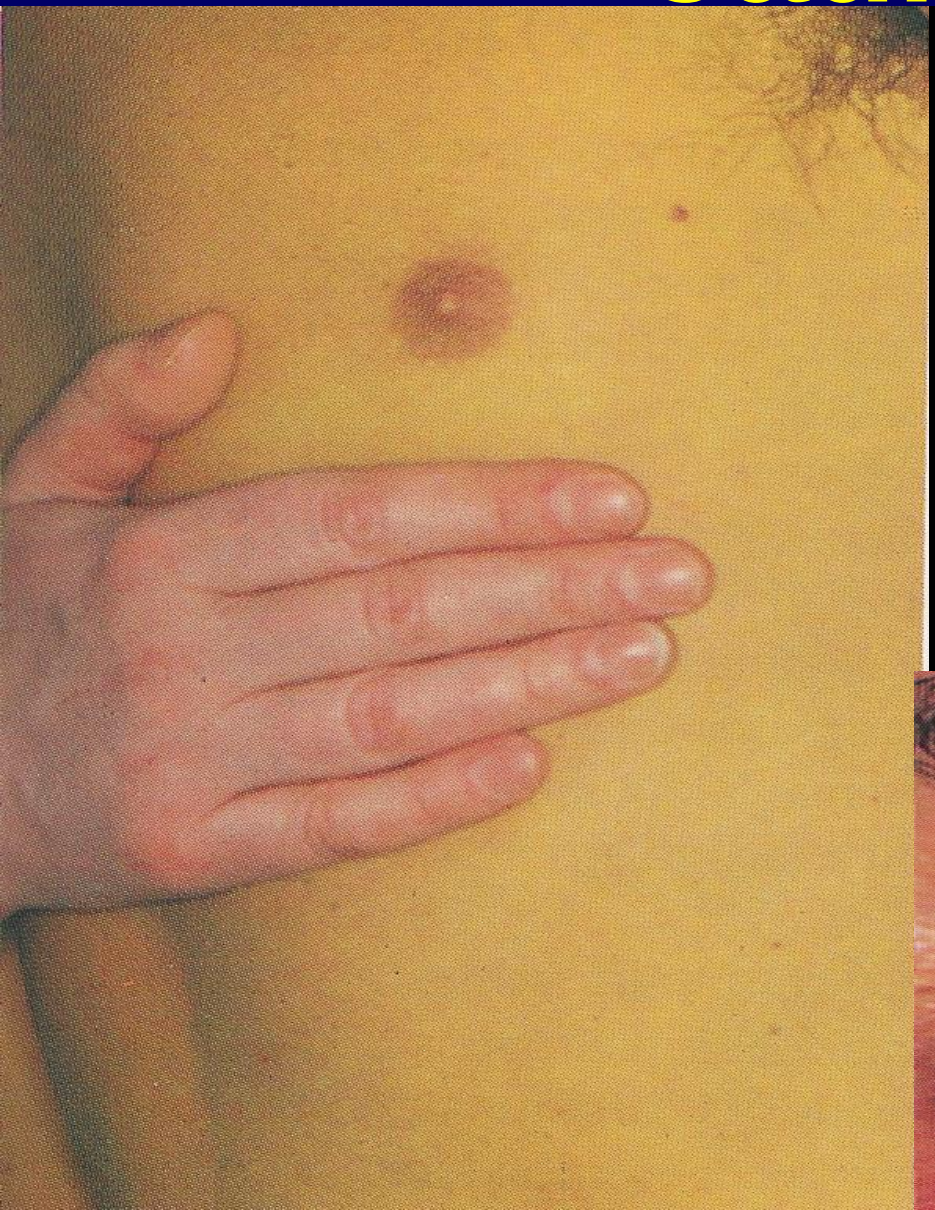
No evidence for trans placental transmission, no evidence of breast feeding transmission.

