

Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection (Text Extract): Executive Summary

World Health Organization

Hepatitis B virus (HBV) infection is a major public health problem and cause of chronic liver disease that led to an estimated 820,000 deaths in 2019, mainly due to cirrhosis and liver cancer. In 2019, WHO estimated that 296 million people were chronically infected and living with hepatitis B, with a disproportionately high burden in low- and middle-income countries. The WHO African region, together with the South-East Asia Region and Western Pacific Region account for 88% of the global burden. Most of the global burden of chronic hepatitis B (CHB) can be attributed to mother-to-child transmission at the time of or shortly after birth, and such perinatal infections lead to a high rate of chronicity. Considerable progress has been made towards eliminating the perinatal transmission of HBV through universal infant HBV immunization, including the timely hepatitis B birth dose, which has been highly effective in reducing new infections among children. However, in 2022 hepatitis B birth-dose coverage was only 45% globally, with the lowest coverage (18%) in the WHO African Region. For people with CHB infection, nucleoside analogue treatment with currently recommended tenofovir and entecavir is highly effective and can delay the progression of cirrhosis, reduce the incidence of hepatocellular carcinoma (HCC) and improve long-term survival. However, a major testing and treatment gap remains. In 2019, only 10% of the estimated 296 million people with CHB had been diagnosed and 2% had been treated. Scaling up testing and treatment towards the elimination goals will require a radical simplification of treatment criteria and care pathways to overcome barriers in access to hepatitis B testing and treatment.

In 2015, WHO issued the first comprehensive guidelines on prevention, care and treatment for people with CHB, followed in 2017 with guidelines on testing for viral hepatitis B and C and in 2021 with WHO guidelines on preventing the mother-to-child transmission of HBV using antiviral prophylaxis in pregnancy. Several significant developments have occurred since the 2015 guidelines were published. These include new study data on the following: diagnostic performance of non-invasive tests for staging of liver disease and cut-off thresholds for diagnosing significant fibrosis

or cirrhosis; natural history of CHB in different regions and antiviral therapy effectiveness according to different HBV DNA and ALT levels; comparison of the effectiveness and safety of dual combination of tenofovir + lamivudine or emtricitabine and also tenofovir alafenamide fumarate (TAF), a prodrug of tenofovir compared to tenofovir; diagnostic performance and impact of HBV DNA point-of-care viral load testing technologies; testing for hepatitis D virus coinfection (who to test and how to test), and impact of reflex testing approaches for HBV DNA and hepatitis D infection; and evaluation of impact of different service delivery models for care and treatment of CHB on outcomes across the cascade of care. In addition, there are opportunities to further expand use of antiviral prophylaxis to prevent mother-to-child transmission linked with the global initiative for triple elimination of HIV, hepatitis B and syphilis.

The objective of the 2024 guidelines is to provide updated evidence-informed recommendations on key priority topics. These include expanded and simplified treatment criteria for adults but now also for adolescents; expanded eligibility for antiviral prophylaxis for pregnant women to prevent mother-to-child transmission of HBV; and improving HBV diagnostics through use of point-of-care HBV DNA viral load and reflex approaches to HBV DNA testing; and who to test and how to test for HDV infection.

The 2024 guidelines include 11 updated chapters with new recommendations:

Expanded treatment eligibility and antiviral prophylaxis

- use of non-invasive tests for staging of liver disease (Chapter 4);
- who to treat among people with CHB (Chapter 5);
- first-line antiviral therapies for CHB (Chapter 6);
- preventing mother-to-child transmission of hepatitis B using antiviral prophylaxis (Chapter 7);
- treatment of adolescents and children with CHB (Chapter 8);

Hepatitis B DNA and HDV infection diagnostics

- measurement of HBV DNA to guide treatment eligibility and monitor response (Chapter 9);
- HBV DNA reflex testing (Chapter 10);
- HDV testing - who to test and how to test, including reflex testing for hepatitis delta coinfection (Chapters 12–14);

HBV Service Delivery

- Eight approaches to promote access and delivery of high-quality health services for CHB (no new recommendations but includes

Copyright © 2024 The Chinese Medical Association, published by Wolters Kluwer Health, Inc.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Infectious Diseases & Immunity (2024) 4:3

Received: 22 May 2024

First online publication: 12 June 2024

<http://dx.doi.org/10.1097/ID9.0000000000000128>

existing recommendation on strategies to promote linkage to care) (Chapter 15).

