

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

Session 10

Clinical management of
hepatitis B virus (HBV) infection

Learning objectives

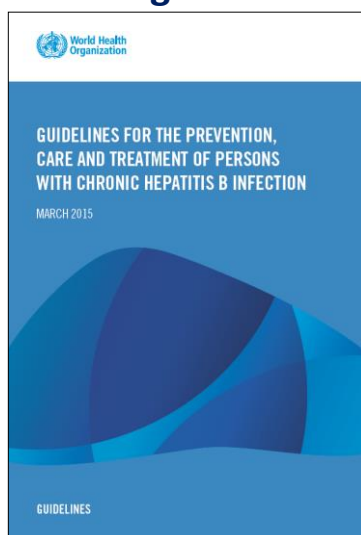
At the end of this session, participants will understand and know:

- clinical and laboratory assessment of HBV-infected persons
- antiviral drugs available for the treatment of HBV infection
- treatment and follow-up strategies recommended for HBV
- identify the appropriate treatment strategy for a particular patient with HBV infection.



At the end of this session, we shall be able to assess a patient by clinical examination and laboratory investigation. We shall also be able to plan the appropriate management of the patient.

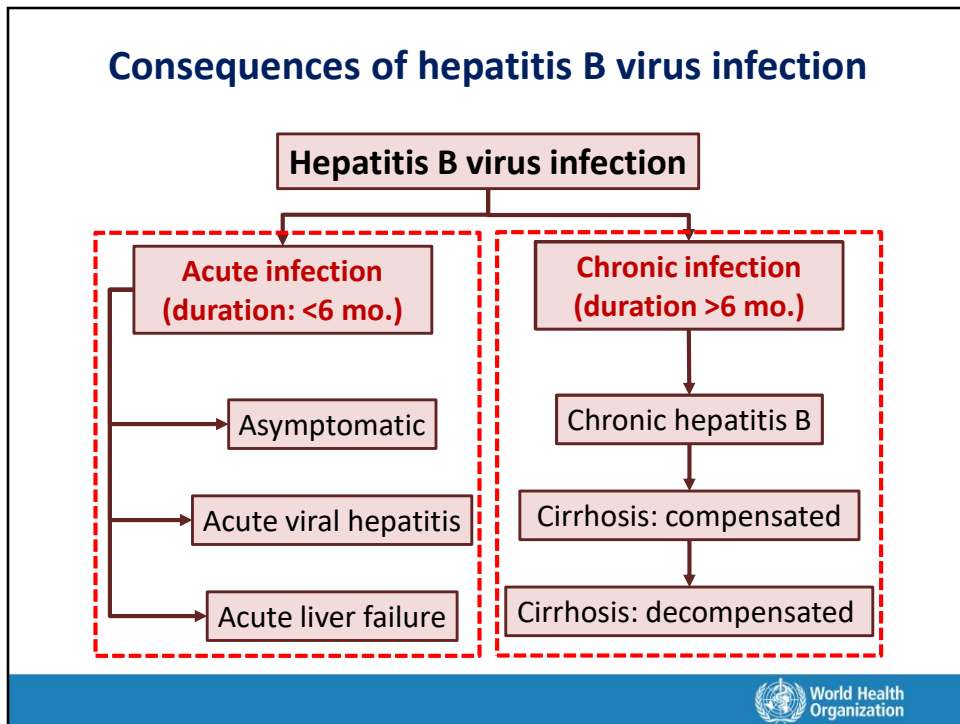
WHO guidelines



Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015)



This session is based on the WHO HBV guidelines launched in 2015.



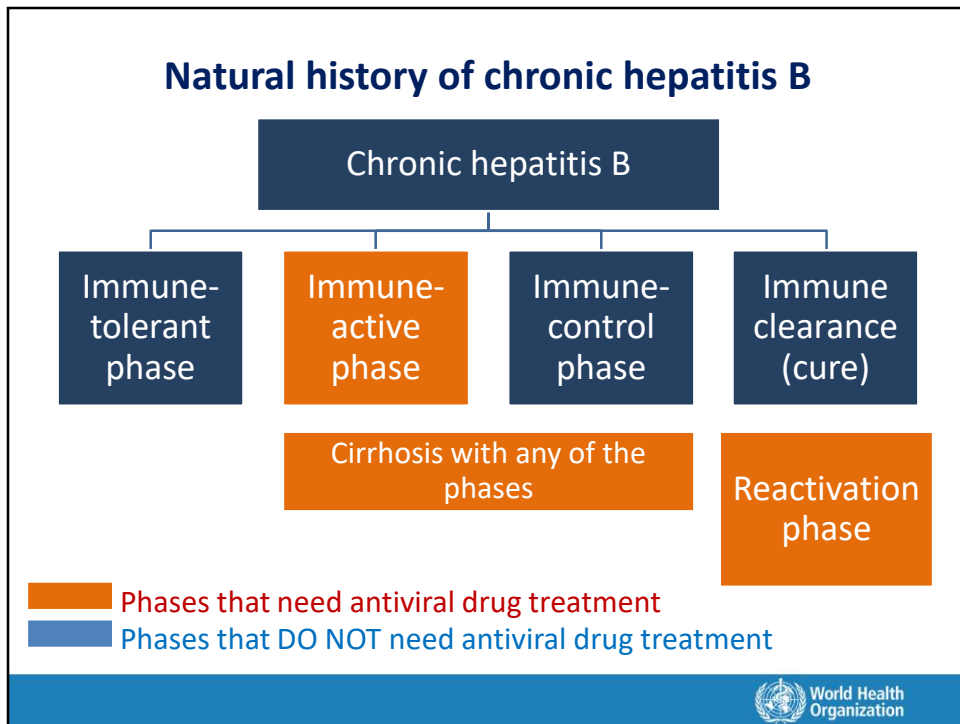
Once HBV infection is established in a host, the clinical illness may take one of two possible courses: first, acute infection and second, chronic infection.

