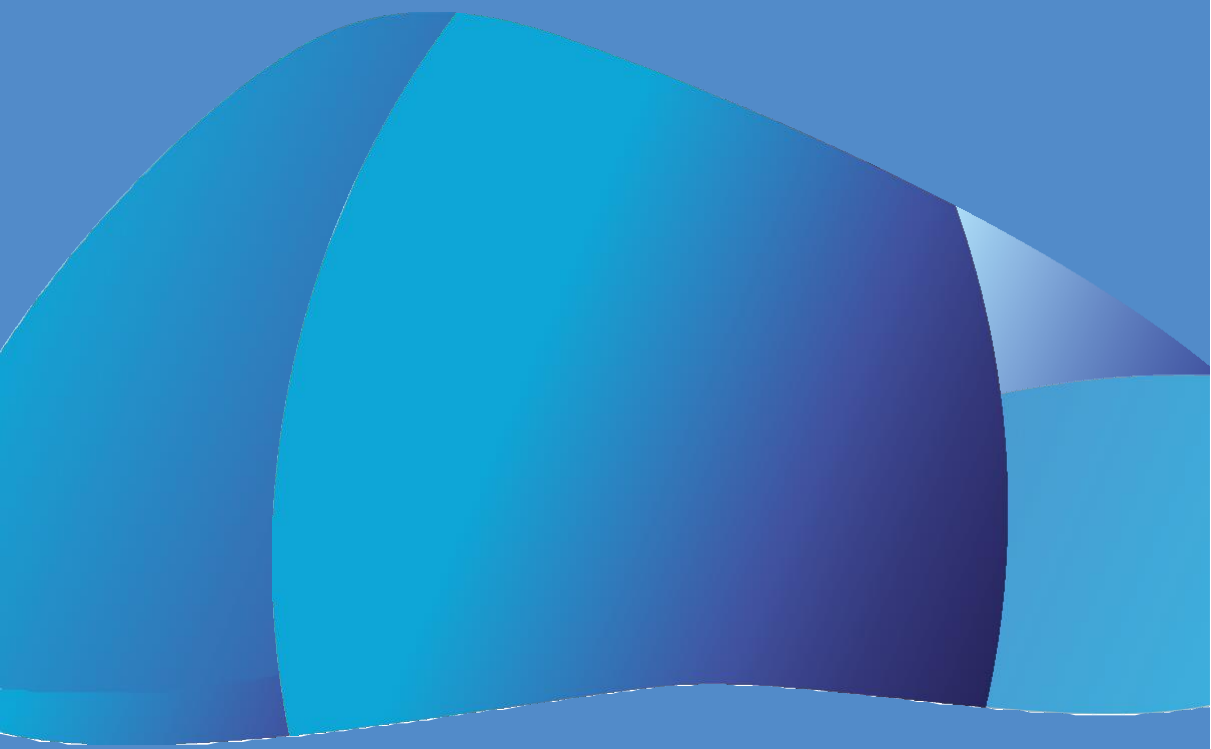
World Health Organization

Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection

March 2024



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CORRIGENDA (21/02/2025)

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Page xi, lines 22	
Insert:	Service delivery and care cascade outcomes for people living with chronic hepatitis B: systematic review and meta-analysis: Alexander J. Stockdale (University of Liverpool, Liverpool, United Kingdom), Bethany Holt (Harvard Medical School, USA), Ajeet Singh Bhadoria (All India Institute of Medical Sciences, Rishikesh, India) Abishek Sadasivan (All India Institute of Medical Sciences, Rishikesh, India), Daniel Ikeda (Harvard Medical School, USA),Todd Pollack (Harvard Medical School, USA), Janus Ong (National Institute of Health, Manila, Philippines), Thuy Pham (Health Advancement In Vietnam (HAIVN)), David Duong (Harvard), Vy Nguyen (Harvard), Gibril Ndow (The Medical Research Council Unit The Gambia, Banjul, The Gambia), Philippa Easterbrook (WHO).
Page xi, lines 24	
Insert:	HBV DNA and Delta laboratory-based reflex testing case studies: Lindsey Hiebert and John Ward (Coalition for Global Hepatitis Elimination, Task Force for Global Health, United States of America).
Page xxii, lines 2	
Delete:	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.
Insert:	Hepatitis B virus (HBV) infection is a major public health problem and cause of chronic liver disease that led to an estimated 1.1 million deaths in 2022, mainly due to cirrhosis and liver cancer. In 2022, WHO estimated that 254 million people were chronically infected and living with hepatitis B, with a disproportionately high burden in low- and middle-income countries, of whom 65% were in the African and Western Pacific regions.
Page xxii, lines 16	
Delete:	In 2019, only 10% of the estimated 296 million people with CHB had been diagnosed and 2% had been treated.

Insert:	In 2022, only 13% of the estimated 254 million people with CHB had been diagnosed and 3% had been treated.
Page xxxi, lines 26	
Delete:	In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate (TDF)b is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAga (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.
Insert:	In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate (TDF)b is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.
Page xxxi, lines 36	
Delete:	All pregnant women and girls of reproductive age should be assessed first for eligibility for long-term treatment for their own health.
Insert:	It is advised that all pregnant women and girls of reproductive age should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of prophylaxis.
Page xlii, lines 7	
Delete:	ASSESSMENT OF ELIGIBILITY FOR ANTIVIRAL PROPHYLAXIS
Insert:	ASSESSMENT OF ELIGIBILITY FOR ANTIVIRAL PROPHYLAXIS [b]
Page xlii, lines 32	
Delete:	HEPATITIS B BIRTH DOSE VACCINATION OF THE INFANT FOLLOWED BY 2 OR 3 DOSES OF VACCINE [b]
Insert:	HEPATITIS B BIRTH DOSE VACCINATION OF THE INFANT FOLLOWED BY 2 OR 3 DOSES OF VACCINE [c]
Page xlii, lines 36	
Delete:	[b] Hepatitis B timely (within 24 hours) birth dose vaccination of the infant followed by 2 or 3 doses of hepatitis B vaccine should be given regardless of HBsAg status of the pregnant mother. HBIG (if available) is also offered mainly in high income settings for infants born to HBsAg positive mothers, especially with high HBV DNA.
Insert:	[b] It is advised that all pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of antiviral prophylaxis.

[c] Hepatitis B timely (within 24 hours) birth dose vaccination of the infant followed by 2 or 3 doses of hepatitis B vaccine should be given regardless of HBsAg status of the pregnant mother. HBIG (if available) is also offered mainly in high income settings for infants born to HBsAg positive mothers, especially with high HBV DNA.

Page 6, lines 3

Delete:

HBV is spread predominantly by percutaneous or mucosal exposure to infected blood and body fluids, such as saliva, menstrual and vaginal discharge, seminal fluid, colostrum and breastmilk and serous exudates (13). HBV may also be transmitted from accidental inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures or from sharp objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture. HBV may be sexually transmitted (13).

Insert:

HBV is spread predominantly by percutaneous or mucosal exposure to infected blood and various body fluids, including saliva, menstrual, vaginal, and seminal fluids, which have all been implicated as vehicles of human transmission (13). HBV may also be transmitted from accidental inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures or from sharp objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture. Sexual transmission of hepatitis B may occur, particularly in unvaccinated men who have sex with men and heterosexual persons with multiple sex partners or contact with sex workers (13).

Page 37, lines 11

Delete:

d Non-invasive tests including APRI and transient elastography have not yet been validated for children and adolescents.
e Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

Insert:

d Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.
e Non-invasive tests including APRI and transient elastography have not yet been validated for children and adolescents.

Page 63, lines 21

Delete:

All pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health.

Insert:	It is advised that all pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of antiviral prophylaxis.