There are also updates to five chapters relating to monitoring with unchanged recommendations from the 2015 guidelines, but these have been updated with new context, additional studies and research gaps. These chapters are:

- second-line antiviral therapies for managing treatment failure (Chapter 9);
- monitoring for treatment response (Chapter 16) and treatment side effects (Chapter 17)
- surveillance for HCC (Chapter 18);
- when to stop and restart antiviral therapy (Chapter 19).

The development of these guidelines was conducted in accordance with procedures established by the WHO Guidelines Review Committee. Clinical recommendations were formulated by a regionally representative and multidisciplinary Guidelines Development Group at a meeting held in May 2023. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to formulate and categorize strength of recommendations (strong or conditional) and was adapted for diagnostic tests. This includes assessing the certainty of evidence (high, moderate, low or very low), consideration of overall balance of benefits and harm (at individual and population levels), patient and health-care worker values and preferences, resource use, cost-effectiveness and consideration of feasibility and effectiveness across a variety of resource-limited settings, including when access to laboratory infrastructure and specialized tests is limited. The process also identified key gaps in knowledge that will guide the future research agenda.

Fifteen systematic reviews and meta-analyses were undertaken to address the key research questions, in addition to two modelling and cost-effectiveness analyses on the impact of expanded treatment eligibility criteria at the global, regional and country levels and the impact of expanding antiviral prophylaxis for preventing mother-to-child transmission to include all hepatitis B surface antigen (HBsAg)-positive pregnant women. In addition, WHO commissioned various partner organizations to undertake four key surveys among populations affected by hepatitis B, healthcare workers and national hepatitis programme managers to assess the acceptability of potential recommendations relating to topics covered in the guidelines.

The main areas of new recommendations are the following.

Expanded eligibility for treatment

The updated recommendations provide four options for meeting treatment eligibility that apply to all adults with CHB and now also adolescents (aged 12 years or older). Only one of the four options requires access to HBV DNA testing, which has been considered one of the major barriers to accessing treatment. Overall, these four options will capture a much higher proportion (at least 50%) of all HBsAg-positive people (depending on the region) compared to about 8–15% previously. They include:

1. Treat all with significant fibrosis (previously only cirrhosis) based on revised thresholds of non-invasive tests for staging of liver disease (APRI score > 0.5 or transient elastography (if available) >7 KPa), regardless of HBV DNA or ALT levels. This recommendation will capture an estimated 20–25% of all HBsAg-positive people.
2. Treat all with HBV DNA > 2000 IU/mL (previously >20,000 IU/mL) and ALT above the upper limit of normal (ULN). This recommendation will capture an estimated 20–35% of all HBsAg-positive people.

3. Treat all with coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroid use, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction-associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of HBV DNA or ALT levels. This recommendation will capture an estimated 5–8% of HBsAg-positive people.
4. An additional conditional recommendation (where there is no access to HBV DNA) to treat those with CHB based on persistently abnormal ALT levels alone. This recommendation, which is retained from the 2015 WHO hepatitis B guidelines, will capture an estimated 20% of all HBsAg positive people.

Alternative antiviral regimens for treatment

The existing recommendation for use of two nucleoside analogues with a high genetic barrier to resistance - tenofovir disoproxil fumarate (TDF) or entecavir (ETV) as preferred first-line regimens was retained from the 2015 WHO hepatitis B guidelines. The new recommendation is for use of dual regimens of tenofovir + lamivudine or tenofovir + emtricitabine as alternative regimens in settings where access to tenofovir monotherapy is lacking but where there is ready access to the dual regimens at low-cost (as component of ART regimens) through existing ARV drug procurement. The use of tenofovir alafenamide fumarate (TAF) is reserved for special circumstances for those with existing or at risk of renal impairment or osteoporosis.

