Therapeutics Research • Education • AIDS Training
TREATASIA
FACT SHEET
October 2024

Understanding WHO Guidelines for the Prevention, Care, Diagnosis, and Treatment of People with Chronic Hepatitis B Infection

In April 2024, the World Health Organization (WHO) updated its guidelines for the prevention, care, diagnosis, and treatment of people with chronic hepatitis B infection, which are aimed at helping policymakers and healthcare providers in low- and middle-income countries strengthen their efforts to address hepatitis B virus (HBV) and related national responses. The guidelines can also be used by civil society and community organizations to advocate for access to prevention, diagnosis, and treatment of HBV. This fact sheet summarizes the primary messages and recommendations.

WHAT DO THE GUIDELINES SAY?

PREVENTION

Prevention through vaccination remains the major focus, as recommended in earlier guidelines.

- All infants should receive 3–4 doses of HBV vaccine, with the first dose administered as soon as possible after birth and preferably within 24 hours.
- Catch-up vaccination should be scheduled for i) young adolescents; ii) household and sexual contacts of people who have chronic HBV infection (according to a positive HBsAg test); and iii) people at risk of acquiring HBV infection, including family members of people living with chronic HBV, people who inject drugs, men who have sex with men, migrants, people in prison and other closed settings, people living with HIV and their partners, sex workers, and transgender people.

KEY TESTS FOR HEPATITIS B VIRUS AND LIVER DISEASE

HBsAg – Hepatitis B surface antigen
- Used for diagnosis of chronic infection and monitoring

HBV DNA – Hepatitis B DNA or viral load
- Used for assessing treatment eligibility and monitoring

HBeAg – Hepatitis B e-antigen
- Sometimes used in place of the HBV DNA test; indicates the level of virus replication in the blood

HBeAb/anti-HBe – Antibody against hepatitis B e-antigen
- Positive result indicates low infectivity and inactivity of the virus

APRI – AST to Platelet Ratio Index
- Used to calculate a score to assess the condition of the liver
  - Scores greater than 0.5 are considered representative of significant fibrosis
  - Scores greater than 1 are considered representative of cirrhosis

FibroScan® – Also known as transient elastography
- Non-invasive test to assess the condition of the liver
  - Scores greater than 7 are considered representative of significant fibrosis.
  - Scores greater than 12.5 are considered representative of cirrhosis

Guidance on the prevention of mother-to-child transmission of HBV through pre-emptive antiviral prophylaxis has been updated.

- For pregnant women who have positive HBsAg tests:
  - Where HBV DNA and HBeAg testing are available, prophylaxis with tenofovir disoproxil fumarate (TDF) from the second trimester of pregnancy until at least delivery or completion of the infant's immunization schedule should be offered to all women with HBV DNA more than 200,000 IU/mL or positive HBeAg tests.

  or

  - Where HBV DNA and HBeAg testing are *not* available, prophylaxis with TDF from the second trimester of pregnancy until at least delivery or completion of the infant's immunization schedule should be offered to all pregnant women.

DIAGNOSIS AND STAGING OF LIVER DISEASE

Diagnosis confirms whether an individual has chronic HBV infection. The HBV DNA test assesses HBV viral load and is used to determine the amount of HBV in the blood. Staging of liver disease and the HBV viral load guide the need for treatment.

- In children more than 12 months of age, adolescents, and adults, a serological test for HBsAg using either a rapid diagnostic test or laboratory-based test is recom-mended. Having a persistently positive HBsAg test for more than six months is considered to represent chronic infection.
- After a positive HBsAg test, the HBV DNA test should be done to determine whether treatment is indicated.
  - Point-of-care HBV DNA may be used as an alternative to laboratory-based testing, whether to assess treatment eligibility or monitor response to treatment.
- The APRI[i] score includes aspartate aminotransferase (AST) and platelet tests and can be used as a non-invasive way to assess for the presence of significant fibrosis or cirrhosis. Transient elastography (FibroScan®) is another non-invasive test that may be preferred in settings where it is available and cost is not a major constraint.

CARE

All individuals with chronic HBV infection who do not meet treatment eligibility criteria can take steps to prevent liver damage and should have access to appropriate medical care to monitor their health and that of their family members.

This includes:

- Receiving lifestyle counseling on alcohol consumption, diet, and physical activities.
- Having the severity of their liver disease assessed annually using non-invasive tests such as alanine transaminase (ALT) and HBV DNA.
- Screening all family members and sexual contacts with HBsAg tests and facilitating HBV vaccination for those who have not yet been vaccinated.

Monitoring enables early identification of changes in clinical status and risk of disease progression.

TREATMENT

Medical treatment is available that can prevent adverse outcomes from chronic HBV infection. A patient-centered approach with discussions between individuals and their healthcare providers is key to helping them make informed decisions about whether or not to begin treatment. With the currently available antivirals, treatment is lifelong.