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 six months of time. Chronic infection remains asymptomatic and such patients fail to clear the virus.

A person with acute HBV infection may either remain asymptomatic or develop features of acute viral hepatitis or may 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 and natural healing with fibrosis, progression to liver cirrhosis may occur.

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



Our target is chronic HBV infection.

The natural history of chronic hepatitis is shown in this slide.

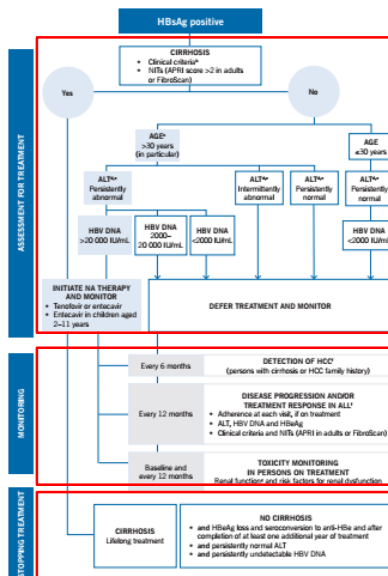
There are basically 4 phases, immune-tolerant phase, immune-active phase, immune-control phase and immune clearance or cure phase.

Another phase is the reactivation phase, which occurs in specific situations.

The orange-coloured phases need antiviral drug treatment: the immune-active phase, cirrhosis and reactivation phase.

The other phases do not need antiviral drug treatment.

WHO guidelines



Assessment for treatment

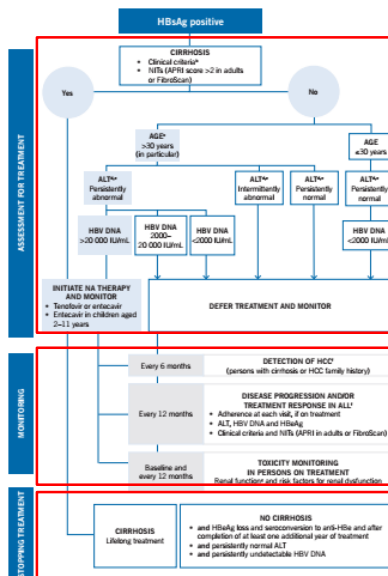
Monitoring

Stopping treatment

This is the algorithm from the WHO HBV guidelines.

It is in three parts – assessment for treatment, monitoring and stopping treatment.

WHO guidelines



Assessment for treatment

Monitoring

Stopping treatment

This is the algorithm from the WHO HBV guidelines.

It is in three parts – assessment for treatment, monitoring and stopping treatment.

Assessment for treatment

- **Host liver injury**
 - Serum alanine aminotransferase (ALT)
Pattern (and not one value)
- **Viral status**
 - HBeAg, anti-HBe antibody
 - **HBV DNA quantitative assay** **IU/mL**
- **Presence/absence of cirrhosis**
 - Compensated cirrhosis
Biopsy, APRI (>2.0)
FIB-4, FibroTest, transient elastography
 - Decompensated cirrhosis
Ascites
Hepatic encephalopathy
Variceal bleeding
Jaundice



Before starting treatment, the person should be evaluated for host liver injury, viral status and presence or absence of cirrhosis.

Host liver injury is assessed with the temporal pattern of serum levels of alanine aminotransferase or ALT.

We need to check the patterns of ALT. Hence, we rely on several values of ALT tested at an interval of 3–4 months. The serum ALT pattern is described as persistently normal, persistently abnormal or intermittently abnormal.

Next, to assess the virus activity, we need to do a HBV DNA quantitative assay. If you cannot do an HBV DNA quantitative assay, you can use HBeAg and anti-HBe antibody.

Finally, we assess for the presence or absence of cirrhosis.

For the assessment of compensated cirrhosis, liver biopsy is the gold standard but invasive. Non-invasive tests, such as APRI, FIB-4, Fibrotest, transient elastography (e.g. FibroScan) are used.

Clinical symptoms such as ascites, hepatic encephalopathy, variceal bleeding and jaundice indicate decompensated cirrhosis.

If the HBV DNA is reported in copies, divide it by 5 get the value in IU.

