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

World Health Organization

Session 11

Clinical management of hepatitis B virus infection:
case studies

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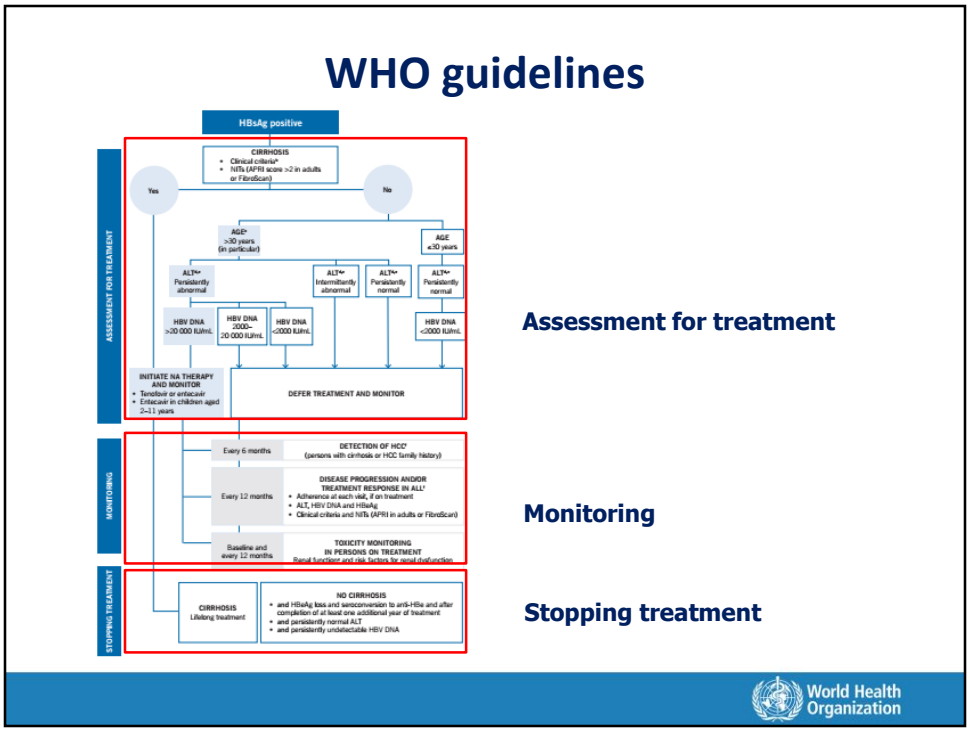
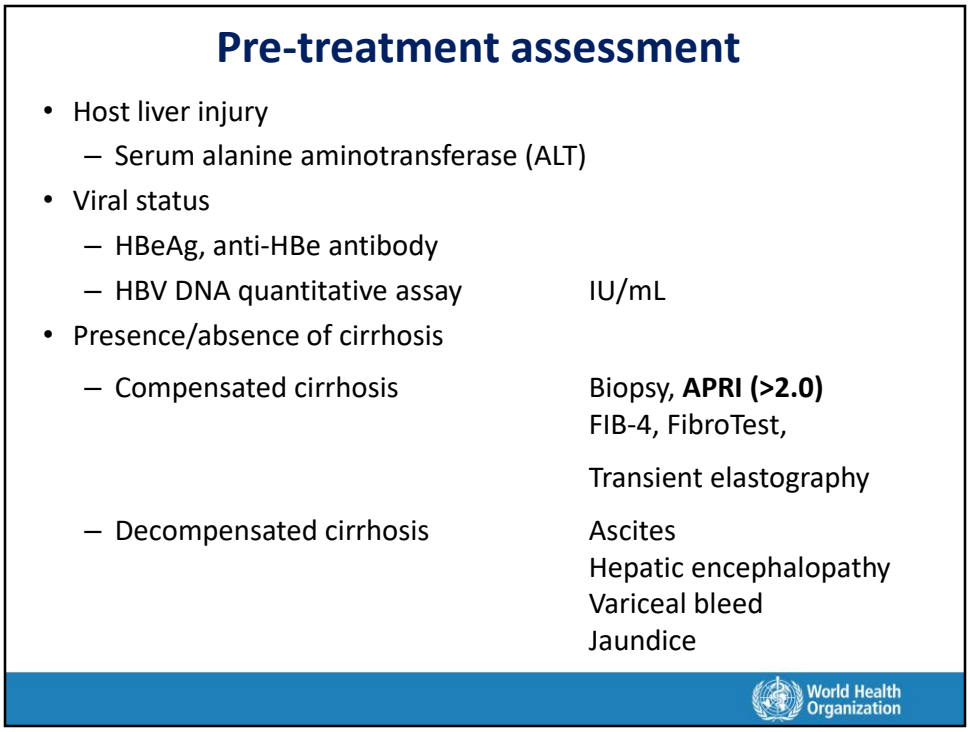