Treatment Criteria

- Treatment is recommended for all adolescents aged 12 years or older and adults, including those who are pregnant, who have chronic HBV infection, and meet any of the following criteria:
  - HBV DNA more than 2000 IU/mL and an ALT level above the upper limit of normal
    - For adolescent boys (12–17 years) and men, an ALT value of 30 units per liter is considered the upper limit of normal, while for adolescent girls and women it is 19 units per liter.
    - For adolescents, ALT should be above the upper limit of normal on at least two occasions in a 6- to 12-month period to meet criteria.
  - Significant fibrosis based on an APRI score of >0.5 or transient elastography >7 kPa, or cirrhosis based on an APRI score of >1 or transient elastography >12.6 kPa
    - *Treatment should be initiated regardless of HBV DNA or ALT levels.*
  - Co-infections with HIV, hepatitis C, or hepatitis D; family history of liver cancer or cirrhosis; immune suppression (such as long-term steroid use, solid organ or stem cell transplant recipients); comorbidities (such as diabetes, metabolic dysfunction-associated steatotic liver disease); extrahepatic manifestations (such as glomerulonephritis or vasculitis)
    - *Treatment should be initiated regardless of APRI score or HBV DNA or ALT levels.*
  - In the absence of DNA tests treatment should be initiated, regardless of APRI score, if there is persistently abnormal ALT.
    - Defined by two ALT values above the upper limit of normal over 6–12 months

A PATIENT-CENTERED APPROACH TO TREATMENT

Individuals who do not meet treatment eligibility criteria may still choose to seek treatment if they have concerns around the risk of disease progression, the potential of infection transmission, or associated stigma.

In such cases, they can discuss available options with their healthcare provider before making an informed decision whether to begin treatment based on considerations of overall risks and benefits, financial implications and need for long-term sustained treatment.

MEDICATIONS USED FOR TREATMENT

The following medications are recommended to treat chronic HBV.

- For all children (2–11 years), adolescents, and adults, medicines that have a high genetic barrier to drug resistance are recommended as preferred treatments. This includes TDF or entecavir (ETV).
- TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) are alternative regimens where TDF monotherapy is not available.
- Treatment options include ETV and tenofovir alafenamide (TAF) for people with established osteoporosis and/or impaired kidney function, if available.
- For those with evidence of treatment failure due to confirmed or suspected antiviral resistance to 3TC, ETV, adefovir, or telbivudine, switching to TDF is recommended. TAF is an alternate regimen, if available.
- Adefovir, 3TC, and telbivudine should not be used due to their low barrier to resistance.

PREFERRED AND ALTERNATIVE FIRST-LINE ANTIVIRAL REGIMENS

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Children (2–11 years)	TDF ETV		
Adolescents (12–17 years)	TDF ETV	TDF + 3TC TDF + FTC TAF	Osteoporosis and/or impaired kidney function: ETV, TAF
Adults	TDF ETV	TDF + 3TC TDF + FTC	

TDF: tenofovir disoproxil fumarate; **ETV**: entecavir; **3TC**: lamivudine; **FTC**: emtricitabine; **TAF**: tenofovir alafenamide fumarate

DOSING OF MEDICINES IN CHILDREN AND ADOLESCENTS

Drug	Patient group	Dose
TDF[a]	Age ≥2 years	8 mg/kg once daily (maximum 300 mg daily)
	Age ≥12 years	300 mg daily
TAF[b]	Age ≥12 years	25 mg once daily
ETV[c]	Weight <30 kg	0.015 mg/kg once daily (maximum 0.5 mg daily)
	Weight ≥30 kg	0.5 mg once daily

[a]TDF: The European Medicines Agency (EMA) has approved TDF for children two years or older with chronic HBV and the U.S. Food and Drug Administration (US FDA) for children two years and older weighing at least 10 kg.

[b]TAF: The EMA has approved TAF for children six years and older and weighing more than 25 kg and the US FDA for children 12 years and older with compensated liver disease.

[c]ETV: Approved by EMA and US FDA for children two years or older.

MONITORING FOR TREATMENT RESPONSE

Monitoring enables an understanding of the response to treatment, adverse effects, and the progression of liver disease.

People who are receiving treatment should be monitored at least annually with:

- Non-invasive tests—APRI or transient elastography—to assess stage of disease and progression of fibrosis or cirrhosis.
- ALT and AST level, HBV DNA (where HBV DNA testing is available), HBsAg, and HBeAg/anti-HBe.

People with advanced liver disease, people living with HIV, people with renal impairment, and people with concerns of adherence may be monitored more frequently—including every 3–6 months for the first year.

REGIONAL RELEVANCE

The WHO estimates 254 million people are living with chronic HBV globally. The Asia-Pacific region bears 62% of this burden, with more than 154 million people. Regional action plans for viral hepatitis have been published,[ii,iii] and national governments either have initiated diagnosis and treatment programs or are in the process of developing their own strategies.

HBV-associated mortality is trending upwards, with 1.1 million deaths in 2022 compared to 820,000 reported in 2019; 67% of these deaths were in the Asia-Pacific.

High-quality generic TDF is broadly available and can cost approximately US$28 per person per year. However, ETV can cost up to $180 per person per year, depending on the dosing. Access to pediatric formulations is more limited.

To advance toward the elimination of HBV by 2030, national programs in the region need to rapidly expand screening, vaccination, diagnosis, and treatment of HBV through the adoption of the updated guidelines.

The full guidelines can be accessed at https://www.who.int/publications/i/item/9789240090903.

[i] Online score calculators are available at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri

[ii] http://www.wpro.who.int/hepatitis/resource/features/regional_action_plan/en/ and https://www.who.int/publications/i/item/9789290620136

[iii] World Health Organization, Regional Office for South-East Asia https://iris.who.int/handle/10665/361834