Summary of WHO Recommendation

HBsAg

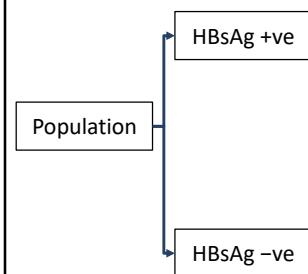
Population



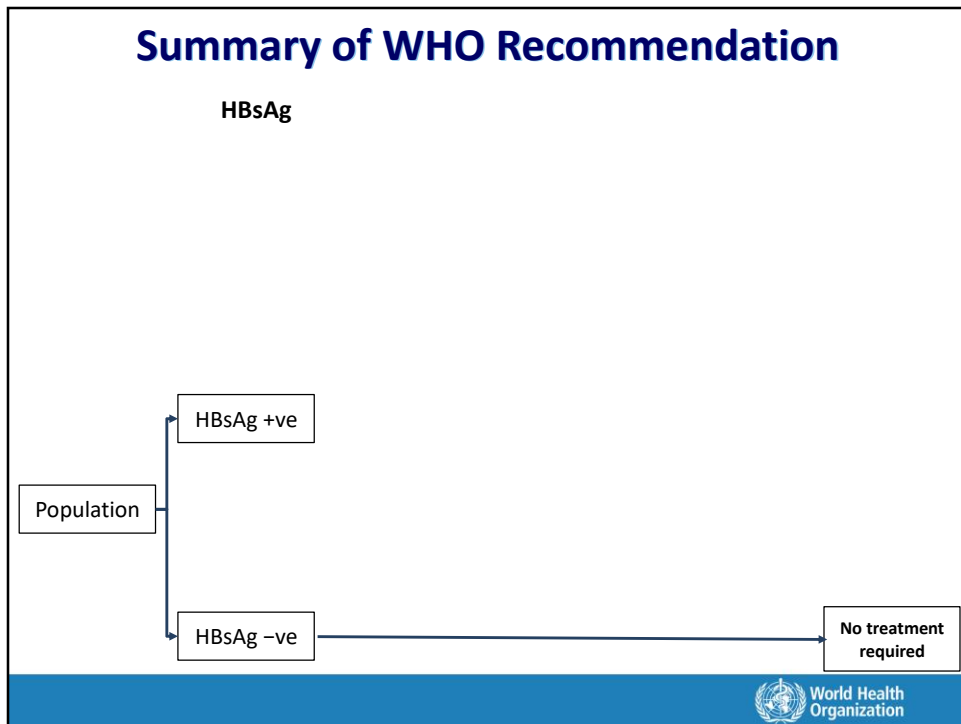
- HBsAg is used as a screening test.