Page 65, lines 6

Delete:	All pregnant women should be assessed first for eligibility for long-term treatment for their own health and then for antiviral prophylaxis to prevent mother-to-child transmission (if not eligible for treatment or pregnant mother declines).
Insert:	It is advised that all pregnant women should be assessed first for eligibility for long-term treatment for their own health and then for antiviral prophylaxis to prevent mother-to-child transmission (if not eligible for treatment or pregnant mother declines). However, this assessment for long-term treatment should not delay the initiation of prophylaxis.

Page 114, lines 29

Delete:	Routes of transmission: HDV shares the same routes of transmission as HBV, including percutaneous or other contact with infected blood and body fluids (such as semen and saliva) through injecting drug use involving sharing contaminated needles and syringes, sex with a partner with HDV infection, needle-stick injuries, transfusion of contaminated blood products and sharing items such as razors with people with HDV infection (12). MTCT of HDV may occur but appears to be rare (13,14).
Insert:	Infection with HDV is parenterally transmitted. Transmission of HDV can occur by inapparent intrafamilial household transmission, facilitated by poor hygiene and the sharing of hygiene items, such as razors or toothbrushes. Transmission can occur as well in high-risk populations, such as people who inject drugs and people exposed to blood or blood products. Sexual transmission and perinatal transmission of HDV are rare (12,13,14)

These corrections have been incorporated into the electronic file.

Contents

Expanded treatment eligibility

HBV and HDV diagnostics

HBV service delivery and monitoring

Acknowledgements

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Contributors to the systematic reviews and other supporting evidence

WHO would like to credit the following researchers for conducting the systematic reviews, evidence profiles and GRADE tables, values and preferences surveys and programmatic feasibility case studies.

Evidence from systematic reviews

- A systematic review and meta-analysis of the diagnostic accuracy of non-invasive fibrosis tests for staging fibrosis in patients with chronic hepatitis B infection: a systematic review and meta-analysis: Emmanouil Tsochatzis, Mirko Zoncape, Antonio Liguori (UCL Institute of Liver and Digestive Health, United Kingdom), Giovanni Cassazza (University of Milan, Italy).
- Natural history of chronic HBV infection by HBV DNA and ALT levels at baseline: a systematic review and meta-analysis: Daniela Yucuma Conde, Arthur Rakover, Zakary Warsop, Yu Ri Im, Rukmini Jagdish, Emma Chen, Yusuke Shimakawa (Institut Pasteur, France).
- The efficacy of antiviral therapy at preventing clinical outcomes in people with HBV at different baseline HBV DNA and ALT levels: a systematic review and meta-analysis: Yu Ri Im, Rukmini Jagdish, Emma Chen, Daniela Yucuma Conde, Arthur Rakover, Zakary Warsop, Yusuke Shimakawa (Institut Pasteur, France).
- Proportion of pregnant women with chronic hepatitis B virus infection eligible for antiviral prophylaxis to prevent vertical transmission: a systematic review and meta-analysis: Hugues Delamare (University of Paris-Saclay, France), Yusuke Shimakawa (Institut Pasteur, France).
- Impact and cost-effectiveness of HBV prophylaxis in pregnancy: a modelling study: Shevanthi Nayagam, Margaret J. de Villiers (Imperial College London, United Kingdom), Yusuke Shimakawa (Institut Pasteur, France), Maud Lemoine, Mark R. Thursz (Imperial College London, United Kingdom), Nick Walsh (Monash University, Australia), Timothy B. Hallett (Imperial College London, United Kingdom).
- Tenofovir disoproxil fumarate (TDF) versus tenofovir alafenamide fumarate (TAF) or TDF/emtricitabine (TDF + FTC) to treat hepatitis B: a systematic review and meta-analysis: Andrew Hill (University of Liverpool, United Kingdom).
- Diagnostic accuracy of point-of-care HBV HBV DNA assays for quantifying hepatitis B virus DNA: a systematic review and meta-analysis: Yusha Tao, Chengxin Fan, Yifan Dai, Feifei Li, Weiming Tang, Joseph D. Tucker (University of North Carolina Project-China, Guangzhou, China), Roger Chou (Oregon Health & Science University, United States of America), Philippa Easterbrook (WHO), Weiming Tang (University of North Carolina at Chapel Hill, United States of America).

- Impact of hepatitis B virus point-of-care DNA viral load testing compared with laboratory-based standard-of-care approaches on uptake of HBV viral load testing and treatment and turnaround times: a systematic review and meta-analysis: Shuqin Gu, Yusha Tao, Chengxin Fan, Yifan Dai, Feifei Li, Joseph D. Tucker (University of North Carolina Project–China, Guangzhou, China), (University of North Carolina at Chapel Hill, United States of America), Chengxin Fan, Yifan Dai, Feifei Li, Joseph D. Tucker, Roger Chou (Oregon Health & Science University, United States of America), Philippa Easterbrook (WHO), Weiming Tang (University of North Carolina at Chapel Hill, United States of America).
- Laboratory-based and clinic-based hepatitis B virus DNA viral load reflex testing following initial positive HBsAg results: a systematic review and meta-analysis: Yusha Tao, (University of North Carolina at Chapel Hill, United States of America), Feifei Li, Chengxin Fan, Yifan Dai, Weiming Tang, Joseph D. Tucker, (University of North Carolina Project–China, Guangzhou, China), Roger Chou (Oregon Health & Science University, United States of America), Philippa Easterbrook (WHO), Weiming Tang (University of North Carolina at Chapel Hill, United States of America).
- Immediate laboratory-base reflex testing of those HBsAg positive for delta serology: a systematic review and meta-analysis: Yusha Tao, Yifan Dai, Chengxin Fan, Feifei Li, Weiming Tang, Joseph D. Tucker, (University of North Carolina Project–China, Guangzhou, China), Roger Chou (Oregon Health & Science University, United States of America), Philippa Easterbrook (WHO), Weiming Tang (University of North Carolina at Chapel Hill, United States of America).
- Service delivery and care cascade outcomes for people living with chronic hepatitis B: systematic review and meta-analysis: Alexander J. Stockdale (University of Liverpool, Liverpool, United Kingdom), Bethany Holt (Harvard Medical School, USA), Ajeet Singh Bhadoria (All India Institute of Medical Sciences, Rishikesh, India) Abishek Sadasivan (All India Institute of Medical Sciences, Rishikesh, India), Daniel Ikeda (Harvard Medical School, USA),Todd Pollack (Harvard Medical School, USA), Janus Ong (National Institute of Health, Manila, Philippines), Thuy Pham (Health Advancement In Vietnam (HAIVN)), David Duong (Harvard), Vy Nguyen (Harvard), Gibril Ndow (The Medical Research Council Unit The Gambia, Banjul, The Gambia), Philippa Easterbrook (WHO).
- Who to test for hepatitis D virus: narrative review of evidence: Sahar Bajis, Niklas Luhmann (WHO).
- HBV DNA and Delta laboratory-based reflex testing case studies: Lindsey Hiebert and John Ward (Coalition for Global Hepatitis Elimination, Task Force for Global Health, United States of America).

Market landscaping reviews

- Market landscape of TAF and TDF/XTC therapy: Navya Sharma, Oriel Fernandes, Ritubhan Gautam (Clinton Health Access Initiative, United States of America).
- HBV DNA and HBeAg product and market assessment: Emi Okamoto, Robia Islam (Clinton Health Access Initiative, United States of America).
- HDV diagnostics: product landscape and clinical performance of anti-HDV and HDV RNA assays: Emi Okamoto, Robia Islam (Clinton Health Access Initiative, United States of America).

Modelling

- Impact and cost-effectiveness of antiviral prophylaxis for PMTCT in pregnancy: modelling of impact and cost-effectiveness: Shevanthi Nayagam, Margaret J. de Villiers, Timothy B. Hallett (Imperial College London, United Kingdom).
- Impact of expanded treatment eligibility at global, country and regional levels: Homie Razavi, Devin Razavi-Shearer, Ivane Gamkrelidze (Center for Disease Analysis, CDA Foundation, United States of America).

