

# **Training workshop on screening, diagnosis and treatment of hepatitis B and C**

# **Session 7**

## **Natural history of hepatitis B virus infection**

## Learning objectives

At the end of this session, participants should understand the following:

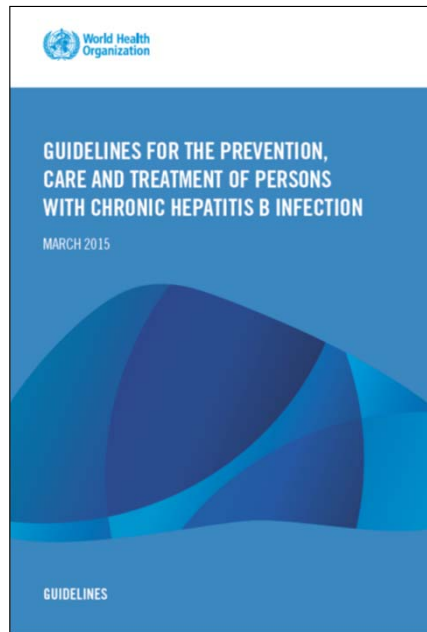
- Natural history of acute and chronic hepatitis B virus infection
- Various phases in the natural history of chronic HBV infection
- Identify the phase of hepatitis B infection in individual patients



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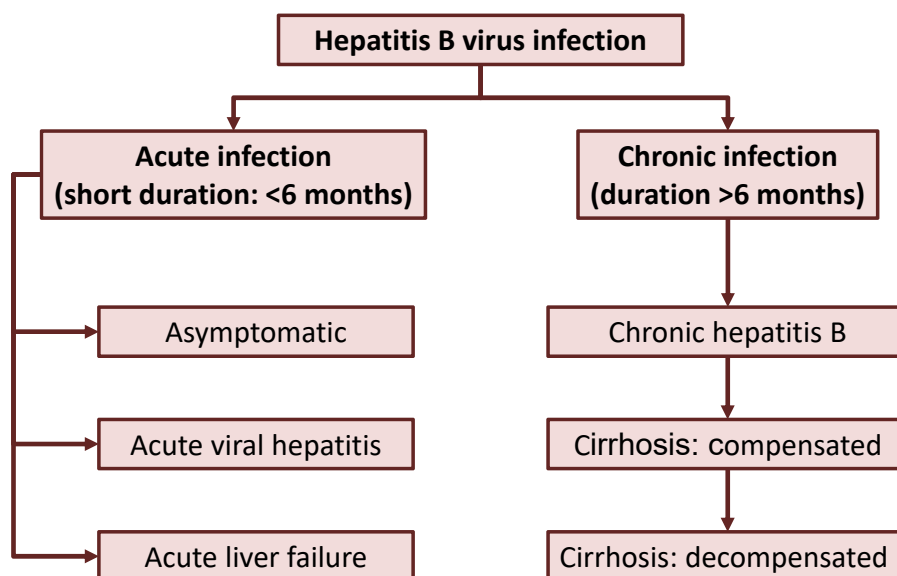
- Natural history of acute and chronic hepatitis B virus infection
- Various phases in the natural history of chronic HBV infection
- Identify the phase of hepatitis B infection in individual patients

# WHO guidelines



This module is based on the WHO HBV guidelines 2015.

## Consequences of hepatitis B virus infection



Once HBV infection is established in a host, the clinical illness may take one of the two possible courses:

First, acute infection, and second, chronic infection.

The probability of developing acute or chronic infection is primarily determined by the age of the host at the time of infection (already discussed).

Acute infection is characterized by marked elevation of serum levels of liver enzymes; these patients clear the virus in 6 months' time.

Chronic infection remains asymptomatic and patients fail to clear the virus. A person with acute HBV infection may remain asymptomatic or develop features of acute viral hepatitis or progress to acute liver failure.

In a person with chronic HBV infection, the liver is constantly exposed to virus-induced injury. After decades of virus-induced liver injury followed by natural healing with fibrosis, the condition may progress to liver cirrhosis.

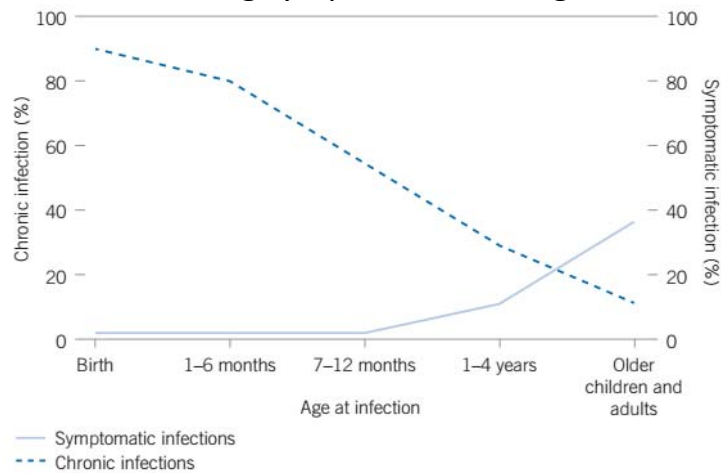
If cirrhosis is left unchecked for a long time, patients may develop complications of cirrhosis such as ascites, variceal bleed and hepatic encephalopathy (called decompensation).