Summary of WHO Recommendation

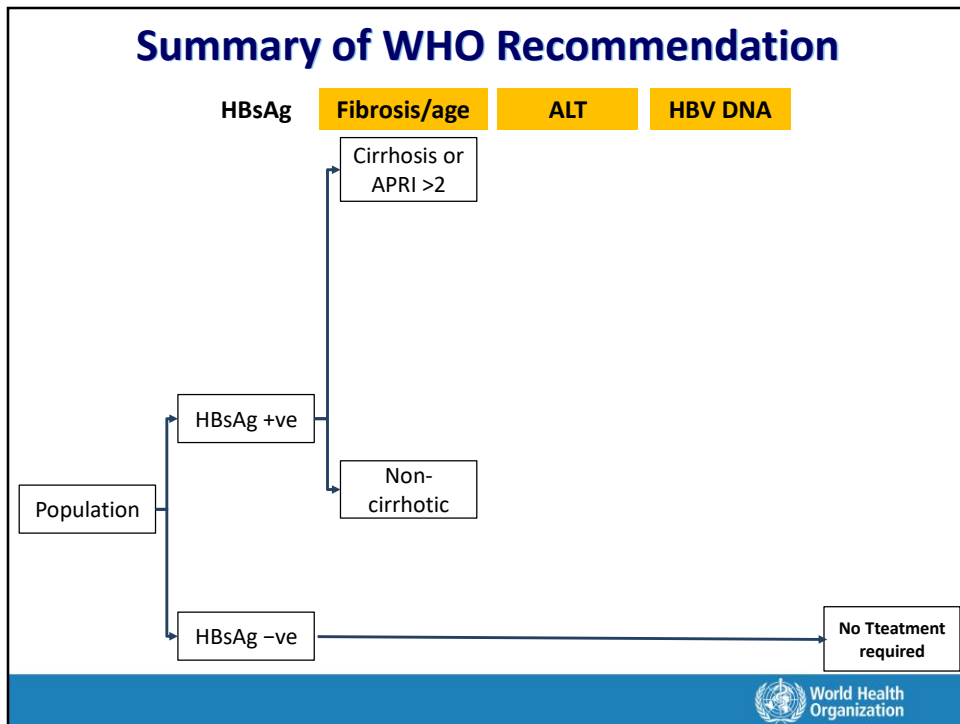
HBsAg



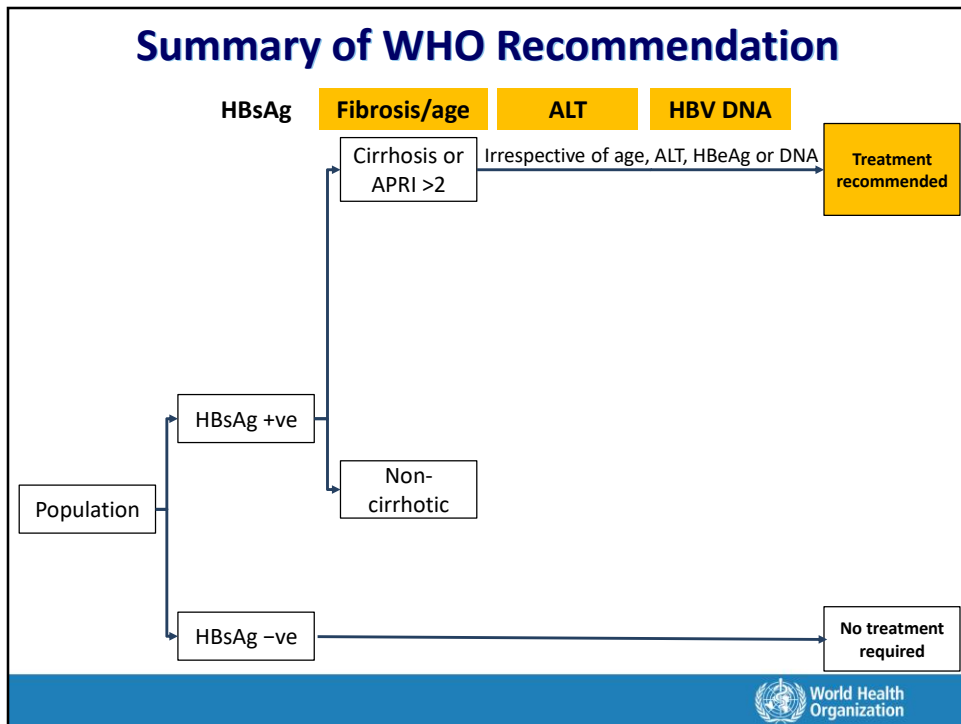
- In case of HBsAg-negative persons, what should you do?



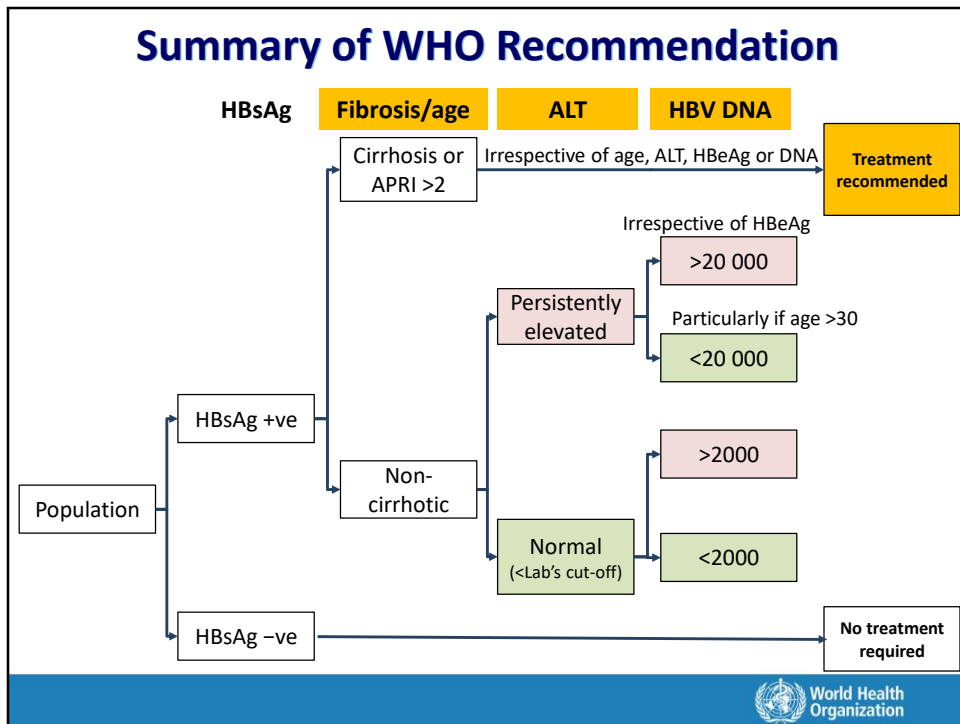
- In the case of an HBsAg-negative person, no treatment is required because there is no infection with HBV.