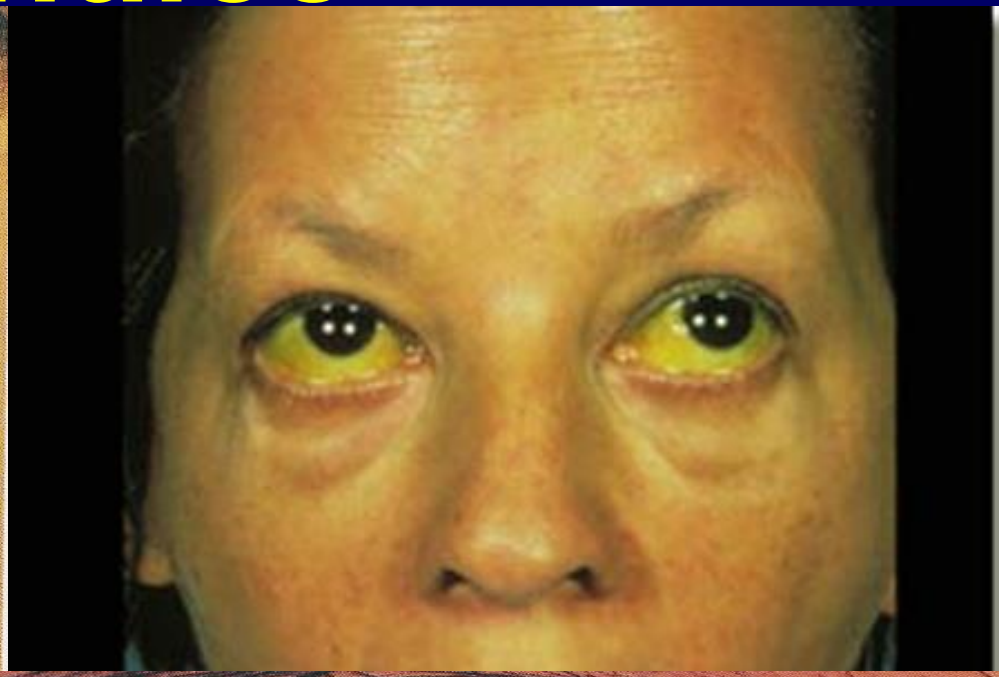
Clinical findings

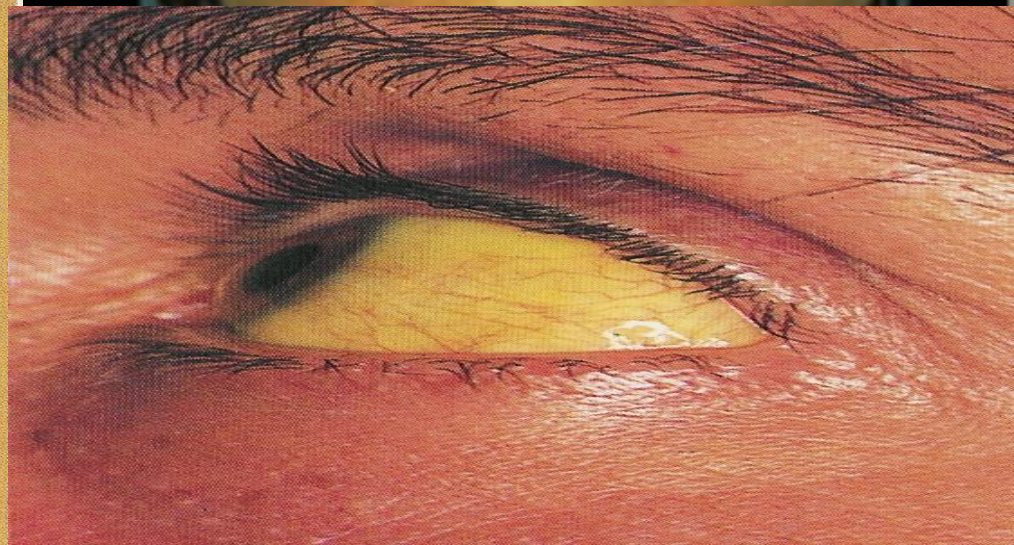
- **The mean incubation period is 8 weeks.**
- **The acute infection is often asymptomatic.**
- If symptoms ,such as malaise ,nausea, and upper quadrant pain but symptoms in general are **less severe** than other viral hepatitis.
- Fever ,anorexia, nausea, vomiting , and jaundice are common. Dark urine ,pale feces , and elevated liver enzyme (transaminase) are seen.

Chronic carrier state occur much more often with HCV (75%-85%) infection than with HBV(<9%).