Values and preferences surveys and research

- Values and preferences survey for hepatitis B treatment community perspectives: Key contributors: Catherine Freeland (Hepatitis B Foundation, United States of America), Jessica Hicks and Cary James (World Hepatitis Alliance, United Kingdom), Jack Wallace (Burnet Institute, Australia), Charles Ampong Adjei (University of Ghana, Ghana), Josephine M. Dina Moussa, Marvad Ahad, Gibril Ndow (Hepatitis Research Group, MRC Unit, The Gambia at London School of Hygiene and Tropical Medicine, United Kingdom), Peyton Thompson (University of North Carolina, United States of America).
- Global health care worker preference survey on HBV treatment and diagnostics: Capucine Penicaud (International Coalition to Eliminate Hepatitis B, Australia), Camilia Picchio (Institute of Global Health, Spain), Daryl Lau (Beth Israel Deaconess Hospital, United States of America), Catherine Freeland (Hepatitis B Foundation, United Kingdom), Manal Hamdy El-Sayed (Ain Shams University, Egypt).
- Health-care worker values and preferences survey of treatment of chronic hepatitis B infection in children and adolescents: Farihah Malik, Philippa Easterbrook (WHO), Giuseppe Indolfi (University of Florence, Italy), Simon Ling (University of Toronto, Canada).
- National hepatitis programme managers preferences survey on new directions in hepatitis B care and treatment and HBV PMTCT: Philippa Easterbrook, Doroux Aristide Charles Billy, Myat Sandi Min (WHO).
- HBV and HDV laboratory-based reflex testing case studies: John W. Ward, Lindsey Hiebert, Jana Manning, Neil Gupta (Coalition for Global Hepatitis Elimination, Task Force for Global Health, United States of America).

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Abbreviations and acronyms

AFP	alpha-fetoprotein
aHR	adjusted hazard ratio
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
ARFI	acoustic radiation force impulse (imaging)
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
Anti-HBc	hepatitis B core antibody (total: IgM and IgG)
Anti-HBe	antibody to hepatitis B e antigen
Anti-HBs	antibody to hepatitis B surface antigen
BMI	body mass index
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
CHD	chronic hepatitis D
CI	confidence interval
CrCl	creatinine clearance
DALY	disability-adjusted life-year
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMTCT	elimination of mother-to-child transmission
FDA	United States Food and Drug Administration
FIB-4	fibrosis-4 score
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBcAg	hepatitis B core antigen
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D (delta) virus
HepBD	hepatitis B vaccine given within 24 hours of birth
HepB3	three doses of hepatitis B vaccine given in infancy
HR	hazard ratio
IFN	interferon

IgG	immunoglobulin G
IgM	immunoglobulin M
LDL	low-density lipoprotein
MDRD	modification of diet in renal disease
MTCT	mother-to-child transmission
NAT	nucleic acid testing
NRTI	nucleos(t)ide reverse-transcriptase inhibitor
OR	odds ratio
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PEPFAR	United States President's Emergency Plan for AIDS Relief
PICO	population, intervention, comparison, outcomes
POC	point of care
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
RDT	rapid diagnostic test
RR	relative risk
TB	tuberculosis
ULN	upper limit of normal

Abbreviations and names of antiviral drugs

3TC	lamivudine
DTG	dolutegravir
EFV	efavirenz
ETV	entecavir
FTC	emtricitabine
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate

Glossary of terms

Natural history of hepatitis B virus (HBV) infection	
Acute HBV infection	New-onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg, with seroconversion to anti-HBs (anti-bodies to hepatitis B surface antigen), usually within three months
Chronic HBV infection	Defined as persistence of HBsAg for six months or more after acute infection with HBV. Throughout the guidelines, chronic hepatitis B (CHB) is used to indicate chronic HBV infection
Immune-tolerant phase	High replicative phase of infection in the early stage of CHB among people infected at birth or in early childhood
Immune-active phase	Phase of hepatitis B e antigen (HBeAg)-positive disease characterized by fluctuating aminotransferases and high HBV DNA concentrations. May result in seroconversion from HBeAg to antibody to hepatitis B e antigen (anti-HBe)
Inactive phase (or immune-control phase)	Low replicative phase of CHB characterized by HBeAg negativity, anti-HBe positivity, normal alanine aminotransferase (ALT) and HBV DNA concentration below 2000 IU/mL
HBeAg seroconversion	Loss of HBeAg and seroconversion to anti-HBe
HBeAg-negative CHB (immune-escape phase)	HBeAg-negative but anti-HBe-positive disease with varying levels of HBV replication and liver injury
HBsAg seroconversion	Loss of HBsAg and development of anti-HBs
HBeAg reversion	Reappearance of HBeAg among people who were previously HBeAg negative and usually associated with increased HBV replication
Cirrhosis	An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation
Decompensated cirrhosis	Clinical complications of cirrhosis become manifest, including jaundice, ascites, spontaneous bacterial peritonitis, oesophageal varices and bleeding, hepatic encephalopathy, sepsis and renal failure
Hepatocellular carcinoma (HCC)	Primary cancer of the liver arising in hepatocytes

Serological markers of HBV	
Hepatitis B surface antigen (HBsAg)	HBV envelope protein and excess coat particles detectable in the blood in acute and CHB infection
Hepatitis B core antigen (HBcAg)	HBV core protein, coated with HBsAg and therefore not found free in serum
Hepatitis B e antigen (HBeAg)	Viral protein found in the high replicative phase of hepatitis B. HBeAg is usually a marker of high levels of replication with wild- type virus but is not essential for viral replication
Hepatitis B surface anti-body (anti-HBs)	Antibody to HBsAg that develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity
Anti-HBe	Antibody to HBeAg detected among people with lower levels of HBV replication but also in HBeAg-negative disease (HBV that does not express HBeAg)
Hepatitis B core antibody (total anti-HBc)	Antibody to hepatitis B core (capsid) protein. Total anti-HBc antibodies are not neutralizing antibodies and are a marker of both exposure and prior infection.
IgM anti-HBc	Subclass of anti-HBc. Detected by sensitive assays during acute hepatitis B and a flare or reactivation of chronic HBV
Occult HBV infection	People who have cleared hepatitis B surface antigen: they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL); most are also total anti-HBc positive
Hepatitis D infection	
HBV and HDV coinfection	Infection simultaneously with HBV and HDV. People with coinfection have increased risk of severe acute hepatitis and acute liver failure. Recovery is usually complete and chronic infection rare
HDV superinfection	When a person with an established CHB infection becomes infected with HDV. Superinfection frequently leads to chronic hepatitis D and increased risk of rapid progression to cirrhosis and development of HCC
Total anti-HDV	Total antibodies (IgM and IgG) to hepatitis D virus occurring only among people who are HBsAg positive. Detection of anti-HDV antibodies indicates exposure to hepatitis D virus
HDV RNA	HDV RNA can be detected and quantified in serum or plasma. Testing for the presence of HDV RNA confirms active viraemic infection and differentiates it from past cleared infection

Tests for assessing and monitoring hepatitis B infection	
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes that reflect liver cell injury since they are released after cell injury or death
HBV DNA	HBV DNA that can be detected and quantified in serum or plasma. HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL. 1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5 (10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). All HBV DNA values in the recommendations in these guidelines are reported in IU/mL. An undetectable viral load is an HBV DNA level below the level of sensitivity of the laboratory assay. For sensitive polymerase chain reaction assays, this is generally a concentration below 15 IU/mL.
Alpha-fetoprotein (AFP)	A host cellular protein. High levels can occur among people with hepatocellular carcinoma.
Persistently abnormal or normal ALT level	ALT levels fluctuate among people with CHB and require longitudinal monitoring to determine the trend. The upper limits for normal ALT have been defined as below 30 U/L for men and boys and 19 U/L for women and girls, although local laboratory normal ranges should be applied. Persistently normal or abnormal may be defined as two ALT values below or above the upper limit of normal (ULN) at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend. In adolescents, treatment of those with HBV DNA >2000 IU/mL and ALT > ULN should be based on at least two elevated ALT >ULN over a 6- to 12-month period.
Assessment of liver fibrosis by non-invasive tests	
Aspartate aminotransferase (AST)-to-platelet ratio index (APRI)	A simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations The formula for calculating the APRI is: APRI = (AST/ULN) Í 100)/ platelet count (10^9/L). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
Fibrosis-4 score (FIB-4)	An index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. The formula for calculating FIB-4 is: FIB-4 = (age (years) Í AST (IU/L))/(platelet count (10^9/L Í [ALT (IU/L)(1/2)]). An online calculator is available at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
Transient elastography	A technique to measure liver stiffness (as a surrogate for fibrosis) based on the propagation of a shear wave through the liver