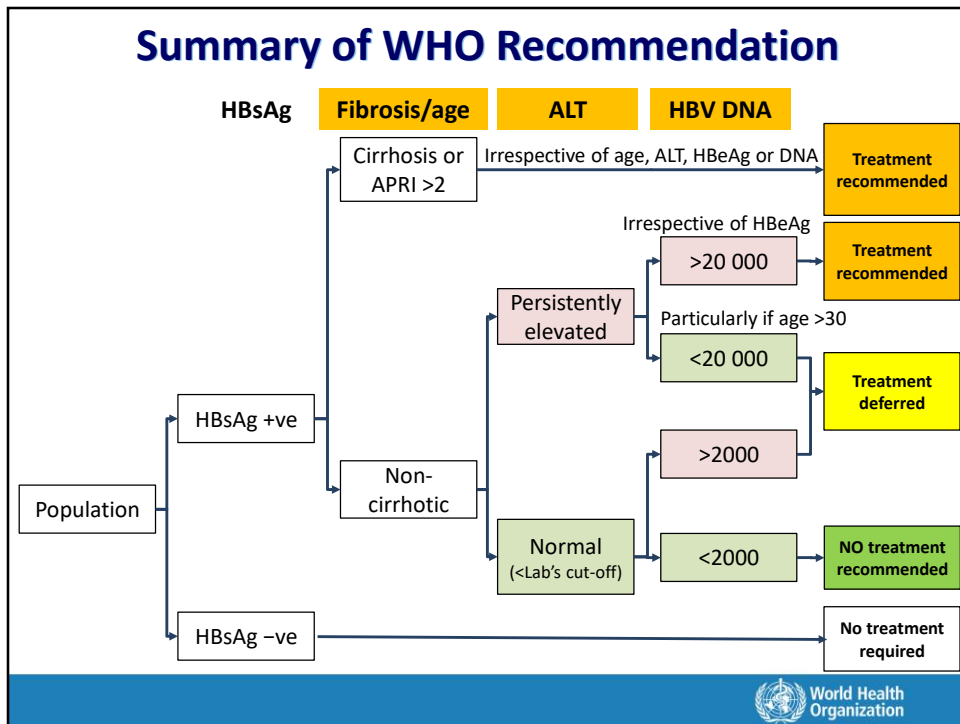
- In case of an HBsAg-positive person, you must assess for the presence or absence of cirrhosis.
- For assessment of cirrhosis, the APRI score is convenient and cirrhosis is present if the score is more than 2.
- Of course, other assessments for cirrhosis also show the presence of cirrhosis.
- What should you do?



- In case of cirrhosis, all infected persons should be treated, irrespective of age, ALT, HBeAg or DNA.



- In case of non-cirrhotic persons, you should assess the pattern of ALT to see if it is persistently elevated or normal.



- In case of a non-cirrhotic person, if the ALT is persistently elevated and HBV DNA is more than 20 000 IU/L, treatment is recommended.
- But if the HBV DNA is less than 20 000 IU/L, treatment is deferred.
- If the ALT is normal and HBV DNA is less than 2000 IU/L, no treatment is recommended.
- If the ALT is normal and HBV DNA is more than 2000 IU/L, treatment is deferred.

What is normal ALT?

- Suggested upper limits of normal (ULN)
 - Men: up to 30 U/L
 - Women: up to 19 U/L
- Note: WHO recommends that the local laboratory's reference range should be used



- What is normal ALT?
- Usually, normal ALT means a value that is lower than the upper limit of normal (ULN).
- For men, it is 30 U/L, for women, 19 U/L.
- Note - WHO recommends that the local laboratory's reference range be used.

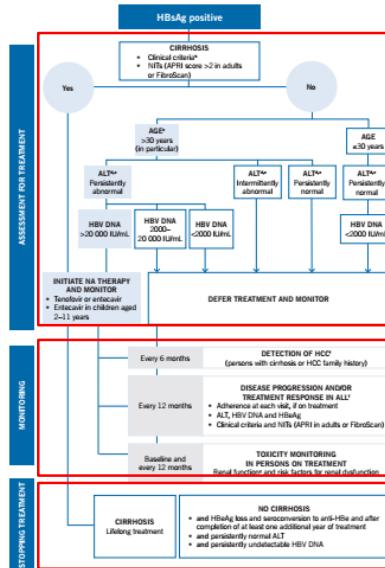
What is a persistently normal/elevated ALT?

- Three ALT determinations below or above the upper limit of normal
- Made at unspecified intervals during a 6–12-month period or at predefined intervals during a 12-month period



- Next, what is a persistently normal or elevated ALT?
- These are usually interpreted as three ALT determinations that are below or above the upper limit of normal.
- The three are measured at unspecified intervals during a 6–12-month period or at predefined intervals during a 12-month period.