## Outcome of HBV infection: acute vs chronic

**Outcome depends largely on age at the time of infection**

Younger the age at infection: greater the risk of chronic infection

Lower the risk of being symptomatic during the initial phase



The natural history of HBV infection depends on the age of the host at the time of infection.

There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host.

Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. Up till the age of 5 years, about 20% develop chronic infection. After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis and clear the virus in 6 months' time.

## Acute versus chronic hepatitis B

From a public health viewpoint:

- We are worried primarily about chronic hepatitis B, because
    - it causes long-term morbidity and early death
    - it is a reservoir for transmission of HBV
  - Acute hepatitis B is not a public health concern
    - causes a short-lasting illness, with loss of work-days
    - but no long-term morbidity and very little excess mortality
    - unlikely to be responsible for transmission of HBV
- So HBV infection acquired during childhood is the primary concern and focus from the public health viewpoint



From a public health perspective, chronic hepatitis B is more important than acute hepatitis B because of several reasons:

- It causes long-term morbidity and early death.
- It acts as a reservoir for HBV transmission to a susceptible host .

In contrast, acute hepatitis B causes a short-lasting illness and poses limited medical disability, mortality and financial burden.

Further, acute hepatitis B is unlikely to be responsible for transmission of HBV.

But ongoing cases of acute hepatitis B among adults indicates that measures to prevent the spread of HBV are inadequate and more efforts for prevention are needed.

# Acute hepatitis and acute liver failure



A small proportion of those with acute hepatitis may progress to develop acute liver failure.

Hence, we need to know the difference between the two conditions.



## Acute hepatitis (for all hepatitis viruses)

- Incubation period                      HBV: 6 weeks to 6 months  
(different for different viruses)
- Three phases of illness
  - Prodrome                              Malaise, fatigue, low-grade fever  
nausea, vomiting, aversion to food,  
mild itching, joint/muscle pain  
lasting a few days
  - Icteric phase                          Dark urine, yellow eyes, light-coloured  
stools  
Prodromal symptoms improve;  
last a few days to weeks (usually <6 wks)
  - Convalescence                      Gradual recovery is the rule



Following exposure to HBV, a susceptible host develops acute hepatitis after an incubation period of 6 weeks to 6 months.

The entire illness of acute hepatitis B sequentially passes through three phases, namely prodromal phase, icteric phase and convalescence phase.

The prodromal phase is characterized by **MARKED LOSS OF APPETITE**, and other flu-like symptoms such as low-grade fever, nausea and vomiting, and lasts for a few days.

Once the prodromal symptoms start subsiding, the patient develop yellow discoloration of the eyes and urine (icteric phase). This phase usually lasts for a few weeks, usually less than 6 weeks. During this phase, serum levels of liver enzymes are extremely high, usually more than 20–30 times the upper limit of normal.

In a period of 1–2 weeks, the icteric phase reaches its peak, which is soon followed by recovery of all the symptoms and regaining of natural well-being.

Almost complete recovery is the rule.

## Acute liver failure (due to any virus)

- Features similar to those of acute hepatitis to begin with
- But more severe liver damage and leads to serious clinical state
- Altered behaviour and consciousness (encephalopathy)
- Bleeding tendency (poor coagulation)
- Small liver (hepatic atrophy)
- Brain oedema
- High risk of death without liver transplantation



A very small proportion of those with acute hepatitis B may worsen and progress to acute liver failure, which is a life-threatening condition.

The illness in a patient with acute liver failure starts with features similar to those of acute hepatitis though these patients very rapidly progress to liver failure, which is characterized by altered behaviour and altered consciousness (hepatic encephalopathy), bleeding tendency such as ecchymosis, and features of raised intracranial hypertension.

Acute liver failure is a life-threatening condition. It needs to be managed in an intensive care unit, and carries about a 50% risk of death without liver transplantation.

## Acute HBV infection and acute liver failure

	Acute viral hepatitis (AVH-B)	Acute liver failure (ALF-B)
Prodromal symptoms	Present	
Sudden jaundice	Present	
AST/ALT	Markedly elevated	
IgM anti-HBc	Positive	
Encephalopathy	Absent	Present
Coagulation	Near normal	Markedly deranged
Liver size	Slightly large	Small

This table summarizes the distinguishing features between acute hepatitis and acute liver failure.

The prodromal symptoms are the same in both – jaundice, elevation of AST/ALT, and positive IgM anti-HBc, acute phase reactive immunoglobulin.

The differences are the presence of encephalopathy, marked derangement in coagulation and small size of the liver in acute liver failure.