Expanding access to antiviral prophylaxis for prevention of mother-to-child transmission (PMTCT)

The existing recommendation for use of TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA levels $\geq 200\ 000$ IU/mL or a positive HBeAg, in settings where there is ready access to these assays, is retained from the 2020 WHO hepatitis B antiviral prophylaxis guidelines for PMTCT. To address the continued significant challenge in accessing HBV DNA or even HBeAg serology testing to determine eligibility for antiviral prophylaxis, a new conditional recommendation provides the option of using antiviral prophylaxis for all HBsAg-positive pregnant mothers. Use of prophylaxis is preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series, in addition to hepatitis B infant vaccination, including hepatitis B birth dose for HBV PMTCT. It provides the option to continue TDF for mothers who meet the criteria for antiviral therapy for their own health and among women of childbearing age planning additional pregnancies.

Point-of-care and reflex HBV DNA testing

The use of POC HBV DNA nucleic acid testing (NAT) assays is now recommended as an alternative approach to laboratory-based HBV DNA testing to assess treatment eligibility and to monitor treatment response. Reflex HBV DNA testing in those with a positive HBsAg test result is recommended as an additional strategy to promote linkage to care and treatment. This can be achieved either through automatic laboratory-based reflex HBV DNA testing using a specimen already held in laboratory, or clinic-based reflex testing in a health facility through immediate specimen collection

for HBV DNA testing following a positive rapid HBsAg test result, avoiding the need for a second visit and further blood sample.

HDV infection testing - who to test and how to test, and use of reflex Delta antibody serology and HDV RNA NAT testing

The guidelines now include recommendations for who to test and how to test for chronic hepatitis D (CHD), a major contributor to more rapid progression and HBV liver-related morbidity and mortality. For who to test - WHO recommends a universal HDV antibody testing approach among people with CHB, or where this approach may not be feasible because of limited laboratory capacity - for testing to be prioritised in specific HBsAg-positive populations or settings with well-established higher prevalence of HDV infection. These include people born in HDV-endemic countries and regions; people at higher risk of acquiring HDV (people who inject drugs, men who have sex with men, sex workers, people living with HCV or HIV, and haemodialysis recipients); children and family members of people with HDV infection; people with advanced liver disease; and those already receiving HBV treatment. For how to test - WHO recommends a serological assay to detect total anti-HDV followed by a NAT to detect HDV RNA and active (viraemic) infection among those who are anti-HDV positive. Reflex testing is recommended for anti-HDV antibody testing following a positive HBsAg test result and also for HDV RNA testing (where available) following a positive anti-HDV antibody test result, as an additional strategy to promote diagnosis, and improve care and monitoring.

Key approaches for delivering high-quality services for hepatitis B care

Hepatitis B still has a very limited direct evidence base to guide formal recommendations on service delivery. Eight key approaches are promoted for high-quality health service delivery for hepatitis B care applied from similar principles in HIV and HCV care. These include: strategies to promote uptake of testing and strengthen linkage to care, treatment and prevention; strategies to promote

and sustain adherence to long-term antiviral therapy; strategies to promote retention in care and track and re-engage those disengaged from care; integration of hepatitis testing, care and treatment with other services (such as HIV services and primary care) to increase the efficiency and reach of hepatitis services; decentralization of testing and treatment services at primary health facilities to promote access to care supported through task-sharing and a differentiated care strategy; and community engagement and peer support.

These guidelines are addressed primarily to clinicians as well as national hepatitis programme managers and other policy-makers in health ministries, especially in low- and middle-income countries, who are responsible for developing national hepatitis testing and treatment plans, policy and guidelines. Implementation of the recommendations in these guidelines should be informed by local context, including hepatitis B epidemiology and prevalence of other comorbidities, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.

Overall, this guideline update is consistent with the modular approach to updating guidelines for diagnosis and treatment of chronic hepatitis B and C virus infections adopted since 2020. In 2025, all updates will be compiled along with existing recommendations into consolidated guidelines on prevention, testing, care and treatment for hepatitis B and C, containing all relevant guidance.

Acknowledgment

World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection [EB/OL]. [2024-03-29]. <https://www.who.int/publications/item/9789240090903>.

Edited By Wei Zhao

How to cite this article: World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis b infection (text extract): executive summary. *Infect Dis Immun* 2024;4(3):103–105. doi: 10.1097/ID9.000000000000128