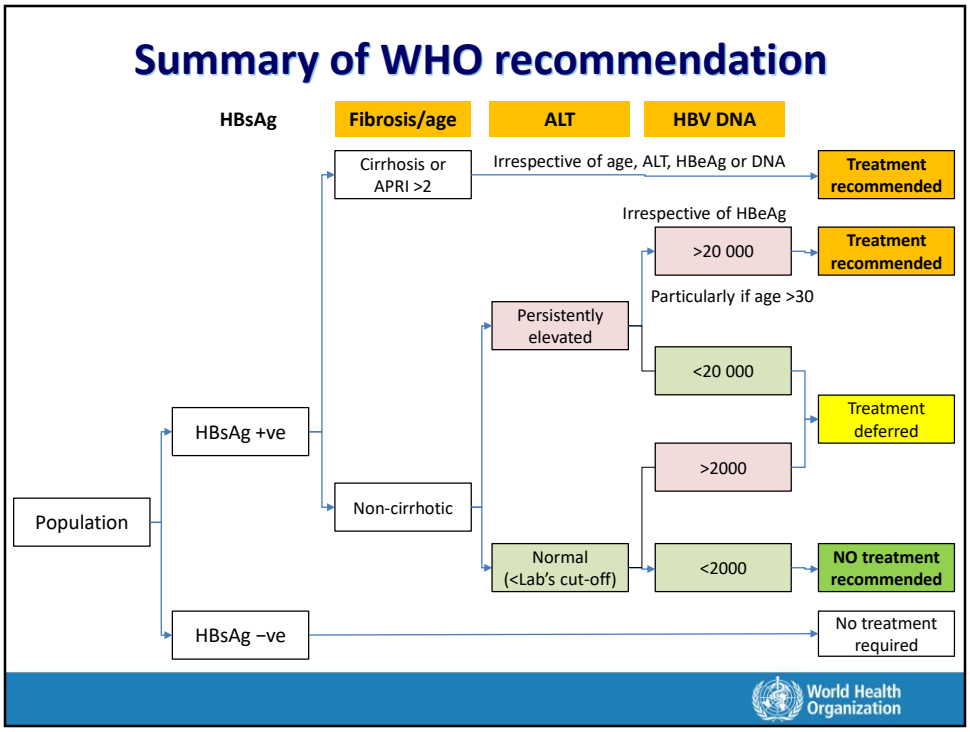
The decision to initiate antiviral therapy is usually based on an assessment of the stage of liver disease.

Persons with chronic hepatitis B (CHB) need follow up and monitoring before, during and after discontinuation of antiviral therapy.

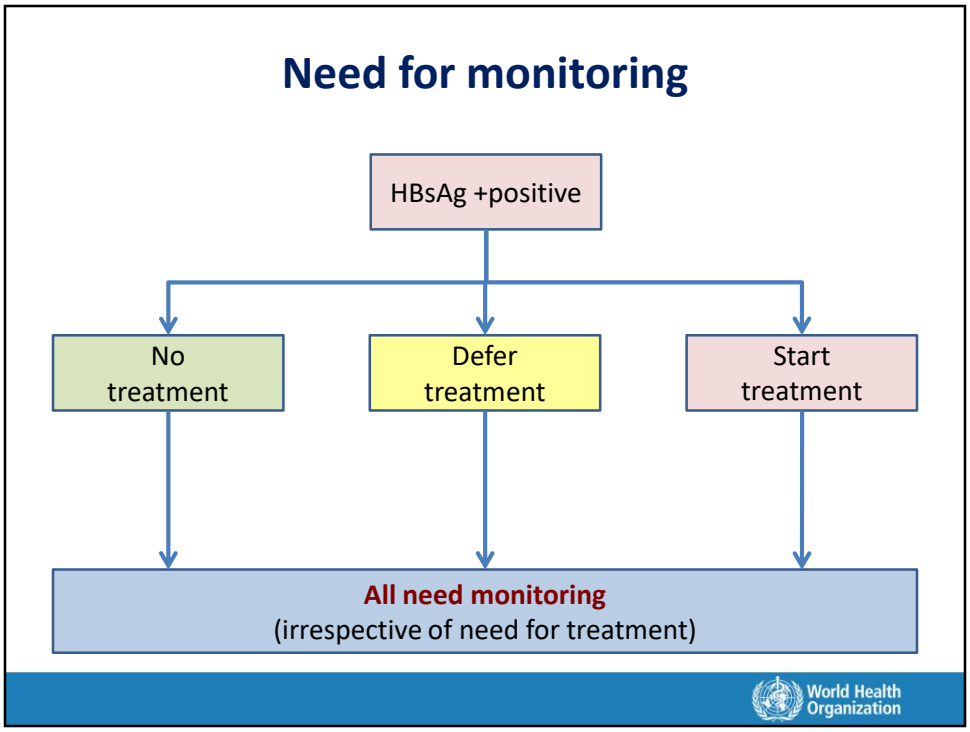
We are first going to re-cap some important concepts



- 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 level of alanine aminotransferase (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. Serum ALT patterns are described as persistently normal, persistently abnormal or intermittently abnormal.
- Next, to assess the virus activity, we need to do an HBV DNA quantitative assay. If you cannot perform an HBV DNA quantitative assay, you can use alternatively 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 and transient elastography (e.g. FibroScan) are used.
- Clinical symptoms such as ascites, hepatic encephalopathy, variceal bleeding and jaundice indicate decompensated cirrhosis.