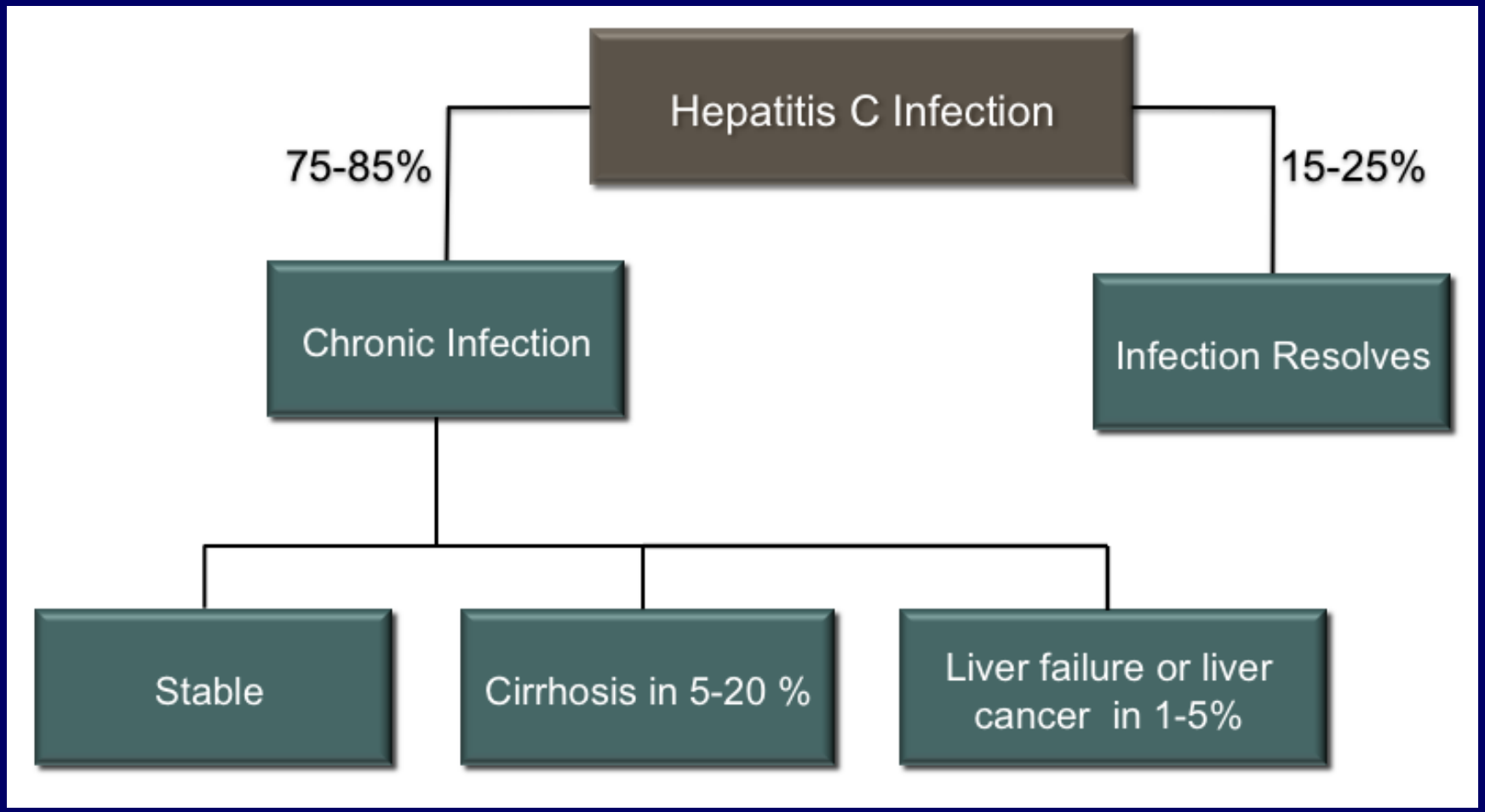
Jaundice







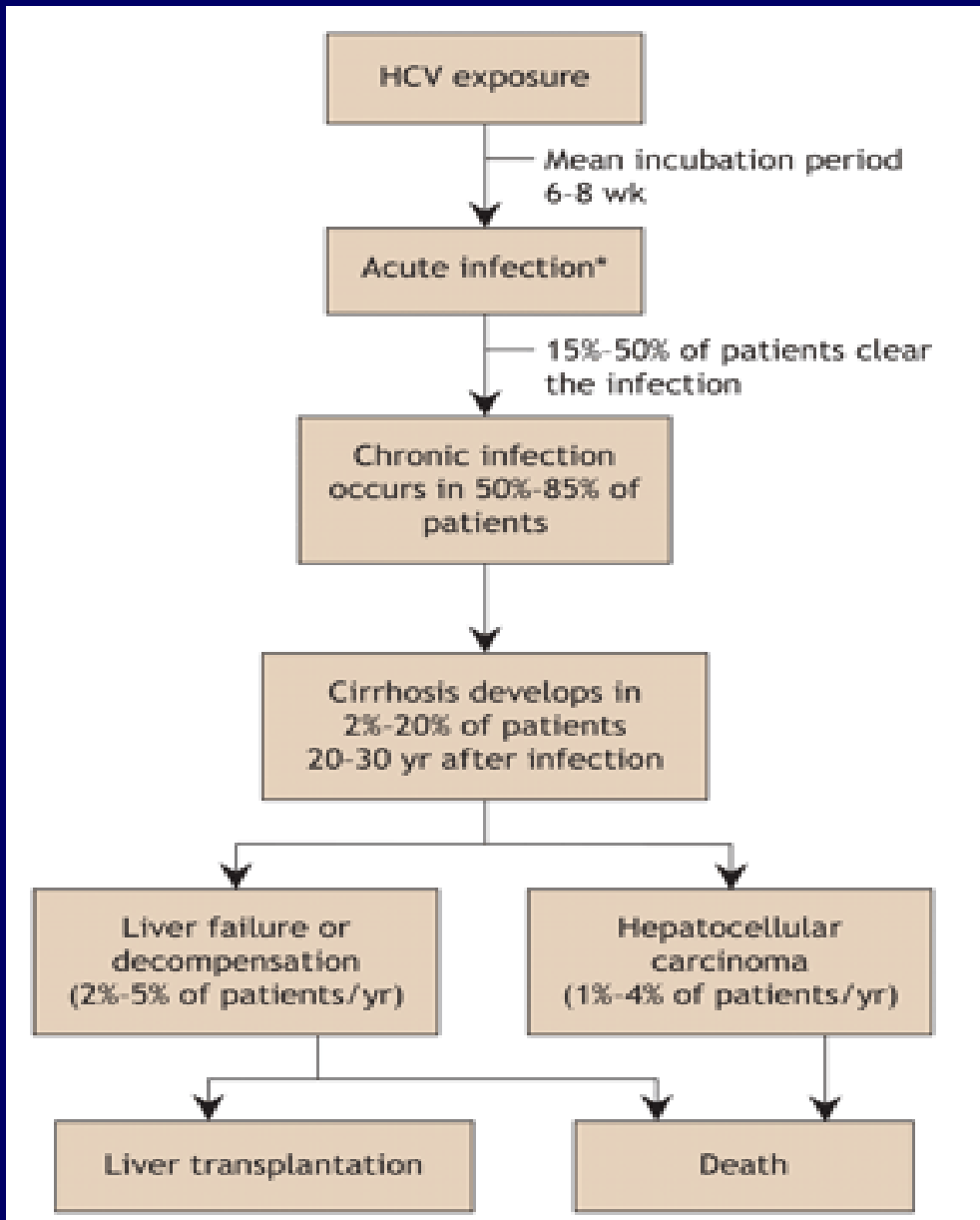
The clinical outcome of HCV



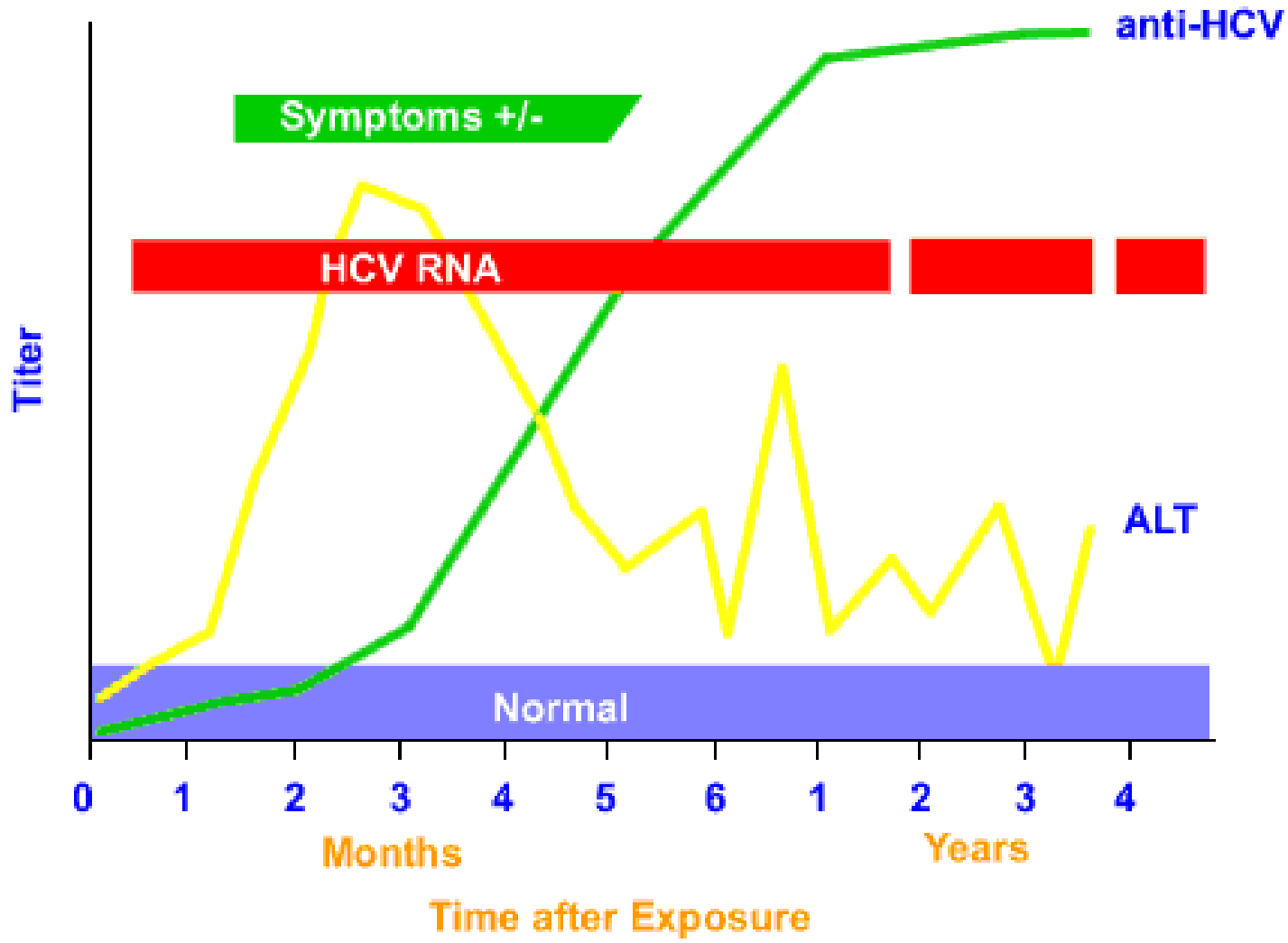
The clinical outcome of HCV infection

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