## HBV serological markers

Test	Clinical interpretation
<b>HBsAg (hepatitis B surface antigen)</b>	<b>Hallmark of infection</b> Positive in the early phase of acute infection and persists in chronic infection Quantification of HBsAg is a potential alternative marker of viraemia and it is also used to monitor the response to antiviral treatment
<b>Anti-HBc IgM (hepatitis B core antibody)</b>	IgM subclass of anti-HBc and observed during <b>acute infection</b> (used to differentiate between acute and chronic HBV infection) Might become positive during severe exacerbation of chronic infection
<b>Anti-HBc (total)</b>	Develops around 3 months after infection (most constant marker of infection) Total anti-HBc (IgM, IgA and IgG) indicates <b>resolved infection</b>
<b>HBeAg (hepatitis B e antigen)</b>	Viral protein usually associated with <b>high viral load</b> and <b>high infectivity</b>
<b>Anti-HBe (hepatitis B e antibody)</b>	Antibody to HBeAg usually indicates decreasing HBV DNA But present in the immune-control and immune-escape phases
<b>Anti-HBs (hepatitis B surface antibody)</b>	Neutralizing antibody that confers protection from infection Recovery from acute infection (with anti-HBc IgG) Immunity from vaccination

Here we introduce the various serological markers of HBV infection, which will help us to understand the various phases of acute and chronic hepatitis B.

HBsAg (hepatitis B surface antigen) is the hallmark of HBV infection.

Anti-HBc IgM (hepatitis B core antibody) is observed during acute infection.

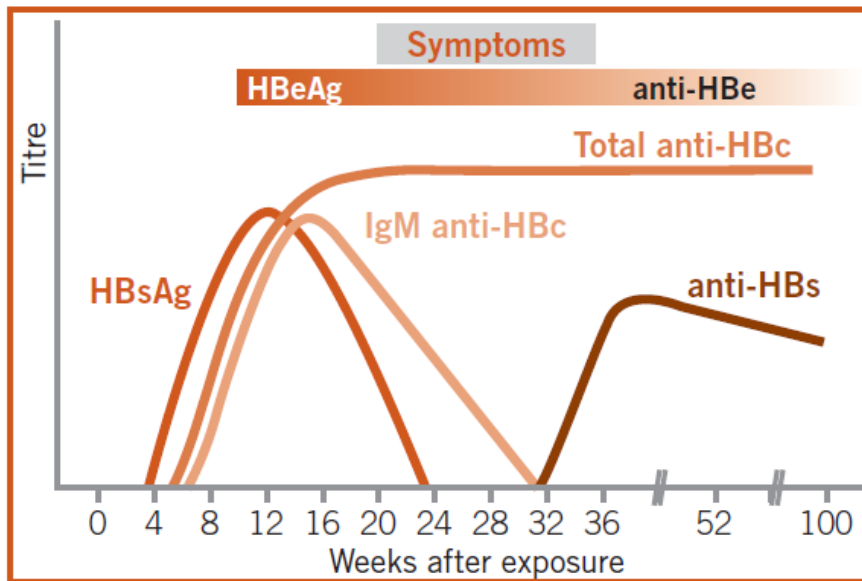
Anti-HBc (total antibody against HBV core antigen) indicates the presence of IgM and/or IgG against the core antigen. A positive total anti-HBc with negative anti-HBc IgM antibodies indicates resolved infection.

HBeAg (hepatitis B envelope antigen) is viral protein associated usually with a high viral load and high infectivity.

Anti-HBe (antibody to HBeAg) usually indicates decreasing HBV DNA.

Anti-HBs is a neutralizing antibody.

## Serological pattern of acute HBV infection



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This slide shows the temporal pattern of various serological markers seen in acute HBV infection.

First, HBsAg appears 2–10 weeks after infection. In the next 1–2 weeks, total anti-HBc and IgM anti-HBc increase and total anti-HBc continues to be positive.

HBsAg and IgM anti-HBc disappear within 6 months and anti-HBs appears.

In most individuals, anti-HBs persists for life and provides long-term immunity

# Chronic hepatitis B

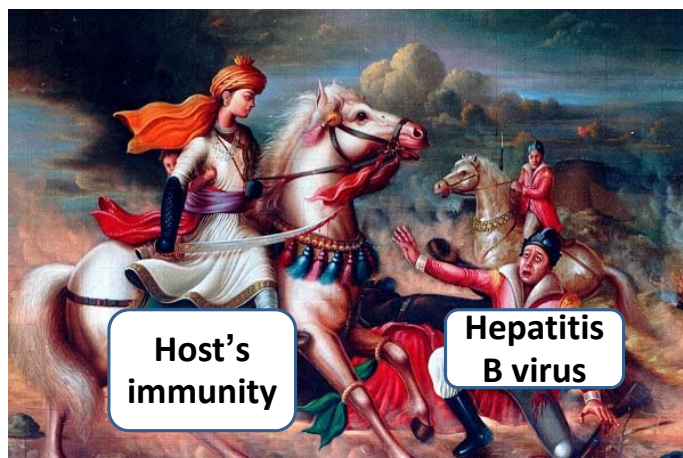


Hepatitis B can cause hepatocellular carcinoma (HCC) even without developing cirrhosis as it is a DNA virus and is integrated into the human genome. It can cause HCC due to replication and mutant types.

HCV is an RNA virus and lies in the cytoplasm only and can be eradicated as it is not integrated into the genome of the host.

Next, we will move to chronic hepatitis.