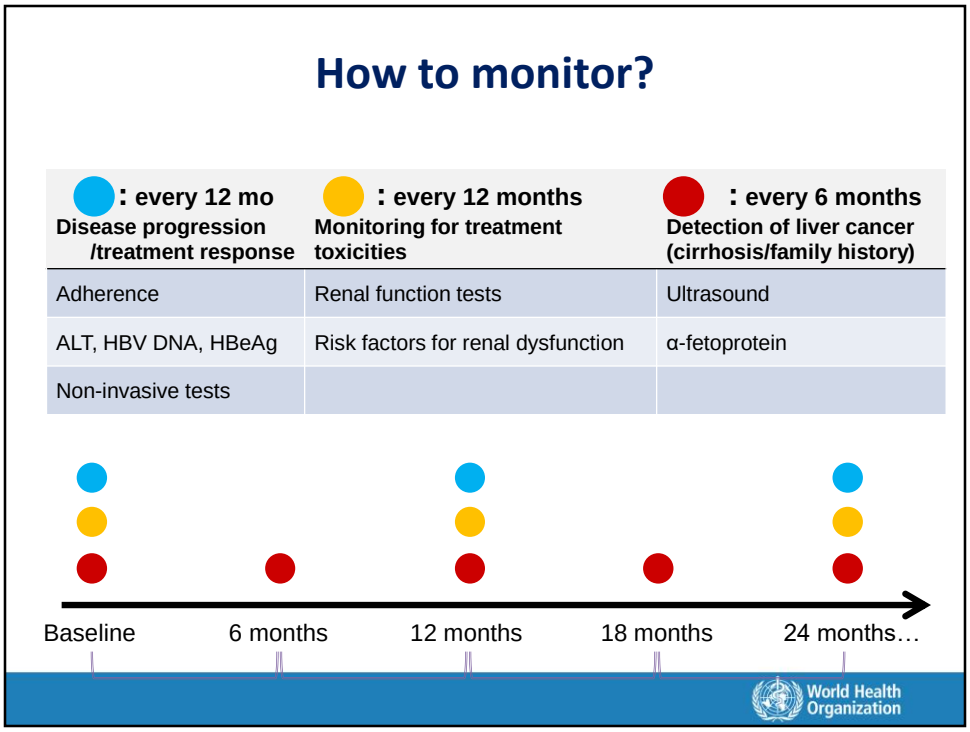


The decision to initiate antiviral therapy is based on an assessment of fibrosis, serum ALT and HBV DNA.



Chronic hepatitis B is a dynamic disease, and persons with CHB need follow up and monitoring before, during and after discontinuation of antiviral therapy for disease progression and development of HCC, treatment response and toxicities.

Prior to treatment, the goal of monitoring is to identify the phase of disease, change in phase and progression of disease. It helps to decide the appropriate timing for treatment initiation.



While on treatment, monitoring is required to assess treatment adherence, status of virus replication (with HBV DNA or HBeAg), progression of liver fibrosis, development of features of portal hypertension and HCC.
The Guidelines Development Group therefore recommended at least annual monitoring of ALT, HBeAg (for seroconversion [to anti-HBe]) and HBV DNA levels (where testing is available), and also non-invasive tests of fibrosis such as APRI to assess for progression to cirrhosis.

HBV genotyping and resistance testing are not required to guide therapy.

More frequent and careful monitoring was recommended conditionally based on limited evidence in the following groups: those with more advanced disease (compensated or decompensated cirrhosis) because the risk of HCC is reduced but not eliminated with treatment, and their higher risk of adverse events; during the first year of treatment to assess treatment response; where adherence to therapy is a concern; and after stopping therapy.

Case study 1

- A 52-year-old male presents with malaise
  - History: no previous hospitalization
  - Social: 120 g alcohol/day (30 years), no tobacco, no record of substance abuse
  - Examination: unremarkable
  - Laboratory data:
    - AST 78 U/L (ULN 30), ALT 64 U/L
    - HBsAg positive, anti-HCV negative
- Clinical question
  - What test would you order?

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A middle-aged man presented with non-specific symptoms and was tested and found to be HBsAg positive. His ALT and AST were mildly elevated. He consumes alcohol regularly for a long period of time.

How would you investigate this person?

Case study 1

- What test would you order?
  - HBV DNA 2.8 x10^8 IU/mL, HIV rapid diagnostic test negative
  - Hb 11.8 g/dL, neutrophils 2.5 x10^9/L, PLT 98 x10^9/L
  - Alb 3.4 g/dL, T-Bil 1.2 mg/dL, PT-INR 1.6
  - Creatinine 1.0 mg/dL
  - Ultrasound: chronic liver disease, mild splenomegaly
- Clinical question
  - What is the stage of liver disease?
  - Is treatment recommended?
  - What monitoring does she require?

World Health Organization

Investigations revealed a low platelet count, deranged LFT, high HBV DNA and features of chronic liver disease on USG abdomen.

With this information we need to decide about the stage of liver disease, whether he has liver fibrosis, the need for antiviral drugs and our follow-up plan.