WHO guidelines



Assessment for treatment

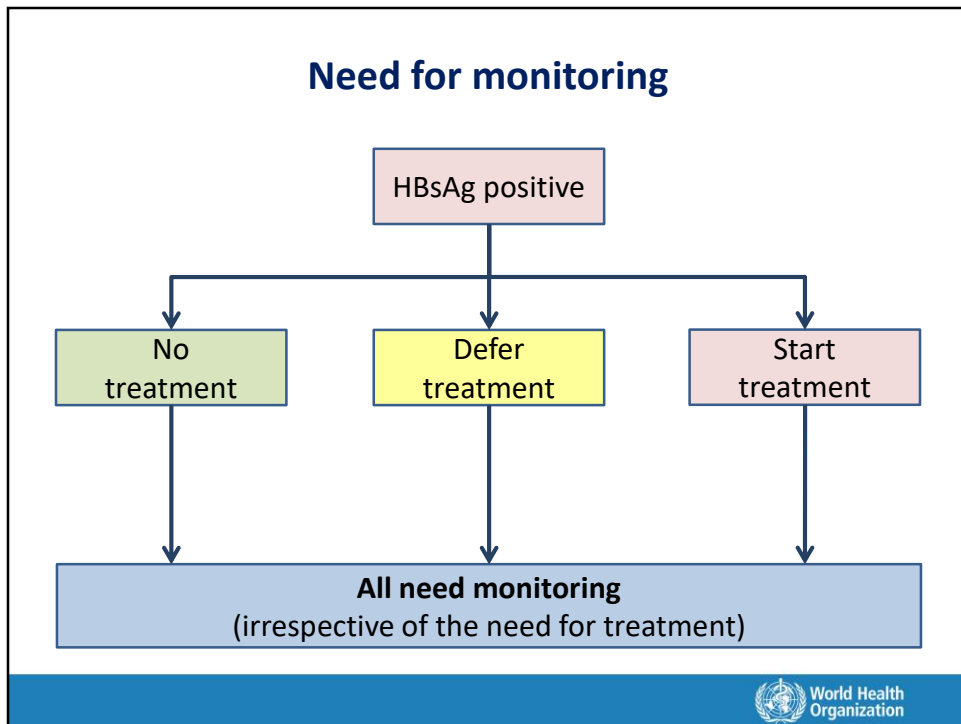
Monitoring

Stopping treatment

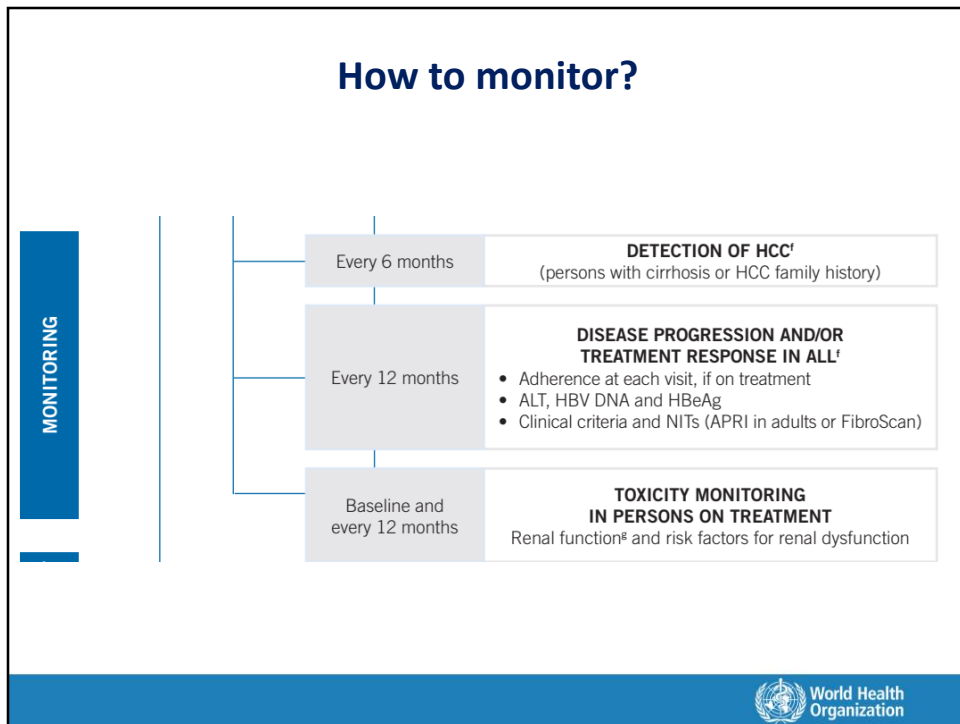
Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) p. xxvi



- Next, we come to monitoring of a person who was initially evaluated.



- All persons who are HBsAg positive need monitoring irrespective of the need for treatment.
- You can easily understand the need for monitoring after starting treatment, that is, to look for efficacy, toxicity and development of cancer.
- In case of deferred treatment or even no treatment, ALT, HBV DNA and onset of cancer should be monitored to avoid missing a change in chronic HBV infection status and disease progression.



- How to monitor?
- In the WHO HBV guidelines, monitoring is divided to three parts, detection of HCC, disease progression and/or treatment response in all, and toxicity monitoring in persons on treatment.

How to monitor?