## Natural history of hepatitis B: another view



A duel between HBV and host's immune response

Depends on who has the upper hand

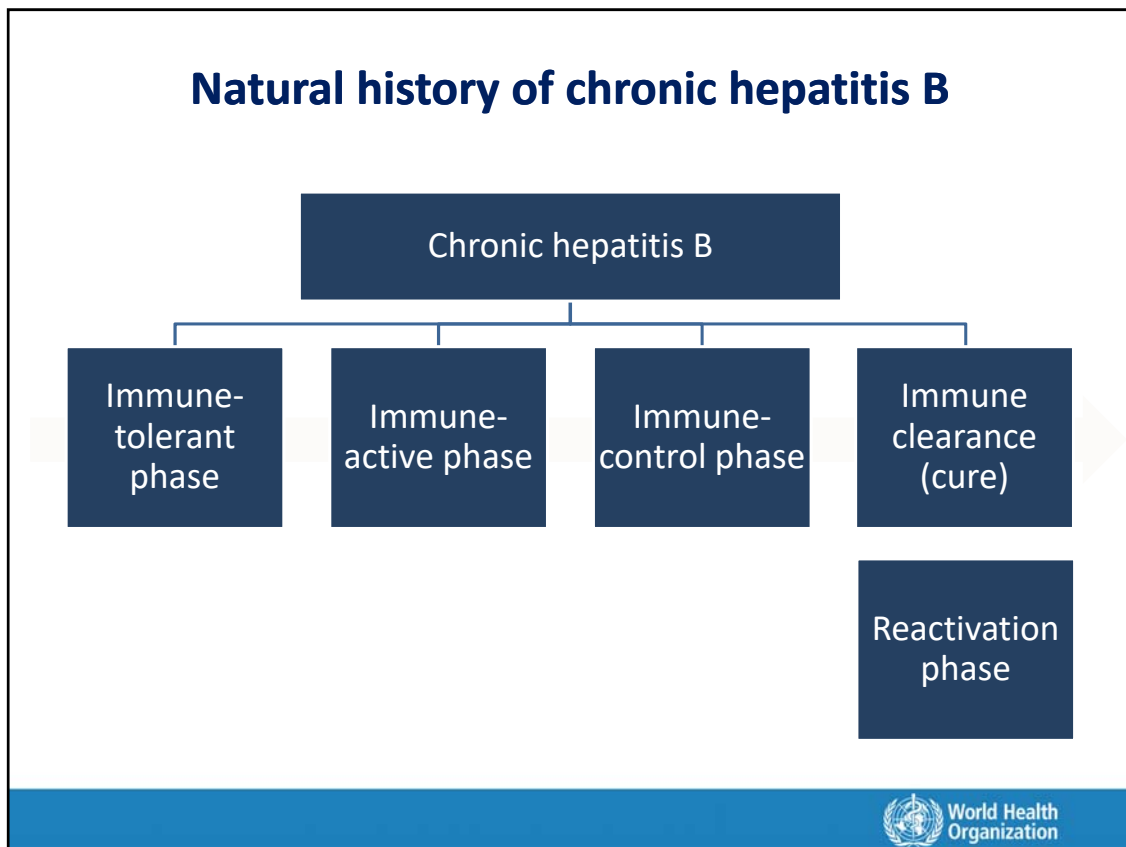


Hepatitis B virus is not a cytotoxic virus, which means that the virus itself does not cause any injury or harm to the hepatocyte. The injury to the infected person is primarily mediated by the host's immune system.

In an attempt to clear the virus, the host's immune cells and cytokines kill the hepatocyte. Hence, in an infected person, liver injury is actually a self-inflicted injury (by the immune system).

The natural history of hepatitis B is a duel between HBV and the host's immune response. If the host immune system is tolerant to the virus (immune-tolerant phase in children), there is no injury to the host despite a high viral load. In contrast, if the host immune system fights against the virus, the host will have liver injury though the viral load will be lower.

- The healing process, after cell injury, is primarily in the form of cellular regeneration and fibrosis.
- The repeated cycles of injury, healing and fibrosis ultimately result in liver cirrhosis.



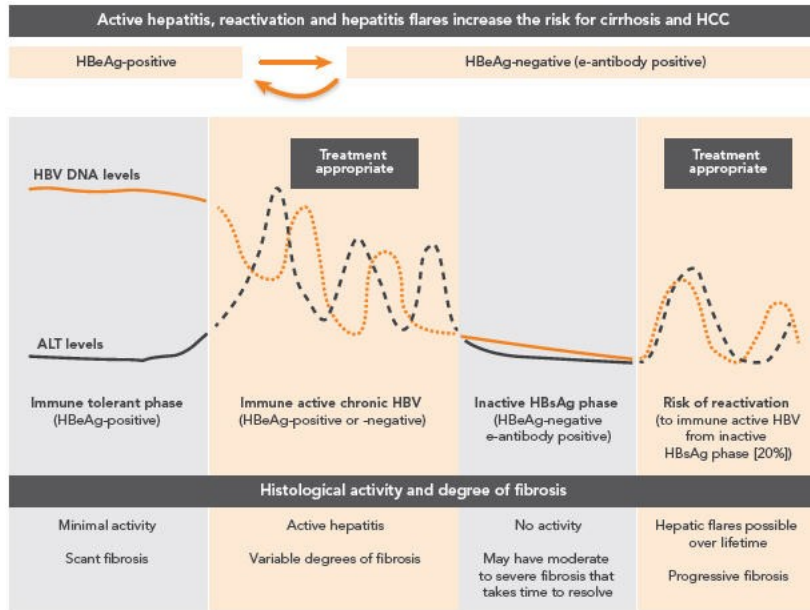
The natural history of chronic hepatitis B infection can be divided into 4 phases: immune-tolerant phase, immune-active phase, immune-control phase, and immune clearance. It is not uncommon to see a backward shift in phase and reactivation of disease from the immune clearance phase.