Case study 1: answers

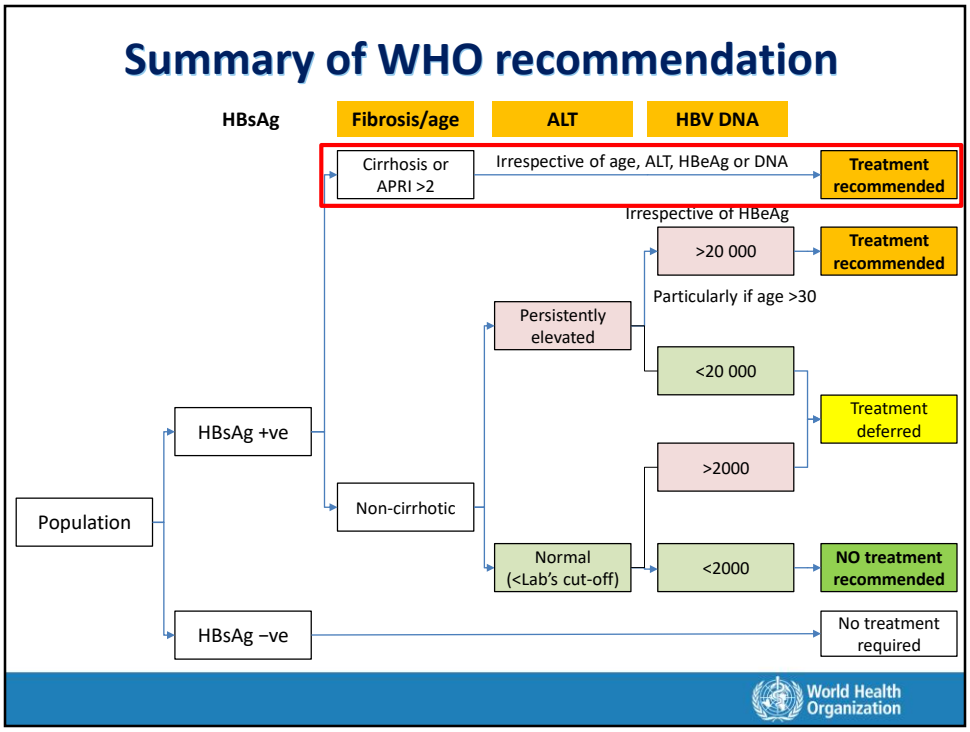
- What is the stage of liver disease?
  - APRI 2.6; [78/30]x100/98 >2.0; liver cirrhosis (compensated)
- Is treatment recommended?
  - Diagnosis: liver cirrhosis B
  - Select recommended preferred regimen:
    - ✓ Tenofovir 300 mg once daily or entecavir 0.5 mg once daily
    - ✓ Lifelong treatment
  - Assist for treatment: stop alcohol intake
- What monitoring does she require?
  - Monitor for efficacy and toxicity (baseline and every 12 months)
  - Lifelong screening for HCC (every 6 months)

World Health Organization

On calculation, APRI is more than 2, which indicates the presence of cirrhosis. For a patient with cirrhosis with any level of detectable HBV DNA, treatment with an antiviral drug is indicted.

The drugs of choice are tenofovir or entecavir, which has to be continued for life.

All such patients will need follow up every six-monthly for compliance, toxicity, complications of portal hypertension and HCC.



This is the flow chart that we learnt in the last session and at the top of it we can see the status of our first patient who requires treatment in view of cirrhosis and detectable HBV DNA.

Case study 2

- A 45-year-old female presents with insomnia
  - History: no previous hospitalization
  - Social: no record of alcohol, tobacco and substance use
  - Examination: unremarkable
  - Laboratory data:
    - Hb 12.6 g/dL, AST 34 U/L (ULN 30), ALT 40 U/L (persistently increased)
    - HBsAg positive, anti HCV negative
- Clinical question
  - What test would you order?

World Health Organization

A 45-year-old lady presented with insomnia and was found to be HBsAg positive on routine work-up. Her ALT is elevated. We need to evaluate this lady.

Case study 2: answers

- What test would you order?
  - HBV DNA 1.2 x10^8 IU/mL (>20 000)
  - Neutrophils 3.0 x10^9/L, PLT 218 x10^9/L
  - Alb 4.0 g/dL, T-Bil 0.8 mg/dL, PT-INR 1.5
  - Creatinine 0.8 mg/dL
  - Ultrasound: normal liver, no ascites, no hepatoma
- Clinical question
  - What is the stage of liver disease?
  - Is treatment recommended?
  - What monitoring does she require?

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Her LFT and USG abdomen were normal. Her HBV DNA was high.