Measures of performance of diagnostic tests	
Clinical or diagnostic sensitivity of a test	The ability of a test to correctly identify those with the infection or disease (true positives/true positives + false negatives)
Clinical or diagnostic specificity of a test	The ability of a test to correctly identify those without the infection or disease (true negatives/true negatives + false positives)
Positive predictive value	The probability that when a person's test result is positive, they truly have the infection or disease (true positives/true positives + false positives)
Negative predictive value	The probability that when a person's test result is negative, they truly do not have the infection or disease (true negatives/true negatives + false negatives). Predictive values (negative and positive) are influenced by the prevalence of the disease in the population
Analytical sensitivity or limit of detection	The lowest concentration of measurement that can be consistently detected in 95% of specimens tested under routine laboratory conditions. It defines the analytical sensitivity in contrast to the clinical or diagnostic sensitivity
Measures of hepatitis B treatment response	
Hepatitis B treatment response	Undetectable HBV DNA in the blood at a defined time point after treatment ends
Hepatitis B treatment failure (primary non-response)	In settings where HBV DNA testing is available: Primary antiviral non response is defined as <1 log10 IU/mL decrease of serum HBV DNA after three months of initiating therapy. Many with high level of baseline HBV DNA will be positive after one year of therapy but have a decline in HBV DNA and would not be classified as non-response. In settings where HBV DNA testing is not available: treatment failure and drug resistance may be suspected based on the following features: receiving antiviral drugs with a low barrier to resistance together with documented or suspected poor adherence; and laboratory measures such as an increase in serum aminotransferases and/or evidence of progressive liver disease. Note: elevated ALT tends to occur late and is a relatively poor predictive marker of resistance. Confirmation of antiviral drug failure can be established by sequencing the HBV DNA polymerase and identifying specific genetic markers of antiviral drug resistance.

Diagnostic testing for hepatitis	
Serological assays	Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary or venous whole blood and dried blood spot samples. These include rapid diagnostic tests (RDTs) and laboratory-based immunoassays, such as enzyme immunoassays, chemiluminescence immunoassays and electro- chemiluminescence immunoassays.
Rapid diagnostic test	Immunoassays that detect antibodies or antigens and can give a result in less than 30 minutes. Most RDTs can be performed with capillary whole blood collected by finger-stick sampling.
Enzyme immunoassay	Laboratory-based serological immunoassays that detect antibodies, antigens or a combination of both
Nucleic acid testing (NAT)	A molecular technology, such as polymerase chain reaction or nucleic acid sequence-based amplification, that can detect very small quantities of viral nucleic acid (RNA or DNA), either qualitatively or quantitatively
Point-of-care testing	Conducted at the site at which clinical care is being provided, with the results being returned to the person being tested or caregiver on the same day as sample collection and test to enable clinical decisions to be made in a timely manner
Population terms	
Age groups	These guidelines use the following definitions for implementing treatment recommendations for adults, adolescents and children three years and older. For consistency, the same age groups are used as those adopted in the majority of trials and for regulatory approval. Countries may have other definitions under national laws. • An adult is a person 18 years or older (which includes young people 20–24 years old). • An adolescent is a person 12–17 years of age inclusive. • An older child is a person 6–11 years of age inclusive. • A younger child is a person 2–5 years of age inclusive.
Most severely affected populations	Groups of people who are either part of a population with higher HBV seroprevalence (such as some mobile or migrant populations from high or intermediate endemic countries and certain indigenous populations) or who have a history of exposure or high-risk behaviour for HBV infection (such as people who inject drugs, people in prisons and other closed settings, men who have sex with men, sex workers, people living with HIV and partners, family members and children of people with chronic hepatitis B).

Key populations	Groups of people who, because of specific high-risk behaviours, have increased risk for HIV infection regardless of the epidemic type or local context. This may also apply to HBV and/or HCV infection. Key populations often have legal and social issues related to their behaviour that increase their vulnerability to HIV, HBV and HCV infection. These guidelines refer to the following groups as key populations: men who have sex with men; people who inject drugs; people in prisons and other closed settings; sex workers; and transgender people.
Service delivery terms	
Adherence	The extent to which a person's behaviour – taking medication, attending scheduled clinic appointments, following a diet and/or changing lifestyle – corresponds with care and treatment plans conjointly agreed between the health-care worker and the person living with hepatitis B or C infection.
Retention in hepatitis B care	Means the person enrolled in hepatitis B care routinely attends these hepatitis B or C services in accordance with their needs
Decentralization	The process of delegating significant authority and resources to lower levels of the health system: provincial, regional, district, subdistrict, primary health care and community
Differentiated service delivery	An approach that simplifies and adapts viral hepatitis services to better serve the needs of people living with viral hepatitis B or C infection, to optimize the available resources and to reduce unnecessary burdens on the health system
Integration	The co-location and sharing of services and resources across disease areas. In the context of hepatitis B or C infection, this may include providing testing, prevention, care and treatment services alongside other health services, such as HIV, TB, sexually transmitted infections, antenatal care, contraceptives and other family planning services.
Integrated service delivery	Health services that are managed and delivered in a way that ensures people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services at the different levels and sites of care within the health system and according to their needs, throughout the life-course
Task sharing	The rational redistribution of tasks from higher-level cadres of health-care providers to other cadres, such as trained lay providers
Linkage to care	A process of actions and activities that support people testing for hepatitis B or C infection to engage with prevention, treatment and care services as appropriate for their hepatitis B and C status
Person-centred care	Care that is focused and organized around the health needs and expectations of people and communities rather than on diseases. People-centred health services are an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants and beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways

Executive summary

Hepatitis B virus (HBV) infection is a major public health problem and cause of chronic liver disease that led to an estimated 1.1 million deaths in 2022, mainly due to cirrhosis and liver cancer. In 2022, WHO estimated that 254 million people were chronically infected and living with hepatitis B, with a disproportionately high burden in low- and middle-income countries, of whom 65% were in the African and Western Pacific regions. 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, nucleos(t)ide 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 2022, only 13% of the estimated 254 million people with CHB had been diagnosed and 3% 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 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, health-care 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) >7KPa), 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 nucleos(t)ide 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 ≥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.

Summary of recommendations

Expanded treatment eligibility

Chapter 4. Non-invasive assessment of liver disease stage at baseline and during follow-up	
Existing and maintained recommendation (2015 hepatitis B guidelines)	APRI (aspartate aminotransferase-to-platelet ratio index) is recommended as the preferred non-invasive test to assess for the presence of significant fibrosis or cirrhosis among adults in resource-limited settings. Transient elastography (FibroScan®) may be a preferable non-invasive test in settings where it is available and cost is not a major constraint. *(strong recommendation, moderate-certainty evidence)*
New recommendation (for non-invasive test thresholds to establish the presence of significant fibrosis (≥F2) or cirrhosis (F4)	Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 or transient elastography value of >7.0 kPa,[a] and cirrhosis (F4) should be based on clinical criteria[b] (or an APRI score of >1.0 or transient elastography (FibroScan®) value of >12.5 kPa [a]). *(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)*

a These cut-offs apply to FibroScan® - other elastography techniques do not necessarily have the same cut-offs.

b Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema or oedema.