The sequence of all these four phases is typically seen in children are infected through perinatal transmission and are followed at regular intervals from birth.

Among adults, on first detection of HBV infection, the infected person might be in any one of the four phases. The priority task will be to evaluate and follow the person for 6–12 months to determine which phase the person is in.



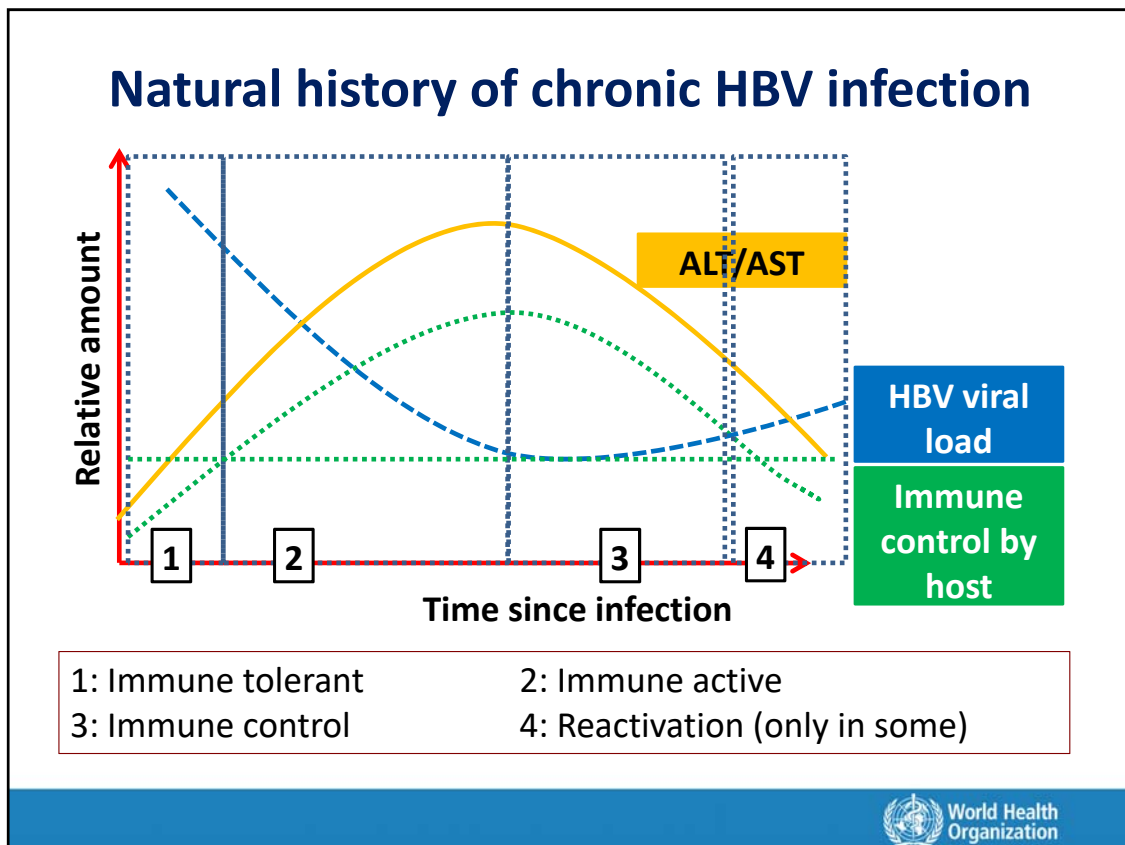
# Natural history of chronic HBV infection



**Discussed further in the next talk**



The natural history of chronic HBV infection is complex. It comprises the immune-tolerant phase, immune-active chronic phase, inactive HBsAg phase and reactivation. The four phases differ from each other in certain parameters such as serum ALT level, HBeAg status and viral load. This is discussed in the next talk.



This slide shows the concept of the natural history of chronic HBV infection.

The blue line shows the viral load. Yellow line is the levels of AST/ALT during hepatitis. Green indicates the host immune response.

In the immune-tolerant phase, the host immunity against HBV is weak. So, the viral load is high. AST/ALT is low because there is no attack on the infected hepatocytes by the weak host immune system.

In the immune-active phase, host immunity become strong and infected hepatocytes are attacked, and AST/ALT increases. Thus, viral load decreases.

In the immune-control phase, host immunity becomes stronger and can control the viral load.

In the reactivation phase, in case of a weakened host immunity caused by drugs such as immunosuppressive agents, the viral load increases.