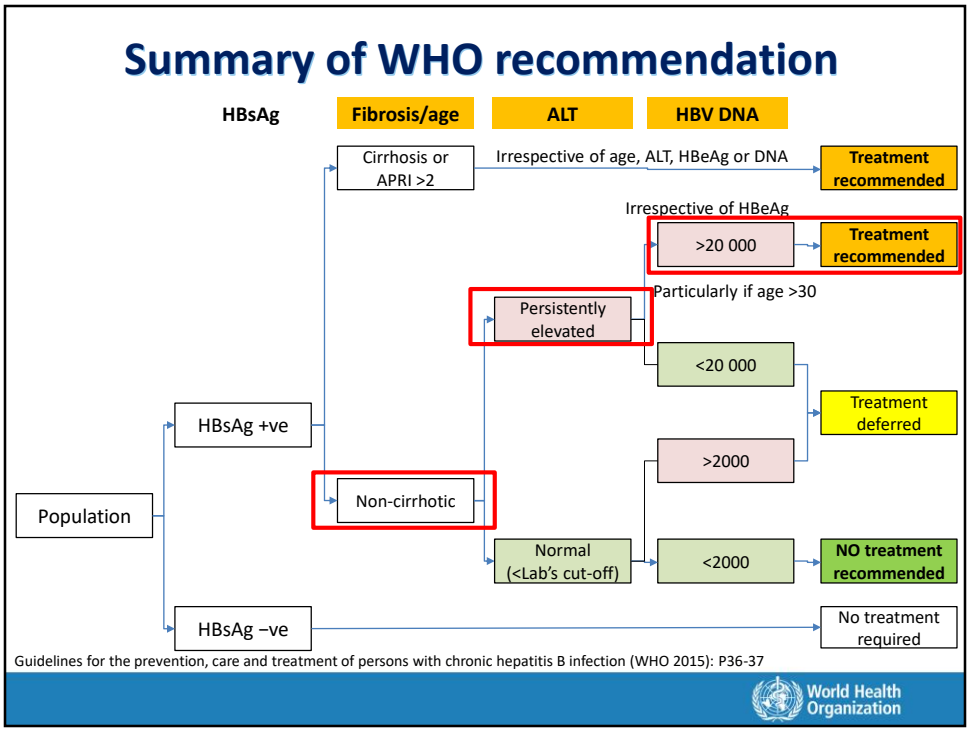
With this information we need to decide about the stage of liver disease, liver fibrosis, need for antiviral drugs and our follow-up plan.

Case study 2: answers

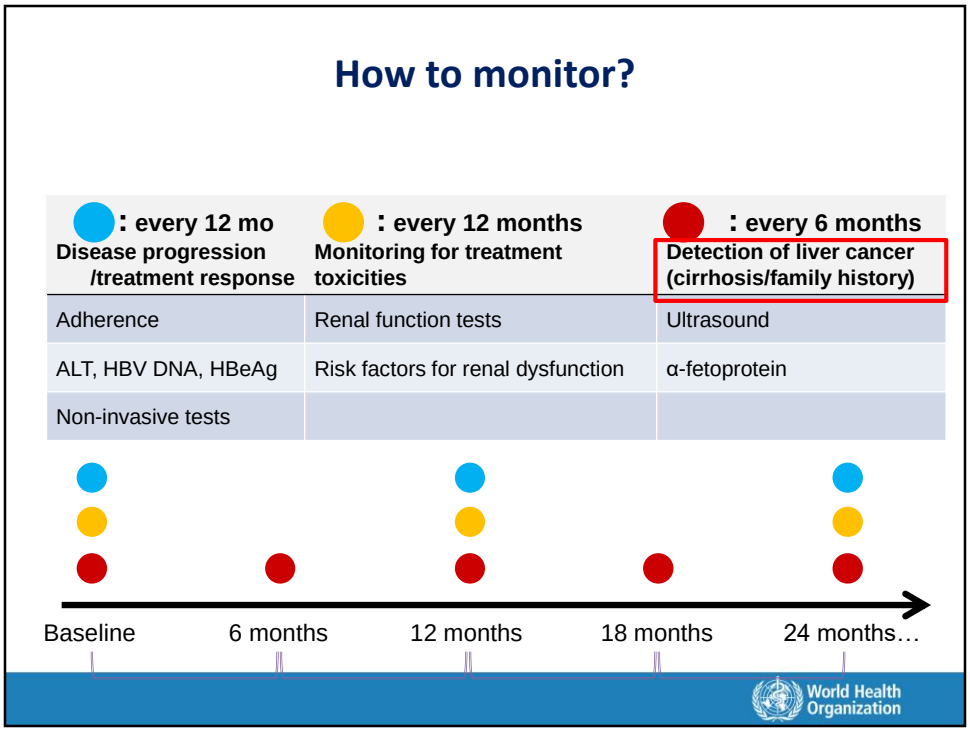
- What is the stage of liver disease?
  - APRI 0.5; [34/30]x100/218 <2.0; not liver cirrhosis
- Is treatment recommended?
  - Diagnosis: chronic hepatitis B
  - Select recommended preferred regimen:
    - ✓ Tenofovir 300 mg once daily or entecavir 0.5 mg once daily
    - ✓ Lifelong treatment
- What monitoring does she require?
  - Monitor for efficacy and toxicity (baseline and every 12 months)

World Health Organization

Her APRI is 0.5 hence she does not have cirrhosis. In view of the elevated ALT, she will need antiviral treatment and we can choose between entecavir and tenofovir.



In this flowchart, we can see the status of our present patient who requires treatment in view of the elevated ALT and high DNA.



The WHO Guidelines recommended at least annual monitoring of ALT, HBeAg (for seroconversion [to anti-HBe]) and HBV DNA levels (where testing is available), and also non-invasive tests of fibrosis such as APRI to assess for progression to cirrhosis. We need to monitor every 6-monthly for HCC with USG and alpha-fetoprotein.