Chapter 5. Who to treat among people with CHB (adults and adolescents)

New recommendations

Treatment is recommended for all adults and adolescents (aged ≥12 years) with chronic hepatitis B (CHB)[a] (including pregnant women and girls and women of reproductive age) with:

1. Evidence of significant fibrosis (≥F2[b]) based on an APRI score of >0.5 or transient elastography value of >7 kPa or evidence of cirrhosis (F4) based on clinical criteria[c] (or an APRI score of >1 or transient elastography value of >12.5 kPa[b]), regardless of HBV DNA or ALT levels.

(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)

OR

2. HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period.[d]

(adults: strong recommendation, high-certainty evidence [HBV DNA >20 000 IU/mL] and low-certainty evidence [HBV DNA 2000-20 000,]; adolescents: conditional recommendation, low-certainty evidence)

OR

3. Presence of **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 the APRI score or HBV DNA or ALT levels.

(adults: strong recommendation, moderate-certainty evidence; adolescents: conditional recommendation, low-certainty evidence)

OR

In the absence of access to an HBV DNA assay:

4. Persistently abnormal ALT levels alone (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score.[e]

(adults and adolescents: conditional recommendation, very-low-certainty evidence)

a Defined as the presence of HBsAg on at least one occasion, and for adolescents and children, persistence of HBsAg for six months or more.

b The thresholds of non-invasive tests (APRI and transient elastography) for diagnosis of significant fibrosis or cirrhosis and treatment recommendation are based on extrapolating data from adults and have not yet been fully validated for adolescents or children.

c Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

d The ULN for ALT have been defined as <30 U/L for men and boys and <19 U/L for women and girls for consistency. Some guidelines use different ULN ALT levels for adolescents and children (<22 U/L for girls and <25 U/L for boys). Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.

e Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

Chapter 6. First-line antiviral therapies for CHB	
Existing and maintained recommendations (from the 2015 hepatitis B guidelines)	Nucleos(t)ide analogues with a low genetic barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. *(strong recommendation, moderate-certainty evidence*
Updated recommendation	For all adults, adolescents and children (two years or older) for whom antiviral therapy is indicated, the nucleos(t)ide analogues that have a high genetic barrier to drug resistance – tenofovir disoproxil fumarate (TDF) or entecavir (ETV) are recommended as preferred regimens. TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) are recommended as alternative regimens (where TDF monotherapy is not available). *(strong recommendation, moderate-certainty evidence)*
New recommendation	Entecavir (ETV) or tenofovir alafenamide (TAF)[a] (if available) are recommended for people with established osteoporosis and/or impaired kidney function, and for children (ETV for those aged two years or older) or adolescents (TAF for those aged 12 years or older) as alternative regimen), for whom antiviral therapy is indicated. *(strong recommendation, moderate-certainty evidence)*
a TAF is not recommended if eGFR is <15mL/min	

Chapter 9. Second-line antiviral therapies for managing treatment failure	
Existing and maintained recommendation (2015 HBV guideline)	Among people with evidence of treatment failure due to confirmed or suspected antiviral resistance[a,b,c] (based on history of previous exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen, if available. *(strong recommendation, low-certainty evidence)*

a Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.

b Some countries and health-care providers may consider switching people to TDF (or TAF, if available) from existing antiviral regimens with a low barrier to resistance before evidence of treatment failure, but these guidelines make no formal recommendations.

c To date, there are only isolated case reports of TDF or TAF resistance when used for hepatitis B treatment. If there is primary non-response, then treatment adherence should be reinforced and monitored. At present, there is therefore no indication to switch to an alternative drug regimen.

Chapter 7. Preventing mother-to-child transmission of hepatitis B and use of antiviral prophylaxis	
Existing and maintained recommendations (2017, Strategic Advisory Group of Experts)	**Immunization** a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferable within 24 hours. b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose. c) The birth dose should be followed by two or three additional doses to complete the primary immunization series.
Existing and maintained recommendation (2019 guidelines on HIV testing)	**HBsAg testing among pregnant women and adolescent girls** All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy. *(strong recommendation, low-certainty evidence)*
Updated recommendation (2020 guidelines on antiviral prophylaxis)	**Antiviral prophylaxis among pregnant women and adolescent girls** **In settings where HBV DNA or HBeAg testing is available**, prophylaxis with tenofovir disoproxil fumarate (TDF)[b] is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg[a] (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV. *(strong recommendation, moderate-certainty evidence)*
New recommendation	**Antiviral prophylaxis among pregnant women and adolescent girls** **In settings where neither HBV DNA nor HBeAg testing is available,** prophylaxis with tenofovir disoproxil fumarate (TDF)[b] is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV. *(conditional recommendation, low-certainty evidence)* All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose. Note: It is advised that all pregnant women and girls of reproductive age should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of prophylaxis. For women and adolescent girls of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice.

a The use of the HBeAg recommendation represents an additional option for determining eligibility, but HBeAg RDTs have poor diagnostic performance, which limits their routine use in low- and middle-income countries.

b TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy (see Chapter 6). TAF is not recommended if eGFR is <15 ml/min.

Chapter 8. Who to treat and what antiviral drugs to use for adolescents and children	
New recommendations	**WHO TO TREAT (adolescents) See Chapter 5 (recommendations as for adults)** Treatment is recommended for all adults and adolescents (aged ≥12 years) with CHB (including pregnant women and girls and women of reproductive age) with: 1. Evidence of significant fibrosis (≥F2) based on an APRI score of >0.5 or transient elastography value of >7 kPa or evidence of cirrhosis (F4) (based on clinical criteria (or an APRI score of >1 or transient elastography value of >12.5 kPa), regardless of HBV DNA or ALT levels. *(adolescents: strong recommendation, low-certainty evidence)* **OR** 2. HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period. *(adolescents: conditional recommendation, low-certainty evidence)* **OR** 3. Presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic – associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the APRI score or HBV DNA or ALT levels. *(adolescents: conditional recommendation, low-certainty evidence)* **OR** **In the absence of access to an HBV DNA assay:** 4. Persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score. *(adults and adolescents: conditional recommendation, very-low-certainty evidence)*
New recommendations	**WHAT ANTIVIRALS TO USE (adults, adolescents and children)** **See Chapter 6**
New recommendations	**PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HBV USING ANTIVIRAL PROPHYLAXIS in adolescent pregnant girls.** **See Chapter 7**

HBV DNA testing

Chapter 10. Measuring HBV DNA to guide treatment eligibility and monitor the response	
Existing and maintained recommendation (2017 guidelines on hepatitis testing)	**Laboratory-based HBV DNA assays:** Directly following a positive HBsAg serological test result, the use of HBV DNA nucleic acid testing (NAT) (quantitative or qualitative[a]) is recommended as the preferred strategy to assess viral load level for treatment eligibility and to monitor treatment response. *(strong recommendation, moderate-certainty evidence)*
New recommendation	**Point-of-care (POC) HBV DNA assays:** POC HBV DNA nucleic acid test (NAT) assays may be used as an alternative approach to laboratory-based HBV DNA testing to assess HBV DNA level for treatment eligibility and to monitor treatment response. *(conditional recommendation, low-certainty evidence).*
a Assays should meet minimum quality, safety and performance standards.	