## Serological markers in chronic HBV infection

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT (SGPT)				
HBV DNA				
HBeAg				
Anti-HBe				
<b>Immune system response to control the HBV virus</b>				
Need for treatment				

We will summarize the serological markers in chronic HBV infection.  
Immune-tolerant, immune-active, immune-clearance and reactivation phases.

## Serological markers in chronic HBV infection

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT(SGPT)				
HBV DNA				
HBeAg				
Anti-HBe				
<b>Immune system response to control the HBV virus</b>	<b>Weak</b>	<b>Strong</b>	<b>Strongest</b>	<b>Weak</b>
Need for treatment				

First, let's think of the body's immune system response to control the hepatitis B virus. In the immune-tolerant phase, immunity is weak; in the immune-active phase it is strong; in the immune-clearance phase strongest, and in the reactivation phase it is weak.

## Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT(SGPT)	Low			
HBV DNA	High			
HBeAg	+			
Anti-HBe	-			
<b>Immune system response to control the HBV virus</b>	<b>Weak</b>	<b>Strong</b>	<b>Strongest</b>	<b>Weak</b>
Need for treatment	<b>No</b>			

In the immune-tolerant phase, because of weak host immune response, ALT is low. HBV DNA is high. HBeAg is positive and anti-HBe is negative, reflecting a high viral load. This phase does not need treatment.

Treatment is not needed as we do not need to clear the virus – however, it is important to check for liver injury.

If there is no liver injury (evidenced by liver function tests), no treatment is required.

Other points weighing the balance and risks of starting antiviral drugs for treatment early, is that, if there is treatment interruption and development of drug resistance, the antiviral drug may not be available for the individual in the future.

## Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT (SGPT)	Low	High		
HBV DNA	High	Moderate		
HBeAg	+	+/-		
Anti-HBe	-	-/+		
<b>Immune system response to control the HBV virus</b>	<b>Weak</b>	<b>Strong</b>	<b>Strongest</b>	<b>Weak</b>
Need for treatment	<b>No</b>	<b>Yes</b>		

In the immune-active phase, host immunity is strong, ALT is high and HBV DNA viral load is moderate. HBeAg and anti-HBe are positive or negative.

In this phase, antiviral treatment is needed because liver injury is ongoing.

In this phase as well, the individual can progress directly to developing hepatocellular carcinoma (HCC).

## Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT (SGPT)	Low	High	Moderate	
HBV DNA	High	Moderate	Low	
HBeAg	+	+/-	-/+	
Anti-HBe	-	-/+	+/-	
<b>Immune system response to control the HBV virus</b>	<b>Weak</b>	<b>Strong</b>	<b>Strongest</b>	<b>Weak</b>
Need for treatment	<b>No</b>	<b>Yes</b>	<b>No</b>	

In the immune-clearance phase, host immune response is the strongest. ALT is moderately increased. HBV DNA is controlled and low. Treatment is not needed during this phase.

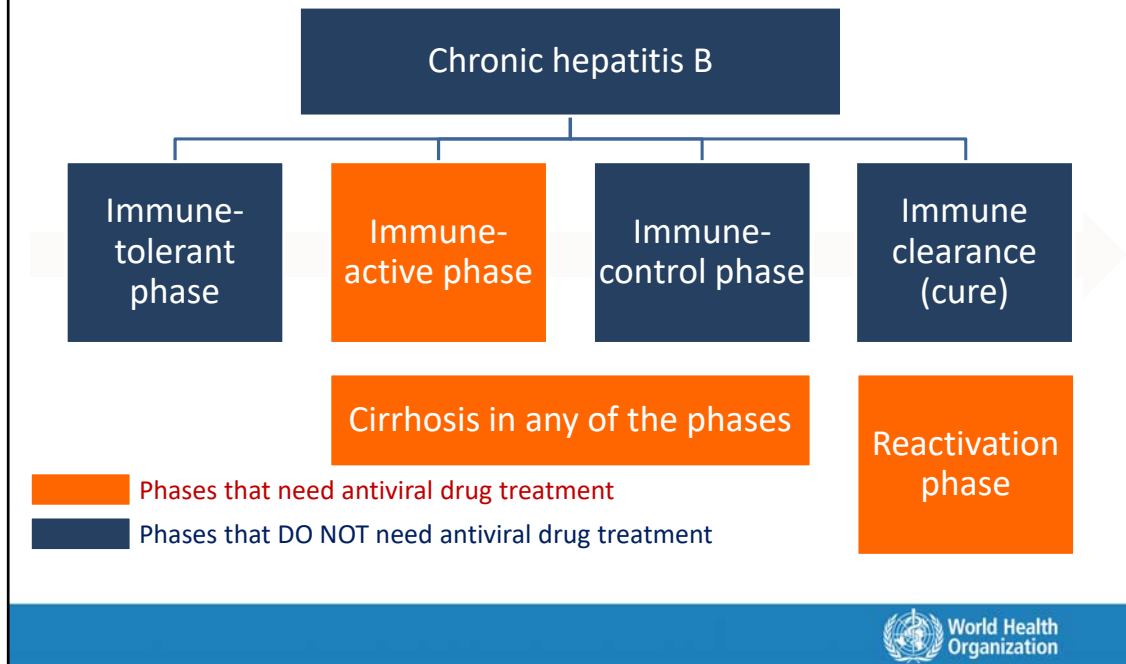
## Serological markers in chronic HBV

	Immune phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT/SGPT	Low	High	Moderate	Low/mod
HBV DNA	High	Moderate	Low	Low/mod
HBeAg	+	+/-	-/+	-/+
Anti-HBe	-	-/+	+/-	+/-
<b>Anti-HBV immune control</b>	<b>Weak</b>	<b>Strong</b>	<b>Strongest</b>	<b>Weak</b>
Need for treatment	<b>No</b>	<b>Yes</b>	<b>No</b>	<b>Yes</b>