- **At least annually:**

ALT

HBsAg, HBeAg, HBV DNA level

APRI

Adherence to treatment

Drug adverse events (renal function)

- **More frequent**

- In those who do not clearly meet the criteria for treatment
- Following treatment discontinuation

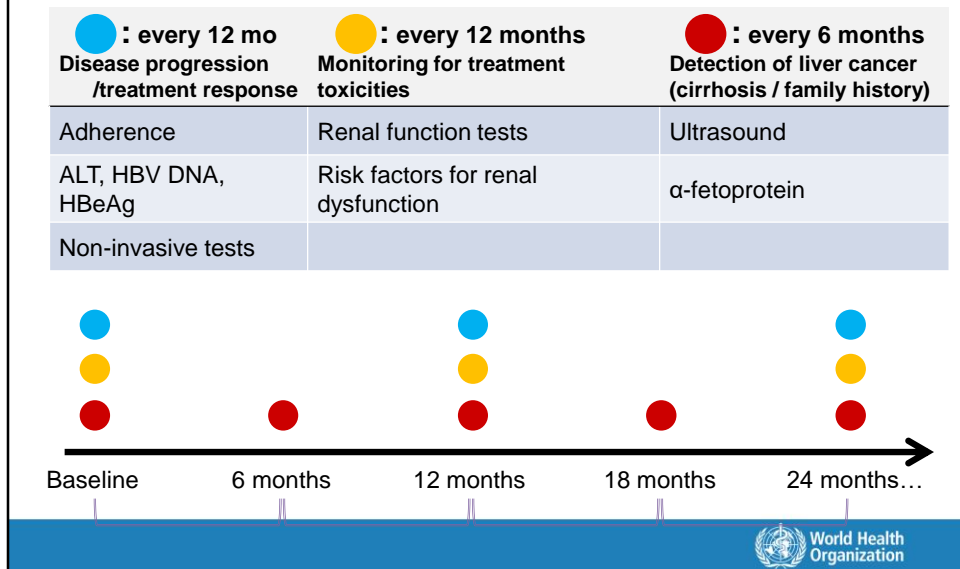
- **Surveillance for hepatocellular carcinoma (HCC)**

- Persons with cirrhosis or a family history of HCC



- At least annually, the following should be monitored: ALT, HBsAg, HBeAg, HBV DNA level, APRI, adherence to treatment and drug adverse events, renal functions.
- In those who do not clearly meet the criteria for treatment, i.e. treatment-deferred cases, or in those following treatment discontinuation, more frequent monitoring is recommended.
- Six-monthly monitoring for surveillance of hepatocellular carcinoma (HCC) is recommended for persons with cirrhosis or a family history of HCC.

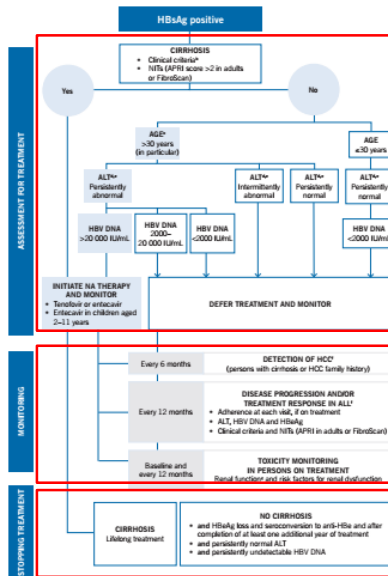
How to monitor?



- This is a visualized figure for monitoring.
- As shown by the blue circles, in all persons with HBV infection, ALT, HBV DNA or HBeAg, non-invasive tests and treatment adherence should be monitored every 12 months.
- As shown by the yellow circles, in persons on treatment, renal function tests and risk factors for renal dysfunction should be monitored every 12 months.
- As shown by the red circles, in persons with cirrhosis or a family history of HCC, ultrasound and alpha-fetoprotein, which is a tumour marker for HCC, should be monitored every 6 months.

How to treat?

WHO guidelines



Assessment for treatment

Monitoring

Stopping treatment

This is the algorithm from the WHO HBV guidelines.
We will now talk about stopping treatment

Drugs to treat HBV infection

Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High
Tenofovir	High	High	High	Low (high in Hong Kong and other Asian countries)
Entecavir	High	High	Weak	High
Emtricitabine	Moderate	Low	High	Low
Telbivudine	High	Low	Unclear	High
Lamivudine	Moderate-high	Low	High	Low
Adefovir	Low	Moderate	None (at 10 mg dose)	High

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) p.21



This table shows the drug that can be used to treat HBV infection as given in the WHO HBV guidelines.

There are 7 drugs to treat HBV infection ranging from interferons to adefovir.

Of these drugs, tenofovir or entecavir is recommended as first-line antiviral treatment.

These two drugs have a high potency against HBV and a high resistance barrier.

The difference between them is activity against HIV.

Tenofovir is highly active against HIV, but entecavir is weakly active against HIV.

WHO recommendation: choice of drug

- **In all adults, adolescents and children aged 12 years or older** in whom antiviral therapy is indicated, nucleos(t)ide analogues that have a high barrier to drug resistance (**tenofovir or entecavir**) are recommended.
- **Entecavir** is recommended in **children.**



WHO recommends the following choice of drug:

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, nucleos(t)ide analogues that have a high barrier to drug resistance (tenofovir or entecavir) are recommended.

Entecavir is recommended in children.