Chapter 11. HBV DNA reflex testing	
New recommendation	Where available, Reflex HBV DNA testing for those testing positive on HBsAg may be used as an additional strategy to promote linkage to care and treatment. This can be achieved through either laboratory-based reflex HBV DNA testing using a sample already held in the laboratory or clinic-based reflex testing in a health-care facility through immediate sample collection following a positive HBsAg rapid diagnostic test (RDT). *(conditional recommendation, low-certainty evidence)*

Hepatitis Delta virus (HDV) testing

Chapter 12. Who to test for HDV infection	
New recommendations	For people with CHB, serological testing for anti-HDV antibodies may be performed for all individuals who are HBsAg positive, as the preferred approach to scale up access to HDV diagnosis and linkage to care. *(conditional recommendation, very-low-certainty evidence)* In settings in which a universal anti-HDV antibody testing approach is not feasible because laboratory capacity or other resources are limited, testing for anti-HDV may be given priority in specific populations of HBsAg-positive individuals, including the following: • people born in HDV-endemic countries, regions and areas; • people with advanced liver disease, those receiving HBV treatment and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and • people considered to have increased risk of HDV infection, including haemodialysis recipients, people living with hepatitis C or HIV, people who inject drugs, sex workers and men who have sex with men. *(conditional recommendation, very-low-certainty evidence)*

Chapter 13. How to test for HDV infection: testing strategy and choice of serological and NAT assays	
New recommendation	People with CHB (HBsAg positive) may be diagnosed with hepatitis D by using a serological assay to detect total anti-HDV followed by an NAT to detect HDV RNA and active (viraemic) infection among those who are anti-HDV positive. Assays should meet minimum quality, safety and performance standards.[a] *(conditional recommendation, low- certainty evidence)*

a The NAT for detecting HDV RNA should be harmonized with the WHO HDV RNA standard and the results reported in IU/mL. The assays should have a limit of detection of 100 IU/mL or better. Primers used in in-house assays should target the ribozyme region, which is the most conserved region of the HDV genome, for genotype inclusivity.

Chapter 14. How to test for HDV infection: laboratory-based reflex testing	
New recommendation	Reflex testing 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, may be used as an additional strategy to promote diagnosis. *(conditional recommendation, low-certainty evidence)*

Monitoring for treatment response and surveillance for HCC

Chapter 16. Monitoring for treatment response among people with CHB receiving treatment or not yet receiving treatment	
Existing and maintained recommendations (2015 hepatitis B guidelines)	**Monitoring for people receiving treatment** For people receiving treatment, the following are recommended to be monitored at least annually: • non-invasive tests (APRI score or transient elastography) to assess stage of disease and progression of fibrosis or cirrhosis; and • ALT levels[a] (and AST for APRI), HBV DNA levels (when HBV DNA testing is available), HBsAg[b] and HBeAg/anti-Hbe.[c] • Treatment adherence[d] should be monitored regularly and at each visit. *(strong recommendation, moderate-certainty evidence)* More frequent on-treatment monitoring (every 3–6 months for the first year) may be performed for: people with more advanced disease (compensated or decompensated cirrhosis); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected people; and for people with renal impairment. *(conditional recommendation, very-low-certainty evidence)*
Existing and maintained recommendations (2015 hepatitis B guidelines)	**Monitoring for people not yet receiving treatment** People who do not currently meet the criteria for antiviral therapy (persistently normal serum aminotransferase results and HBV DNA levels below 2000 IU/mL (when HBV DNA testing is available) or who have expressed a desire to defer treatment may be monitored annually for disease progression and ALT and HBV DNA levels (when HBV DNA testing is available). *(conditional recommendation, low-certainty evidence)*

a ALT levels fluctuate among people with CHB, and longitudinal monitoring is required to determine the trend. The ULN for ALT has been defined as below 30 U/L for men and boys and 19 U/L for women and girls. Persistently abnormal or normal may be defined as two ALT determinations above or below the ULN at unspecified intervals during a 6- to 12-month period or predefined intervals during a 12-month period.

b Among people receiving treatment, monitor for HBsAg loss (although this occurs rarely) and for seroreversion to HBsAg positivity after discontinuing treatment. Quantitative HBsAg, if available, can be used to determine whether HBsAg concentrations are declining, or more rarely, seroclearance.

c Monitoring of HBeAg and anti-HBe mainly applies to those who are initially HBeAg positive. However, those who have already achieved HBeAg seroconversion and are HBeAg negative and anti-HBe positive may subsequently serorevert.

d Decompensated cirrhosis is defined by the development of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease or cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

Chapter 17. Monitoring the safety of nucleos(t)ide analogues	
Existing and maintained recommendations (2015 hepatitis B guidelines)	Before initiating antiviral therapy, people's baseline risk for renal dysfunction[a] and measurement of baseline renal function[b] may be performed. People receiving long-term tenofovir disoproxil fumarate therapy may be monitored annually for renal function and growth monitored carefully in children. *(conditional recommendation, very-low certainty evidence*

Note: In the 2021 WHO consolidated HIV guidelines *(1)*, baseline measurement of creatinine is not required before initiating ART for people living with HIV with the preferred tenofovir-based regimen.

a Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age >60 years, body mass index (BMI) <18.5 kg/m^2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV and solid organ transplantation.

b Measurement of baseline renal function includes: serum creatinine levels and calculation of CrCl/estimated glomerular filtration rate (eGFR) using the MDRD formula.

MDRD formula: eGFR = 175 × (serum Cr)$^{-1.154}$ × (age)$^{-0.203}$ × 1.212 if the person is Black) × 0.742 (if the person is female).

Chapter 18. Surveillance for hepatocellular carcinoma (HCC) among people with CHB	
Existing and maintained recommendations (2015 hepatitis B guidelines)	Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for: • people with cirrhosis, regardless of age or other risk factors; *(strong recommendation, moderate-certainty evidence)* • people with a family history of HCC; and *(strong recommendation, moderate-certainty evidence)* • if there is no family history of HCC or evidence of cirrhosis, people older than 40 years (a lower age may apply depending on the regional incidence of HCC[a]) and with HBV DNA level >20,000 IU/mL (if HBV DNA testing is available). *(conditional recommendation, low-certainty evidence)*

a The GLOBOCAN project of the International Agency for research on Cancer (IARC) (http://globocan.iarc.fr/ia/World/atlas.html) provides current estimates of the incidence of, mortality and prevalence of major types of cancer, including HCC, at the national level, for 185 countries. The GLOBOCAN estimates are presented for 2020, separately for each sex. One-, three- and five-year prevalence data are available for adults only (15 years and older).

Chapter 19. When to stop and restart antiviral therapy	
Existing and maintained recommendations (2015 hepatitis B guidelines)	**Lifelong nucleos(t)ide analogue therapy** All people with cirrhosis[a] based on clinical evidence (or APRI or transient elastography score) require lifelong treatment with nucleos(t)ide analogues and should not discontinue antiviral therapy because of the risk of reactivation, which can cause an acute hepatitis flare. *(strong recommendation, moderate-certainty evidence)*
Existing and maintained recommendations (2015 hepatitis B guidelines)	**Discontinuation** Antiviral therapy is lifelong. Discontinuation of nucleos(t)ide analogue therapy may be considered exceptionally for: • people without clinical evidence of cirrhosis (or based on a non-invasive test score – APRI or transient elastography – suggesting advanced fibrosis); and • who can be followed carefully after discontinuation and long term for reactivation; and • if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment; and • in association with persistently normal ALT levels[b] and persistently undetectable HBV DNA levels (if HBV DNA testing is available). **If HBV DNA testing is not available:** discontinuing nucleos(t)ide analogue therapy may be considered for people who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of previous HBeAg status. *(conditional recommendation, low-certainty evidence)*
Existing and maintained recommendations (2015 hepatitis B guidelines)	**Retreatment** Relapse is common after stopping therapy with nucleos(t)ide analogues. Retreatment is recommended if there are consistent signs of reactivation: HBsAg or HBeAg becomes positive, ALT levels increase or HBV DNA becomes detectable again (if HBV DNA testing is available) *(strong recommendation, low-certainty evidence)*

a Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease or cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

b The ULN for ALT has been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

Summary of existing recommendations on who to test and how to test for CHB (from the 2017 guidelines on testing for viral hepatitis B and C infection)