Reactivation is a specific phase. The markers are varied.  
Antiviral treatment is required during this phase.



## Natural history of chronic hepatitis B

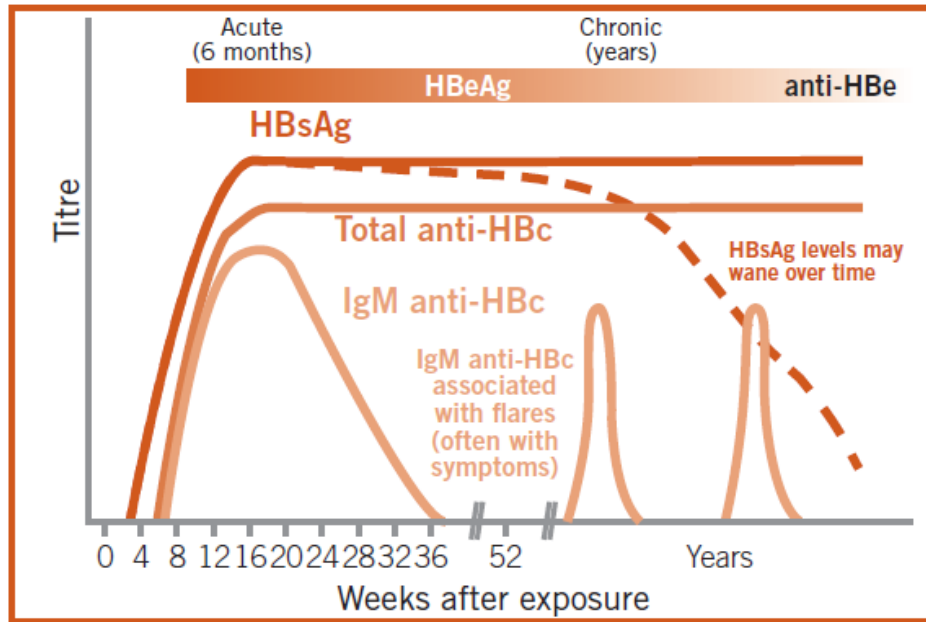


Individuals assessed to be in the ORANGE phases of chronic hepatitis B infection need initiation of treatment.

These are:

- immune-active phase,
- cirrhosis in any of the phases, and
- the reactivation phase.

## Serological pattern of chronic HBV infection



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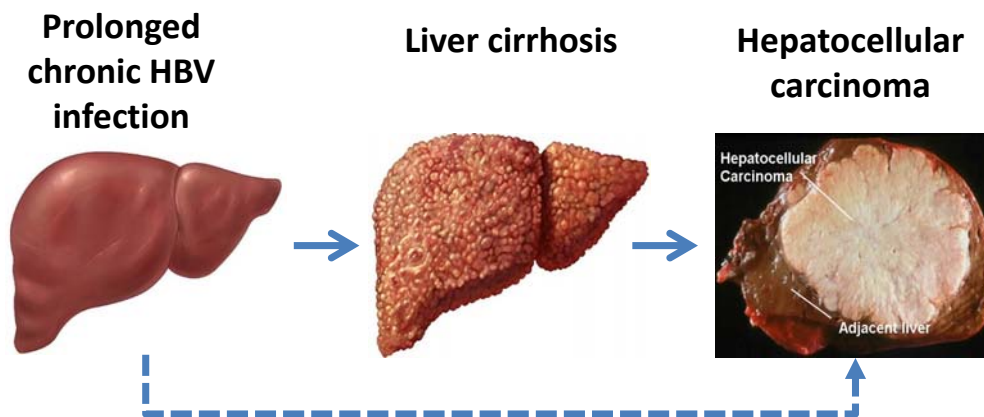
This slide shows the serological pattern of chronic HBV infection.

Basically, HBsAg and anti-HBc continue to be positive and HBeAg gradually decreases and anti-HBe becomes positive, which is a minor seroconversion.

In some cases, IgM anti-HBc becomes positive at a low level and is associated with a hepatitis flare.

HBsAg levels may wane over time in older age groups.

## Natural history of chronic hepatitis



This slide shows the natural history of chronic hepatitis.

Prolonged HBV chronic infection may result in cirrhosis and hepatocellular carcinoma (liver cancer).

In the case of HBV chronic infection, hepatocellular carcinoma can develop at any time, even in the absence of cirrhosis (i.e. the liver is not cirrhotic)

This is one reason why, regular ultrasound scan screening for liver masses among people living with chronic infection is recommended.