Case study 3

- A 26-year-old male presents with low-grade fever
  - History: no previous hospitalization
  - Social: 60 g alcohol/day (6 years), there are records of substance abuse, sexually active with several partners
  - Examination: injection scar on arm
  - Laboratory data:
    - Hb 13.0 g/dL, neutrophils 2.8 $x10^9$/L, PLT 282 $x10^9$/L
    - AST 112 U/L (ULN 30), ALT 120 U/L, HBsAg positive
- Clinical question
  - What test would you order?

World Health Organization

A 26-year-old young male with multiple risk factors for hepatitis B. His ALT and AST were elevated threefold. What next?

Case study 3: answers

- What test would you order?
  - HBV DNA 3.5 x10^8 IU/mL (>20 000)
  - Alb 4.1 g/dL, T-Bil 1.0 mg/dL, PT-INR 1.4
  - Creatinine 0.8 mg/dL
  - Anti-HCV negative, HIV RDT negative
  - Ultrasound: normal liver, no ascites, no hepatoma
- Clinical question
  - What is the stage of liver disease?
  - Is treatment recommended?
  - What monitoring does he require?

World Health Organization

He has high HBV DNA without any evidence of cirrhosis on USG. Such persons should always be screened for HIV.

Case study 3: answers

- What is the stage of liver disease?
  - APRI 1.3; [112/30]x100/282 <2.0; not liver cirrhosis
- Is treatment recommended?
  - Diagnosis: chronic hepatitis B
  - Select recommended preferred regimen:
    - ✓ Tenofovir 300 mg once daily or entecavir 0.5 mg once daily
    - ✓ Lifelong treatment
  - Assist for treatment: alcohol sobriety, drug abstinence
- What monitoring does he require?
  - Monitor for efficacy and toxicity (baseline and every 12 month)

World Health Organization

APRI was <2 and hence he had no cirrhosis. Liver enzymes were elevated and DNA was high. So, the patient qualifies for antiviral drugs.

Besides antiviral drugs, the management of such people should also be focused on rehabilitation such as drug deaddiction, etc.

Case study 4

- 52-year-old man
- Planned for laparoscopic cholecystectomy
- Detected to have HBsAg positive on evaluation
- History
  - no previous hospitalization
  - no addiction
- Examination: unremarkable

What tests would you order?

World Health Organization

A 52-year-old person was planned for laparoscopic cholecystectomy and was incidentally detected to have HBV infection during preoperative work-up.

How would you evaluate this person?

Case study 4: test results

Investigations	Values
Haemoglobin (g/dL)	11.8
Platelets (x 10^9/L)	98
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.4
ALT (IU/L) AST (IU/L)	66 (<40 IU/L) 98 (<40 IU/L)
Prothrombin time (INR)	1.6
HBV DNA (IU/L)	1120
USG abdomen	Coarse echo-texture of liver Portal vein diameter = 14 mm Splenomegaly, no ascites

World Health Organization

His liver enzymes were elevated, HBV DNA was low but USG abdomen showed features of chronic liver disease or cirrhosis.

Case study 4: issues in management

- What is the stage of liver disease?
  - *Cirrhosis versus no cirrhosis*
  - *Compensated versus decompensated*
- Is treatment recommended?
  - *What drug?*
  - *How long?*
- How would you monitor the person during treatment?

World Health Organization

These are the question we need to answer for this patient before starting antiviral drugs.

Case study 4: questions

What is the stage of liver disease?

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

Case study 4: answers (1)

What is the stage of liver disease?

- APRI = [98/40] x 100/98 = ~2.5
- APRI >2.0 → Liver cirrhosis (compensated)

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

Because the APRI is more than 2, hence the patient has cirrhosis.

Case study 4: answers (2)

What is the stage of liver disease?

- APRI = [98/40] x 100/98 = ~2.5
- APRI > 2.0 → Liver cirrhosis (compensated)

Is treatment recommended?

- HBV DNA is detectable: Those with cirrhosis need treatment (irrespective of DNA level)

What is the treatment?

What monitoring is required?

World Health Organization

A patient with cirrhosis and raised HBV DNA needs antiviral drugs, hence we need to start antiviral drugs.

Case study 4: answers (3)

What is the stage of liver disease?

- APRI = [98/40] x 100/98 = ~2.5
- APRI > 2.0 → Liver cirrhosis (compensated)

Is treatment recommended?

- HBV DNA is detectable: Those with cirrhosis need treatment (irrespective of DNA level)

What is the treatment?

- Entecavir 0.5 mg, once daily, oral, lifelong, or
- Tenofovir 300 mg , once daily, oral, lifelong

What monitoring is required?

World Health Organization

For compensated cirrhosis, we have two options – entecavir 0.5 mg or tenofovir 300 mg daily.

Case study 4: answers (4)

What is the stage of liver disease?

- APRI = [98/40] x 100/98 = ~2.5
- APRI > 2.0 → Liver cirrhosis (compensated)

Is treatment recommended?

- HBV DNA is detectable: Those with cirrhosis need treatment (irrespective of DNA level)

What is the treatment?