Who to test for CHB	
Testing approach and population	**Recommendations**
General population testing	In settings with a ≥2% or ≥5%[a] HBsAg seroprevalence in the general population, it is recommended that all adults have routine access to and be offered HBsAg serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or health facility-based testing opportunities or programmes such as at antenatal clinics, HIV or TB clinics. *(conditional recommendation, low-certainty of evidence)*
Routine testing for HIV, HBsAg and testing among pregnant women	• All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy. *(strong recommendation, low-certainty evidence)* • Couples and partners in antenatal care settings should be offered HBV testing services. *(strong recommendation, low-certainty evidence)*
Focused testing in most affected populations	In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that HBsAg serological testing and linkage to care and treatment services be offered to the following individuals: • adults and adolescents from populations most affected by HBV infection[b] (who are either part of a population with high HBV seroprevalence or who have a history of exposure and/or high-risk behaviour for HBV infection); • adults, adolescents and children with a clinical suspicion of chronic viral hepatitis[c] (symptoms, signs, laboratory markers); • sexual partners, children and other family members, and close household contacts of those with HBV infection;[d] and • health-care workers: in all settings, it is recommended that HBsAg serological testing be offered and hepatitis B vaccination given to all health-care workers who have not been vaccinated previously (adapted from existing guidance on hepatitis B vaccination). *(strong recommendation, low-certainty evidence)*
Blood donors	In all settings, screening of blood donors should be mandatory with linkage to care, counselling and treatment for those who test positive.

a A threshold of ≥2% or ≥5% seroprevalence was based on several published thresholds of intermediate or high seroprevalence. The threshold used will depend on other country considerations and the epidemiological context.

b Includes those who are either part of a population with higher seroprevalence (such as some mobile and migrant populations from high and intermediate endemic countries and certain indigenous populations) or who have a history of exposure or high-risk behaviour for HBV infection, such as people who inject drugs, people in prisons and other closed settings, men who have sex with men, sex workers, people living with HIV, partners, family members and the children of people with hepatitis B.

c Features that may indicate underlying CHB include clinical evidence of existing liver disease, such as cirrhosis or HCC or where there is unexplained liver disease, including abnormal liver function tests or liver ultrasound.

d In all settings, it is recommended that HBsAg serological testing with hepatitis B vaccination of those who are HBsAg negative and not previously vaccinated be offered to all children with parents or siblings diagnosed with HBV infection or with clinical suspicion of hepatitis, through community- or facility-based testing.

How to test for CHB	
Which serological assays to use	For the diagnosis of CHB in adults, adolescents and children (>12 months of age[a], a serological assay (in either RDT or laboratory-based immunoassay format[b]) that meets minimum quality, safety and performance standards[b] (with regard to both analytical and clinical sensitivity and specificity) is recommended to detect hepatitis B surface antigen (HBsAg). • In settings where existing laboratory testing is already available and accessible, laboratory-based immunoassays are recommended as the preferred assay format. • In settings where there is limited access to laboratory testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended to improve access. *(strong recommendation, low-certainty evidence)*
Serological testing strategies	• In settings or populations with an HBsAg seroprevalence of ≥0.4%,[d] a single serological assay for detection of HBsAg is recommended, before further evaluation for HBV DNA and staging of liver disease. • In settings or populations with a low HBsAg seroprevalence of <0.4%,[d] confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay for detection of HBsAg may be considered.[f] *(conditional recommendation, low-certainty evidence)*

a A full vaccination schedule including birth dose should be completed in all infants in accordance with the WHO position paper on hepatitis B vaccines from 2017. Testing of exposed infants is problematic within the first six months of life since HBsAg and hepatitis B DNA may be inconsistently detectable in infected infants. Exposed infants should be tested for HBsAg between 6 and 12 months of age to screen for evidence of hepatitis B infection. In all age groups, acute HBV infection can be confirmed by the presence of HBsAg and IgM anti-HBc. CHB is diagnosed if there is persistence of HBsAg for six months or more.

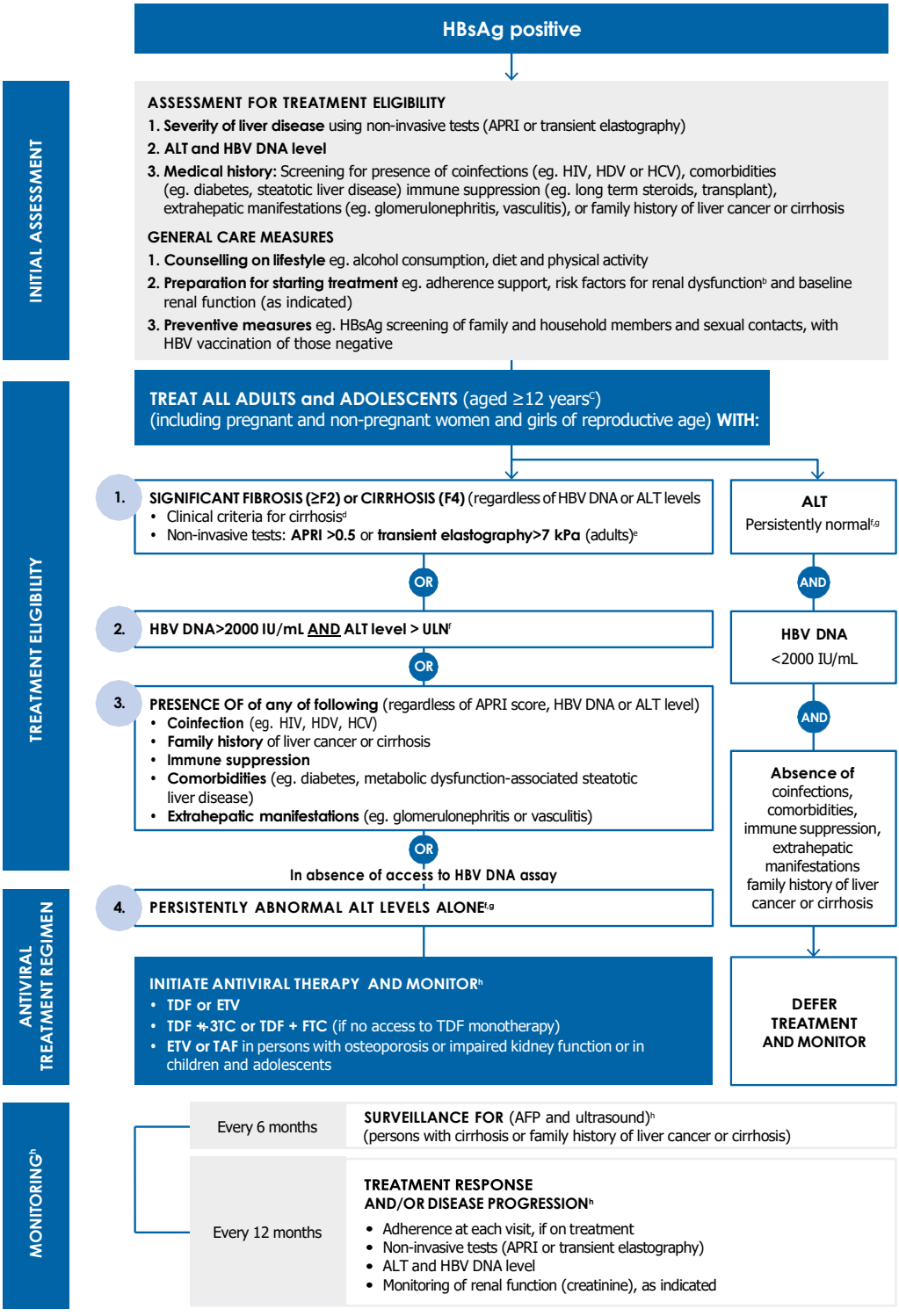
b Laboratory-based immunoassays include enzyme immunoassay, chemoluminescence immunoassay, and electrochemiluminescence assay.

c Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics or a stringent regulatory review for in vitro diagnostics. All in vitro diagnostics should be used in accordance with manufacturers' instructions for use and, where possible, at testing sites enrolled in a national or international external quality assessment scheme.

d Based on the results of predictive modelling of positive predictive values according to different thresholds of seroprevalence in populations to be tested and assay diagnostic performance.

e A repeat HBsAg assay after six months is also a common approach used to confirm the chronicity of HBV infection.