Drug dose

- Adults Entecavir 0.5 mg/day orally
 (1.0 mg/day for decompensated cirrhosis)
 Tenofovir 300 mg/day orally
- Children need dose modification

Drug	Dose																		
Tenofovir (in children 12 years of age and older, and weighing at least 35 kg)	300 mg once daily																		
Entecavir (in children 2 years of age or older and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg)	<p>Recommended once-daily dose of oral solution (mL)</p> <table border="1"> <thead> <tr> <th>Body weight (kg)</th><th>Treatment-naïve persons^a</th></tr> </thead> <tbody> <tr><td>10 to 11</td><td>3</td></tr> <tr><td>>11 to 14</td><td>4</td></tr> <tr><td>>14 to 17</td><td>5</td></tr> <tr><td>>17 to 20</td><td>6</td></tr> <tr><td>>20 to 23</td><td>7</td></tr> <tr><td>>23 to 26</td><td>8</td></tr> <tr><td>>26 to 30</td><td>9</td></tr> <tr><td>>30</td><td>10</td></tr> </tbody> </table>	Body weight (kg)	Treatment-naïve persons ^a	10 to 11	3	>11 to 14	4	>14 to 17	5	>17 to 20	6	>20 to 23	7	>23 to 26	8	>26 to 30	9	>30	10
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>30	10																		

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) p.55

The dose in adults of entecavir is 0.5 mg/day orally, and tenofovir is 300 mg/day orally.

In case of decompensated cirrhosis, entecavir 1.0 mg/day is recommended.

In case of children, an oral solution of entecavir can be used for children 3 years of age or older and weighting at least 10 kg.

As shown in this table, the dose of entecavir oral solution is adjusted according to the body weight.

Drugs need dose adjustment in renal disease

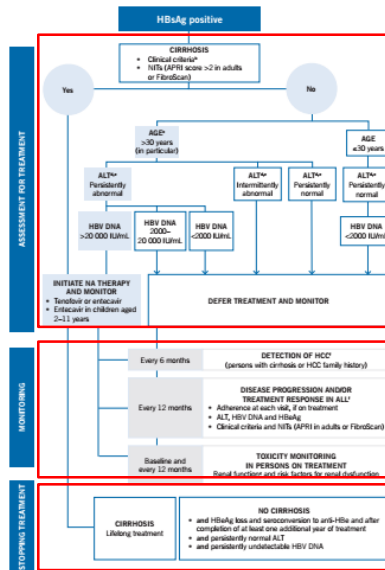
Drug	Recommended dose reduction or dosing interval			
	CrCl (mL/min) ^c			
	≥50	30–49	10–29	<10, Haemodialysis or CAPD
Tenofovir ^{a,b}	One 300 mg tablet every 24 hours (7.5 scoops of powder every 24 hours)	One 300 mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300 mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every 7 days or one 300 mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
Entecavir	0.5 mg once daily ^d	0.25 mg once daily OR 0.5 mg every 48 hours	0.15 mg once daily OR 0.5 mg every 72 hours	0.05 mg once daily OR 0.5 mg every 7 days
Entecavir (decompensated liver disease)	1 mg once daily	0.5 mg once daily OR 1 mg every 48 hours	0.3 mg once daily OR 1 mg every 72 hours	0.1 mg once daily OR 1 mg every 7 days

The dose of tenofovir and entecavir should be adjusted if there is renal disease.

As shown in this table, in case the creatine clearance is less than 50 mL/min, the dose of tenofovir or entecavir should be reduced to half or administered every 48 hours.

The dose reduction recommended varies according to the renal function, as shown in this table.

WHO guidelines



Assessment for treatment

Monitoring

Stopping treatment

Next, we will talk about stopping treatment.

Duration of treatment

- Cirrhosis or APRI >2.0 Lifelong treatment
- Discontinuation may be considered exceptionally in those without cirrhosis (or APRI <2.0 in adults) and all of the following:
 - can be followed carefully long term for reactivation
 - if there is HBeAg loss and seroconversion to anti-HBe, and maintained for one year
 - persistently normal ALT
 - persistently undetectable HBV DNA.



- In case of cirrhosis or APRI more than 2.0, usually you cannot stop treatment and the treatment should continue lifelong.
- Discontinuation may be considered exceptionally in those without cirrhosis or APRI less than 2.0 in adults and all of the following criteria:
 - those who can be followed carefully long term for reactivation
 - if there is HBeAg loss and seroconversion to anti-HBe, and maintained for one year
 - those whose ALT is persistently normal
 - those in whom HBV DNA is persistently undetectable.
- These are very limiting situations and basically treatment should continue lifelong.

Summary

- Patients with acute hepatitis B do not need treatment.
- In patients with chronic hepatitis B, try to identify whether they have
 - chronic HBV or cirrhosis
 - compensated or decompensated cirrhosis.
- Those with cirrhosis (compensated or decompensated) need antiviral drug treatment.
- Patients with chronic HBV and no cirrhosis need an individualized decision about treatment.
- Starting antiviral drugs is easy, but the treatment is often lifelong.
- All patients need monitoring for hepatocellular cancer; those on treatment also need periodic assessment for drug efficacy/toxicity.



- Patients with acute HBV usually recover completely and clear HBsAg in six months of time.
- All those with chronic HBV should be assessed for the presence of cirrhosis.
- All those with cirrhosis need antiviral drugs.
- Among those without cirrhosis, antiviral drugs are needed for a small proportion of people.
- All chronic HBV patients, whether on treatment or not, need lifelong monitoring at regular intervals.