- Entecavir 0.5 mg, once daily, oral, lifelong

What monitoring is required?

- Monitor for efficacy, decompensation and liver cancer
- Renal function tests, if using tenofovir

World Health Organization

We need repeated evaluation during follow up for development of decompensation and HCC.

Case study 4: take-home messages

- Cirrhosis must be looked for in all HBsAg-positive patients.
- In patients with cirrhosis and detectable HBV DNA
  - antiviral drugs should be started (regardless of HBV DNA level)
  - serum ALT level has no role in deciding the need for treatment.

- In patients with cirrhosis, antiviral treatment
  - should be continued for life
  - what drug to provide: should be determined medically if there are absolute contraindications. WHO recommends either entecavir or tenofovir.

World Health Organization

All HBsAg-positive patients should be evaluated for the presence of cirrhosis. All those with cirrhosis and detectable HBV DNA need antiviral drugs for life. All those with cirrhosis need follow up for progression to decompensation and HCC.

Case study 5

- 25-year-old woman
- Detected HBsAg positive during blood donation screening
  - asymptomatic, good health
  - no previous hospitalization, no morbidity, no addiction
  - examination: unremarkable

- What test would you order?

World Health Organization

This is one of the most common scenarios that we come across. A 25-year-old lady donated blood and a got phone call from the blood bank after a few days stating that she was found to be HBsAg positive. Otherwise she does not have any symptoms. How would you proceed in this case?

Case study 5: test results

Investigations	Values
Haemoglobin (g/dL)	12.8
Platelets (x 10^9/L)	218
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
ALT (IU/L) AST (IU/L)	34 (<40 IU/L) 28 (<40 IU/L)
Prothrombin time (INR)	1.1
HBV DNA (copies/mL)	8000
USG abdomen	Normal liver size and echotexture Portal vein diameter = 10 mm Normal spleen; no ascites

World Health Organization

Her laboratory evaluation revealed normal liver enzymes and USG abdomen. HBV DNA is 8000 copies/mL.

How to interpret these laboratory data and proceed?

Case study 5: questions

What is the stage of liver disease?

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

We again have to answer the same questions.

Case study 5: answers (1)

What is the stage of liver disease?

- APRI = [28/30] x 100/218 = ~0.4
- APRI <2.0 → No cirrhosis

Is treatment recommended?

What is the treatment?

What is the monitoring required?

World Health Organization

APRI is 0.4 hence she does not have cirrhosis.

Case study 5: answers (2)

What is the stage of liver disease?

- APRI = [28/30] x 100/218 = ~0.4
- APRI <2.0 → No cirrhosis

Is treatment recommended?

- ALT normal
- HBV DNA = 8000 copies/mL = ~ 8000/5 or 1600 IU/mL (<2000 IU/mL)
- HBV DNA: 2000 IU/mL = 10 000 copies /mL (4 log copies/mL)

What is the treatment?

What monitoring is required?

World Health Organization

Her HBV DNA Is 8000 copies/mL. All the guidelines consider DNA in IU/mL but not in copies. DNA in copies can be converted to IU/mL by dividing the number of copies by five.

Hence, the HBV DNA is relatively low.

Case study 5: answers (3)

What is the stage of liver disease?

- APRI = [28/30] x 100/218 = ~0.4
- APRI <2.0 → No cirrhosis

Is treatment recommended?

- ALT normal
- HBV DNA = 8000 copies/mL = ~ 8000/5 or 1600 IU/mL (<2000 IU/mL)
- HBV DNA: 2000 IU/mL = 10 000 copies /mL (4 log copies/mL)

What is the treatment?

- No treatment (immune-control phase)

What monitoring is required?

World Health Organization

In view of the fact that there is no cirrhosis, the ALT is normal and DNA is low, antiviral treatment is not required.

Case study 5: answers (4)

What is the stage of liver disease?

- APRI = [28/30] x 100/218 = ~0.4
- APRI <2.0 → No cirrhosis

Is treatment recommended?

- ALT normal
- HBV DNA = 8000 copies/mL = ~ 8000/5 or 1600 IU/mL (<2000 IU/mL)
- HBV DNA: 2000 IU/mL = 10 000 copies /ml (4 log copes/mL)

What is the treatment?