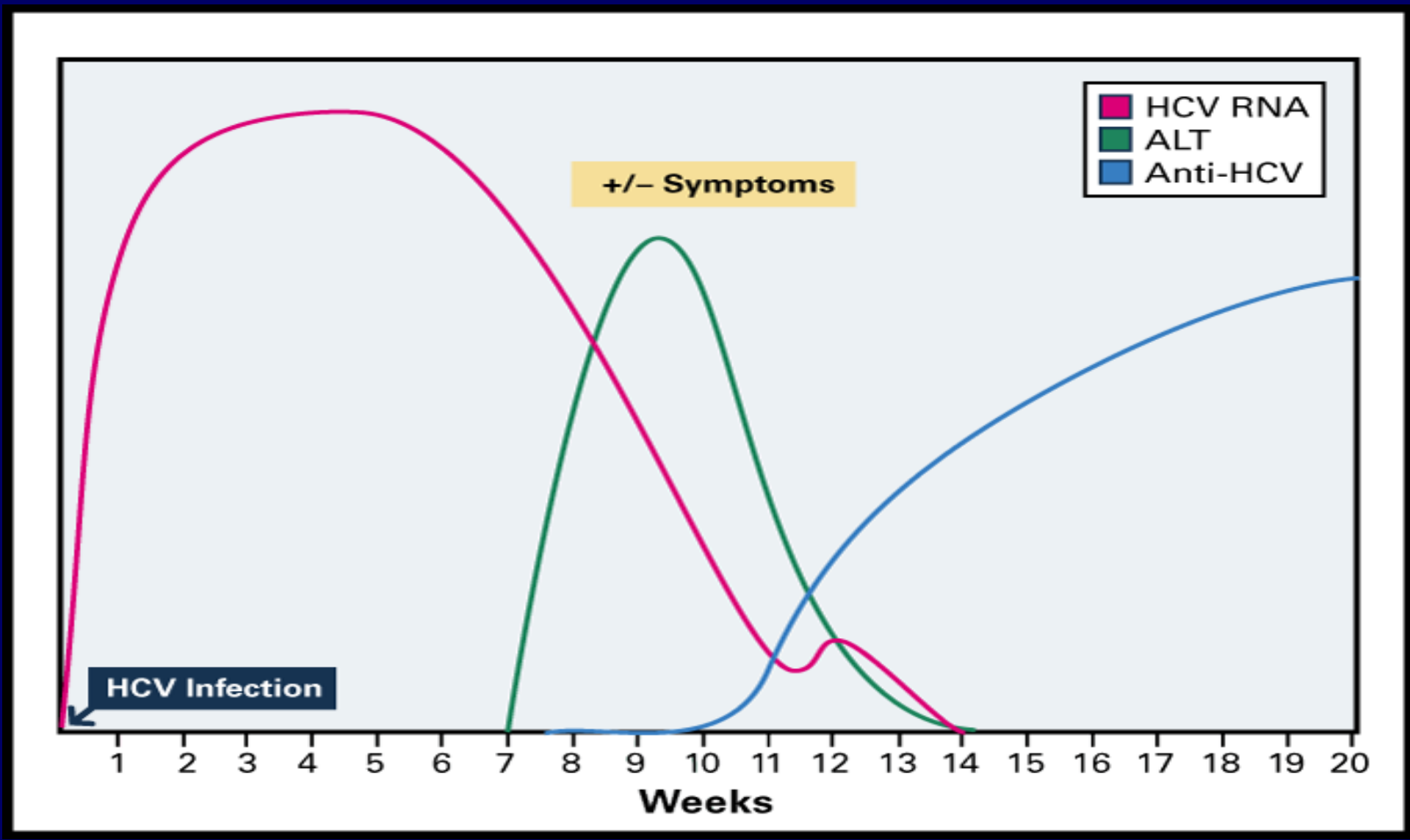
- **About 80 % of the infected will progress to chronic hepatitis C.** *about 10%-30% of them can develop cirrhosis within 30 years and liver cancer*. Less than 1 % will develop acute fulminant hepatitis C , liver failure and death.



Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Serological pattern of acute hepatitis C infection with recovery



Hepatitis C markers

Hepatitis C virus – RNA . •

• Is the first marker that appears in the serum, it appears as early as 2-3 weeks after exposure , **It is a *marker of infection***

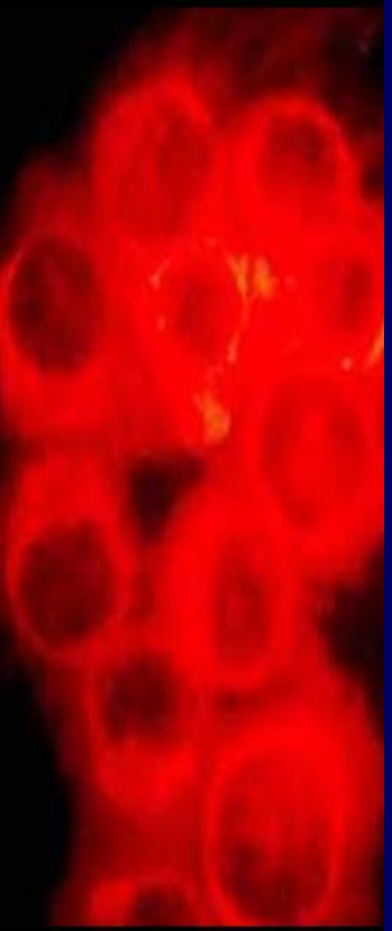
Ig G Antibody to hepatitis C.

❖ **Antibodies to hepatitis C virus is the last marker that appears in the serum , usually appear 50 days after exposure**

long window period.

This Ab present in both

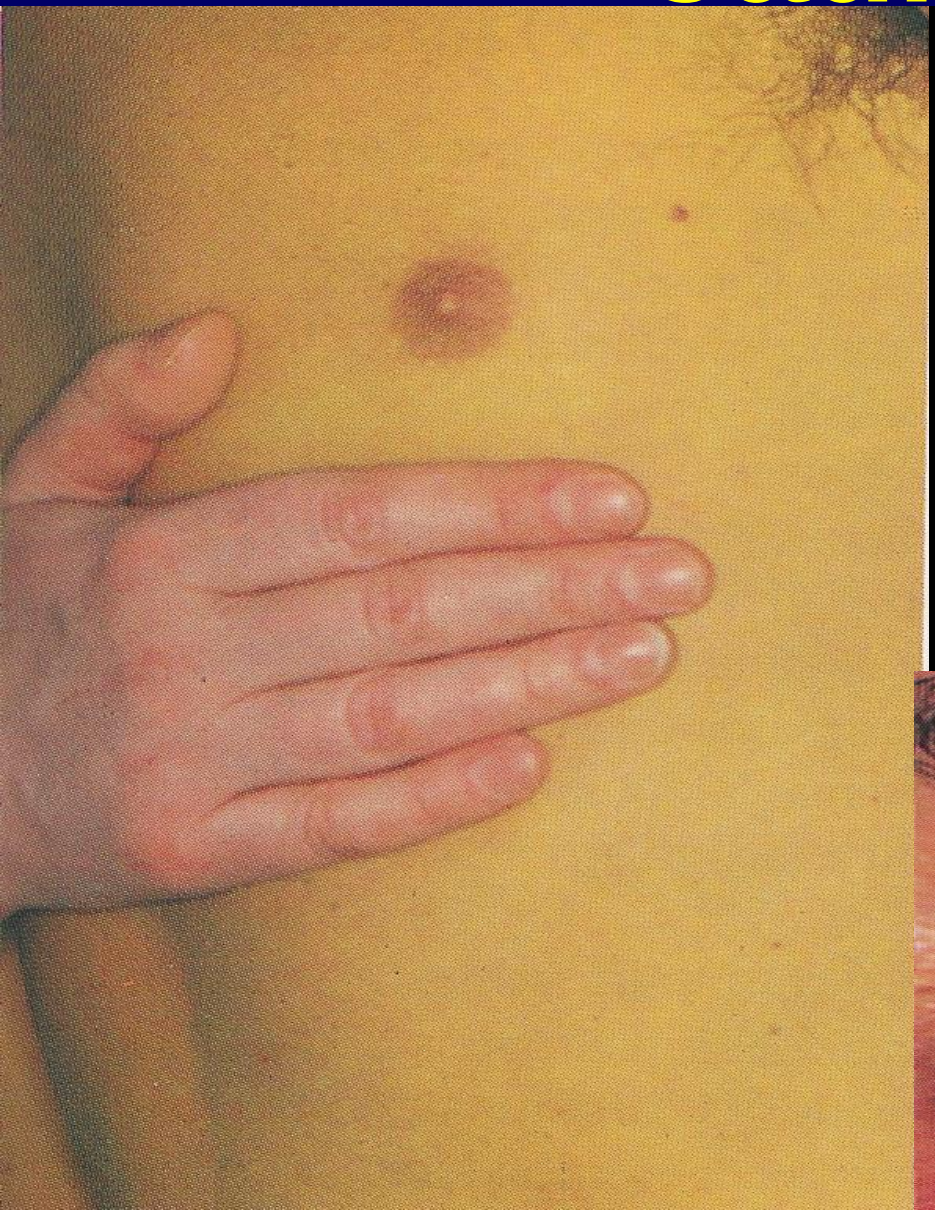
Acute or chronic patient.