# Cirrhosis

An advanced stage of liver disease characterized by

- extensive hepatic fibrosis
- alteration of liver architecture
- disrupted hepatic circulation
- liver nodularity

Cirrhosis is defined as,

- extensive hepatic fibrosis
- alteration of liver architecture
- disrupted hepatic circulation
- liver nodularity

## Compensated versus decompensated cirrhosis

- A person with cirrhosis initially continues to function normally because of the large reserve capacity in liver function
- At some stage, this “compensation” fails, and cirrhosis starts to affect body function and threatens survival: “decompensation”
- Decompensated cirrhosis is characterized by
  - features of portal hypertension
  - plus
  - features of liver failure



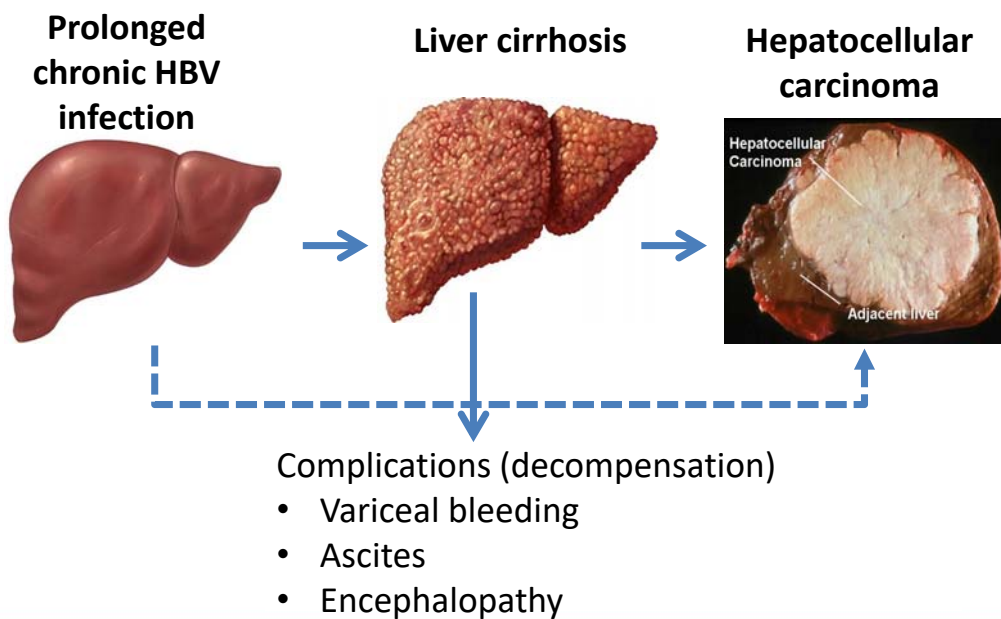
There are 2 clinical states of cirrhosis: compensated and decompensated.

A person with cirrhosis initially continues to function normally because of the large reserve capacity in liver function

At some stage, this “compensation” fails, and cirrhosis starts to affect body function and threatens survival: “decompensation”

Decompensated cirrhosis is characterized by features of portal hypertension plus features of liver failure.

## Natural history of chronic hepatitis



So, cirrhosis with complications such as variceal bleeding, ascites and encephalopathy is defined as “decompensated”.

## Decompensated cirrhosis

Decompensation: presence of one of the following features:

- a) Ascites
- b) Hepatic encephalopathy
- c) Total bilirubin  $>2.5 \times \text{ULN}^*$  and prolonged prothrombin time ( $>3$  second increase or  $\text{INR}^{**} >1.5$ )
- d) Variceal bleed

\* Upper limit of normal

\*\* International normalized ratio (INR)



Decompensation is defined by the presence of one of the following features:

- a) Ascites
- b) Hepatic encephalopathy
- c) Total bilirubin  $>2.5 \times \text{ULN}^*$  + prolonged prothrombin time ( $>3$  second increase or  $\text{INR}^{**} >1.5$ )
- d) Variceal bleed

## Summary

- HBV infection in infants or small children (<5 years) has a high risk of progression to chronic infection.
- HBV infection in older children or adults results in acute hepatitis with spontaneous clearance in 90–95%.
- Chronic HBV infection passes through several stages, with progression to cirrhosis and/or liver cancer in a proportion of infected persons.
- Patients with cirrhosis can develop decompensation and liver-related death.
- Liver cancer can occur even without cirrhosis.
- Among persons with chronic HBV infection, those with elevated ALT and high HBV DNA need drug treatment. Those with cirrhosis will also need treatment.



In summary,

HBV infection in infants or small children (<5 years) has a high risk of progression to chronic infection.

HBV infection in older children or adults results in acute hepatitis with spontaneous clearance in 90–95%.

Chronic HBV infection passes through several stages, with progression to cirrhosis and/or liver cancer in a proportion of infected persons.

Patients with cirrhosis can develop decompensation and liver-related death.

Liver cancer can occur even without cirrhosis.

Among persons with chronic HBV infection, only those with elevated ALT and high HBV DNA need drug treatment. Those with cirrhosis will also need treatment.