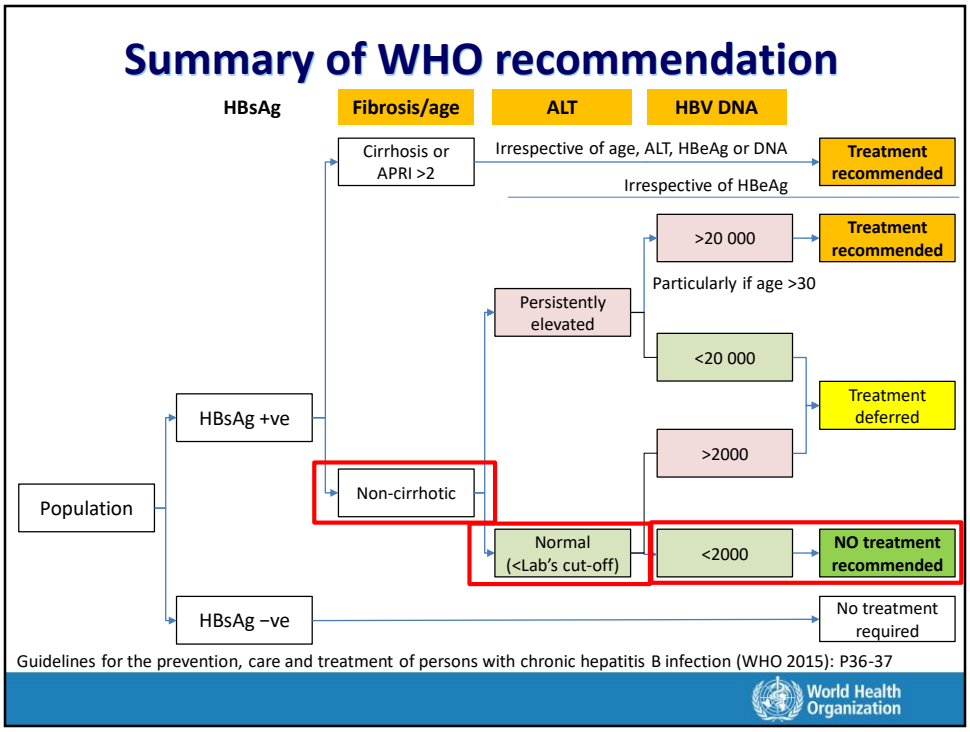
- No treatment (immune-control phase)

What monitoring is required?

- Monitor for disease activity

World Health Organization

We need to re-evaluate very 6–12 months for disease activity.



In this flowchart, we can see the status of our present patient who does not require treatment as she has no cirrhosis, a normal ALT and low DNA.

Case study 5: take-home messages

- In young patients without cirrhosis:
  - no need for treatment, unless ALT as well as HBV DNA are high
  - all patients need periodic monitoring for disease activity and for HCC.
- HBV DNA levels should be expressed as IU/mL
  (if reported as copies/mL, convert before interpretation, divide the value in copies/mL by 5)

World Health Organization

In summary, patients with no cirrhosis, normal ALT and low DNA do not need treatment but need monitoring.

Case study 6

- 38-year-old woman
- Incidentally detected HBsAg positive during treatment for primary infertility
- No previous hospitalization, other disease or addiction
- Examination: normal

What tests would you order?

World Health Organization

Again, we have an incidental detection of HBsAg in a women who was investigated for primary infertility.

Case study 6: test results

Investigations	Values
Haemoglobin (g/dL)	10.8
Platelets (x 10^9/L)	255
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.8
ALT (IU/L) AST (IU/L)	76 (<40 IU/L) 56 (<40 IU/L)
Prothrombin time (INR)	1.2
HBV DNA (IU/ml)	123,000
USG abdomen	Normal liver size and echotexture Portal vein diameter = 10 mm Normal spleen; no ascites

World Health Organization

Investigation revealed elevated liver enzymes and high DNA without any evidence of cirrhosis on USG abdomen.

Case study 6: questions

What is the stage of liver disease?

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

We have to proceed in a similar manner as we did previously.

Case study 6: answers (1)

What is the stage of liver disease?

- APRI = [56/40] x 100/255 = ~0.6
- APRI <0.6 → No cirrhosis

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

APRI of 0.6 indicates there is no cirrhosis.

Case study 6: answers (2)

What is the stage of liver disease?

- APRI = [56/40] x 100/255 = ~0.6
- APRI <0.6 → No cirrhosis

Is treatment recommended?

- ALT high
- HBV DNA = 123 000 IU/mL (>20 000 IU/mL)

What is the treatment?

What monitoring is required?

World Health Organization

ALT and DNA are both high. Hence, antiviral treatment is indicated.

Case study 6: answers (3)

What is the stage of liver disease?

- APRI = [56/40] x 100/255 = ~0.6
- APRI <0.6 → No cirrhosis

Is treatment recommended?

- ALT high
- HBV DNA = 123 000 IU/mL (>20 000 IU/mL)

What is the treatment?

- Tenofovir, 300 mg, once daily, oral

What monitoring is required?

World Health Organization

Tenofovir is the preferred antiviral in those without cirrhosis.

Case study 6: answers (4)

What is the stage of liver disease?

- APRI = [56/40] x 100/255 = ~0.6
- APRI <0.6 → No cirrhosis

Is treatment recommended?

- ALT high
- HBV DNA = 123 000 IU/mL (>20 000 IU/mL)

What is the treatment?

- Tenofovir, 300 mg, once daily, oral

What monitoring is required?

- Monitor for response, drug toxicity and liver cancer

World Health Organization

The patient will require monitoring and repeated evaluation for virus control, drug toxicity and HCC.

Take-home messages: Case study 6

- Patients with HBV infection, who have high ALT and high HBV DNA, need treatment with antiviral drugs.
- In the absence of cirrhosis, either tenofovir or entecavir may be used.
- Such patients need periodic monitoring for drug response, toxicity and HCC.

World Health Organization

AN HBsAg-positive person with high ALT and DNA levels needs antiviral drugs. In the absence of cirrhosis, tenofovir is preferred over entecavir.