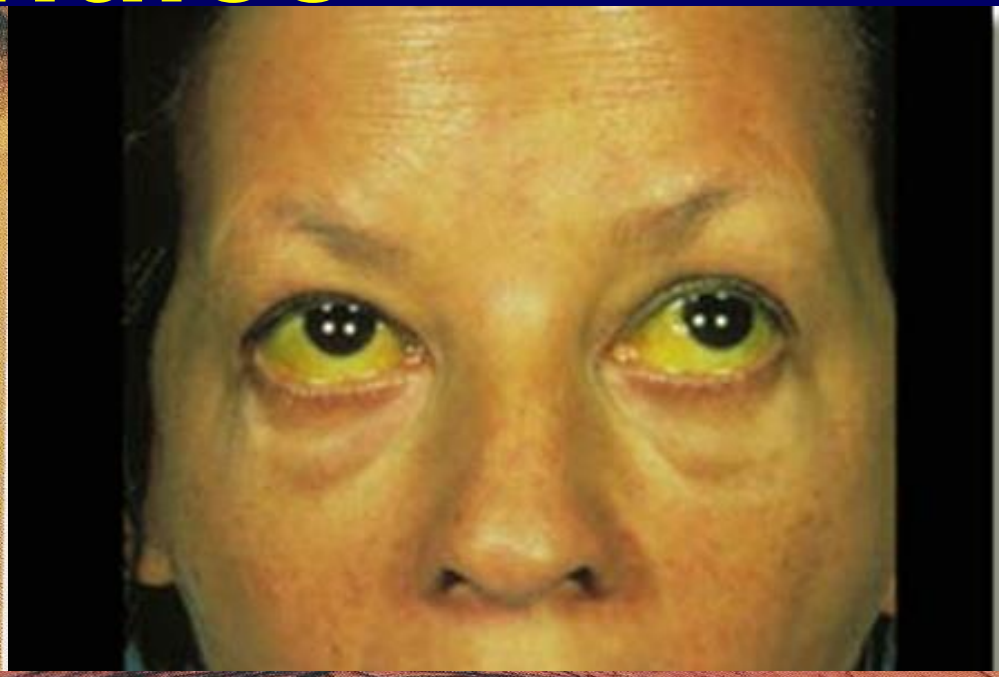


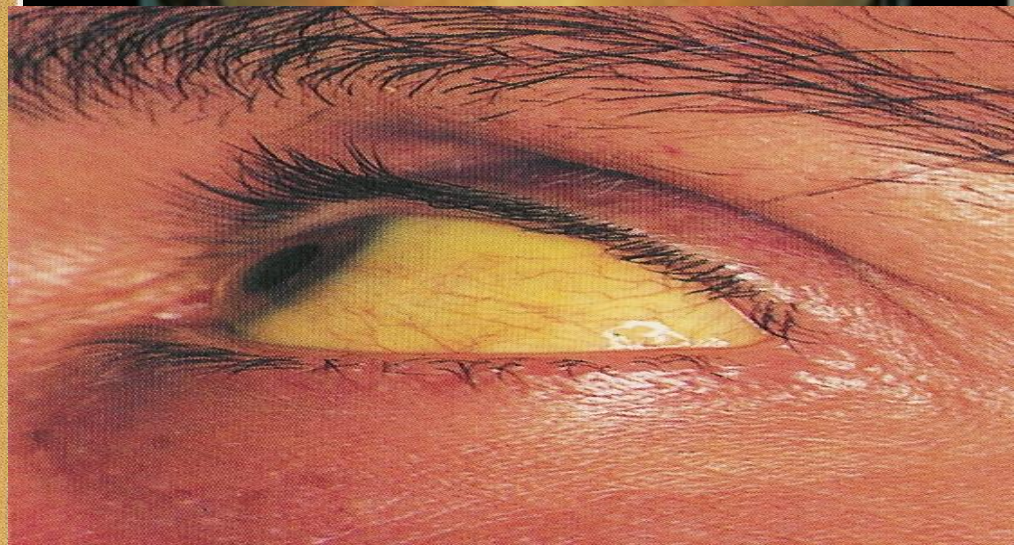
ACUTE HEPATITIS

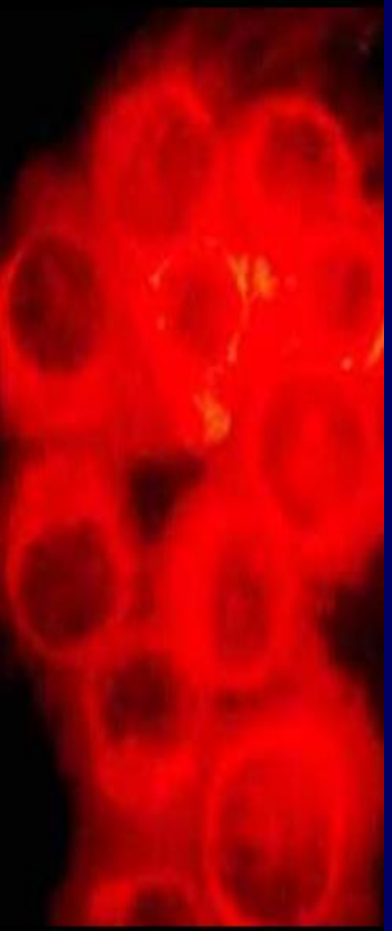
- Mostly asymptomatic ,if symptom : jaundice, fatigue & nausea.
- Elevated serum ALT (usually greater than 10 folds).
- Presence of anti-HCV (-ve in 30-40%) in early stages of disease.
- HCV-RNA is +ve even before the onset of symptoms.

Jaundice









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.

Serologic pattern of acute HCV infection with progression of chronic infection

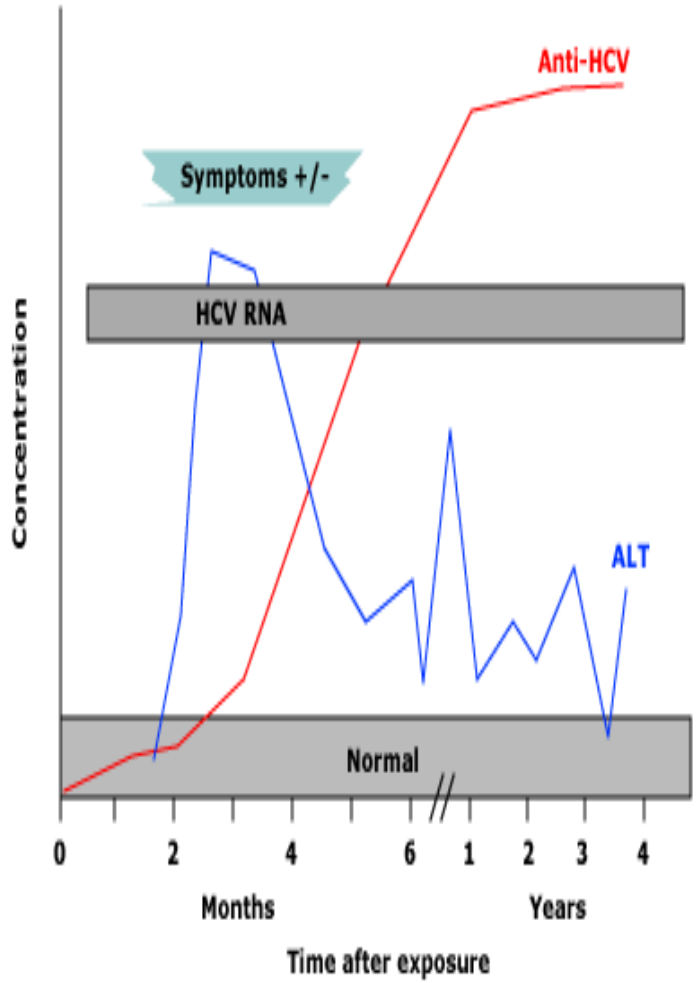


Figure provided by the Centers for Disease Control and Prevention.

Time course of acute HCV infection with recovery

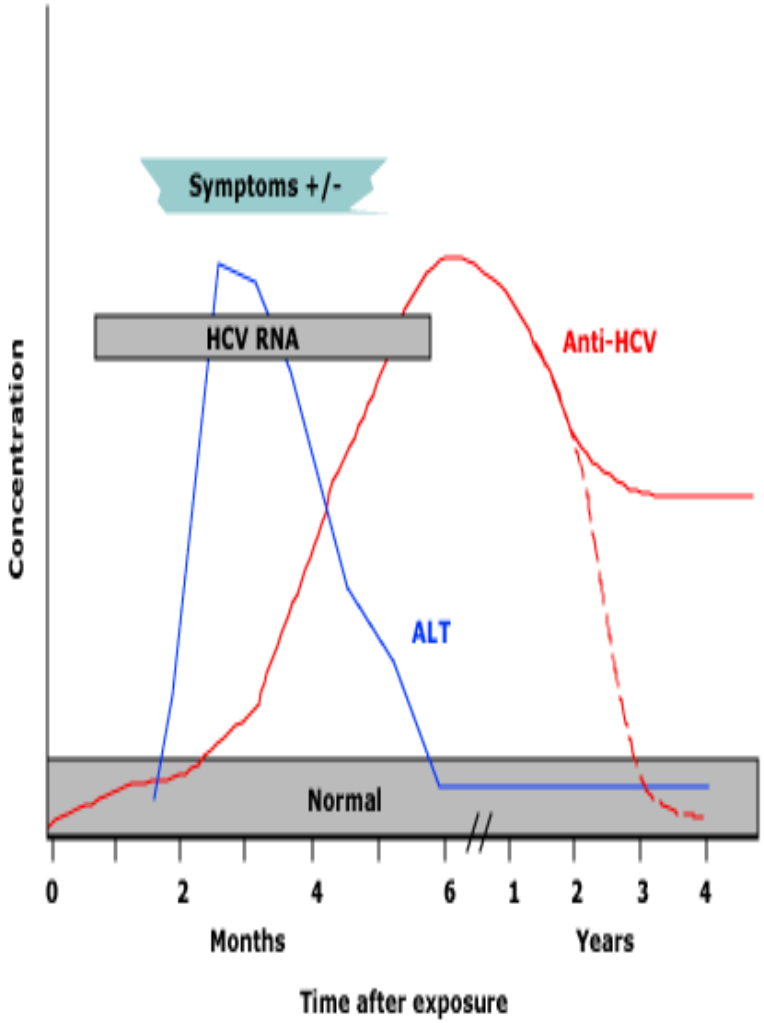
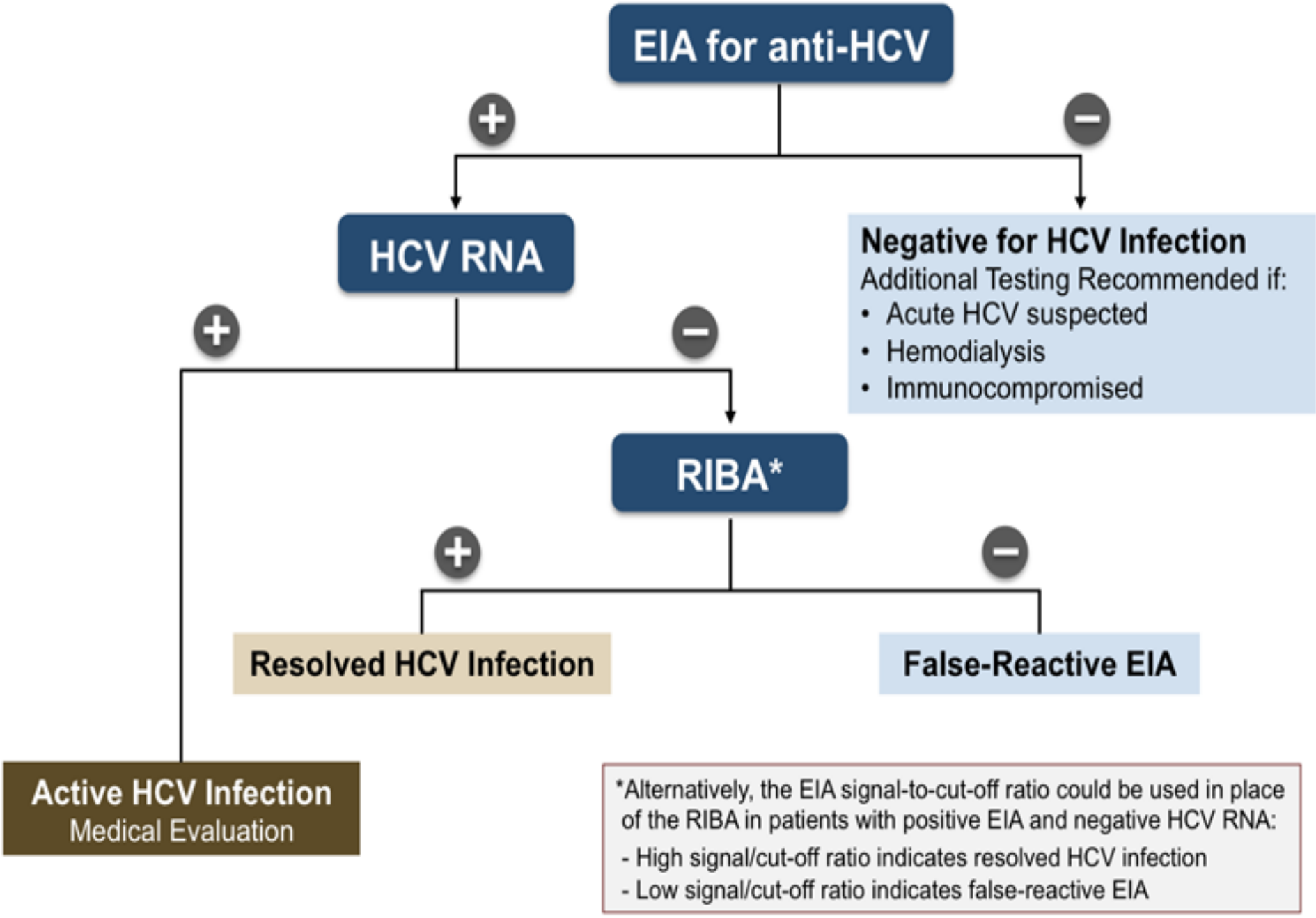


Figure adapted from: the Centers for Disease Control and Prevention.

Laboratory Diagnosis

- **HCV** infection is diagnosed by detecting antibodies by **ELIZA** to **HCV** .
- The test does not distinguish between **IgM** and **IgG** and does not distinguish between an acute, chronic or resolved infection.
- If the result of **ELIZA** antibody test is positive , a **polymerase chain reaction(PCR)** – based test that detect the presence of viral **RNA (viral load)** in the serum should be performed to determine whether active disease exists.
- A chronic infection is characterized by **elevated transaminase level , a positive ELIZA antibody test, and detectable viral RNA for at least 6months.**

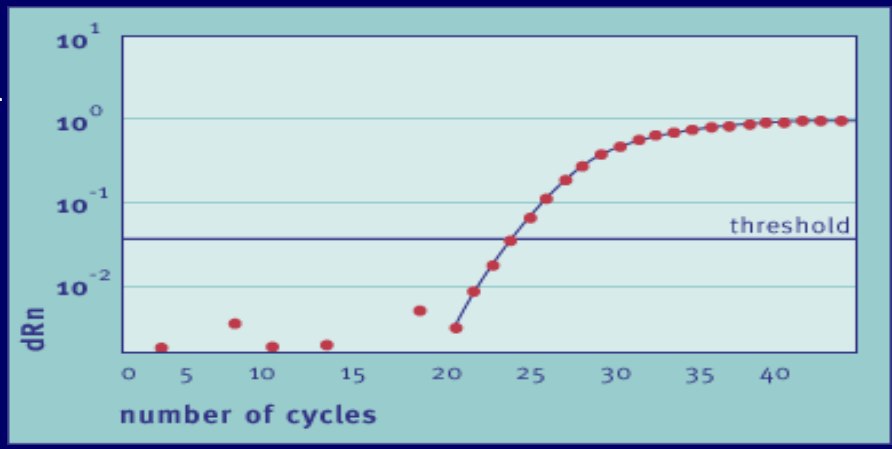

EIA for anti-HCV
+
−
HCV RNA
Negative for HCV Infection
Additional Testing Recommended if:
• Acute HCV suspected
• Hemodialysis
• Immunocompromised
+
−
RIBA*
+
−
Resolved HCV Infection
False-Reactive EIA
Active HCV Infection
Medical Evaluation
*Alternatively, the EIA signal-to-cut-off ratio could be 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

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 .**

2- **HCV-RNA in the blood using PCR.**



Treatment of hepatitis C infection

- **The currently used treatment is the combined therapy using: ******** Pegylated alpha interferon and 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 &PEG-INTERFERON , 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.

Thank you for your attention !