ALGORITHM FOR ASSESSMENT, TREATMENT AND MONITORING OF PEOPLE WITH CHRONIC HEPATITIS B INFECTION[a]



ALT: alanine aminotransferase, APRI: aspartate aminotransferase-to-platelet ratio index

a Defined as the presence of HBsAg for adults and persistence of HBsAg for six months or more for adolescents and children.

b Before initiation, consider assessing renal function: serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria and risk factors for renal dysfunction (decompensated cirrhosis, creatinine clearance <50 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, solid organ transplantation, older age, BMI <18.5 kg/m2 (or body weight <50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV). Monitoring should be more frequent for those at higher risk of renal dysfunction.

c Age groups: these guidelines use the following definitions for the purpose of implementing treatment recommendations for adolescents and children aged two years and older. An adult is a person aged 18 years or older; an adolescent 12–17 years old inclusive; and a child is 2–11 years old. Countries may have other definitions under national laws.

d Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

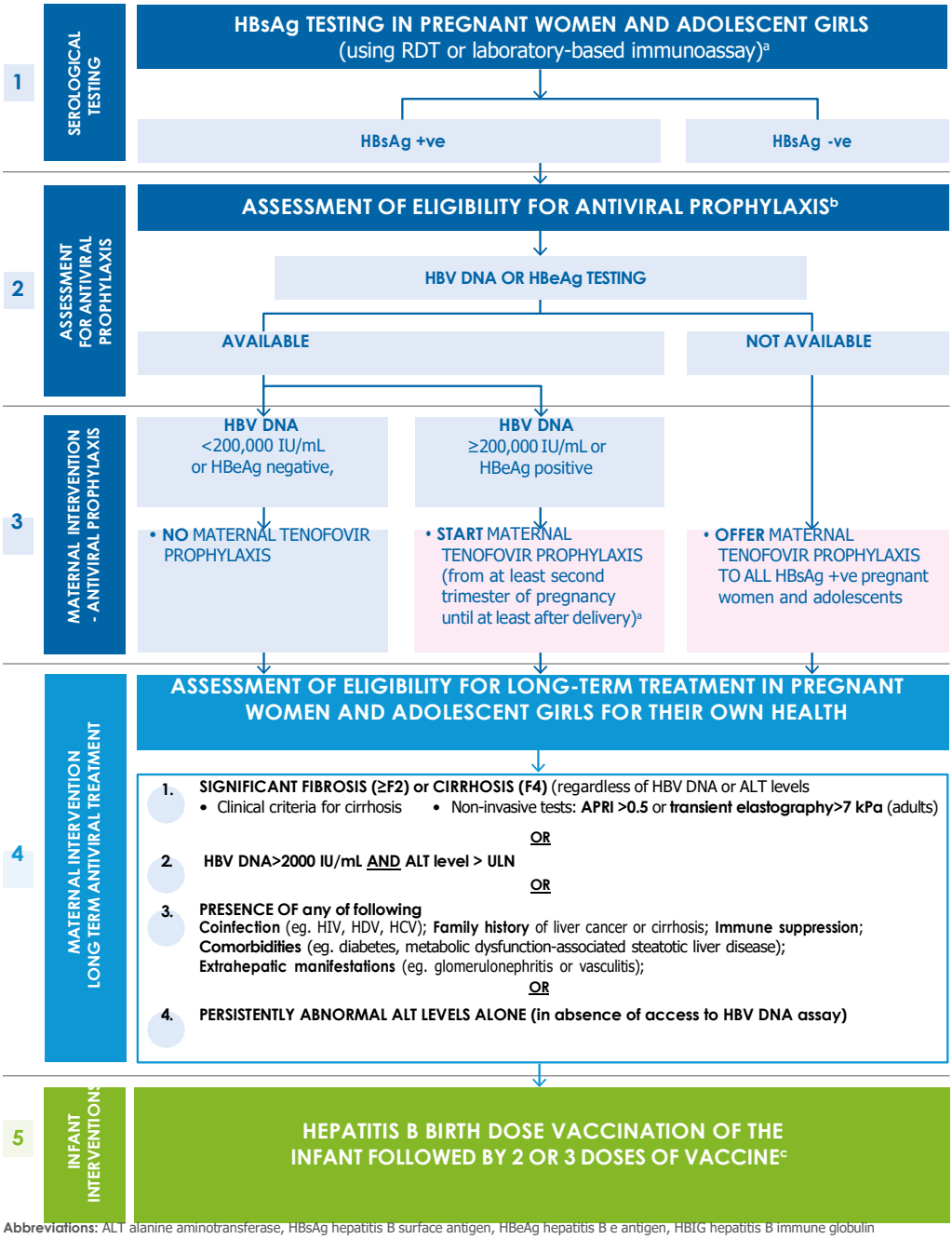
e Non-invasive test cut-offs for APRI and transient elastography have not yet been validated for children and adolescents.

f The ULN for ALT has been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

g Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.

h All people with CHB should be monitored regularly for disease activity and progression and surveillance for HCC and after stopping treatment for evidence of reactivation. More frequent monitoring may be required for those with more advanced liver disease, during the first year of treatment or if adherence is a concern.

ALGORITHM ON USE OF ANTIVIRAL PROPHYLAXIS FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION IN PREGNANT WOMEN AND ADOLESCENT GIRLS WITH CHB AND ASSESSMENT OF TREATMENT ELIGIBILITY FOR THEIR OWN HEALTH



Abbreviations: ALT alanine aminotransferase, HBsAg hepatitis B surface antigen, HBeAg hepatitis B e antigen, HBIG hepatitis B immune globulin

[a] At least once and as early as possible in the pregnancy. HBsAg testing should be undertaken as part of triple testing for HIV, syphilis and HBsAg toward triple elimination initiative.

[b] It is advised that all pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of antiviral prophylaxis.

[c] Hepatitis B timely (within 24 hours) birth dose vaccination of the infant followed by 2 or 3 doses of hepatitis B vaccine should be given regardless of HBsAg status of the pregnant mother. HBIG (if available) is also offered mainly in high income settings for infants born to HBsAg positive mothers, especially with high HBV DNA.

1. Introduction

1.1 Objectives and scope of the updated guidelines

The objective of these updated guidelines is to provide updated evidence-informed recommendations on the management of chronic hepatitis B (CHB).

The priority areas were:

- expanded treatment eligibility for adults and adolescents; and new non-invasive test thresholds for diagnosis of significant fibrosis or cirrhosis;
- expanded antiviral prophylaxis for hepatitis B surface antigen (HBsAg)-positive pregnant women;
- HBV diagnostics – use of point-of-care (POC) HBV viral load and reflex viral load testing, and testing for hepatitis D virus (HDV) infection (who to test and how to test); and
- approaches for simplified service delivery.

1.2 Related guidelines

These guidelines are intended to complement existing WHO guidance on the primary prevention of hepatitis B through vaccination and antiviral prophylaxis and by improving blood and injection safety as well as guidance among people who inject drugs and other groups at higher risk, including those living with HIV *(1–11)*. Key identified topics were based on the 2015 WHO guidelines for care and treatment of people with CHB *(1)*, the 2017 WHO guidelines on hepatitis B and C testing *(2)*, the 2020 WHO guidelines on preventing the mother-to-child transmission (PMTCT) of hepatitis B virus (HBV) using antiviral prophylaxis in pregnancy *(3)* and, for approaches on service delivery, the 2018 and 2022 guidelines on care and treatment for people with chronic hepatitis C infection *(12,13)*.

1.3 Target audience

These guidelines primarily target 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 country-specific guidelines. It is anticipated that nongovernmental agencies and health professionals organizing treatment and screening services for hepatitis B will use the guidelines to define the necessary elements of such services. These guidelines will also be useful for laboratory managers in health ministries, reference laboratories and key hospital laboratories responsible for validating assays, developing national testing algorithms and procuring assays and quality control. Finally, the guidelines will serve as a reference for health-care providers who offer and implement hepatitis testing, care and treatment for people with hepatitis B infection, including those from community-based programmes.

1.4 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

1.4.1 The public health approach

The guidelines are based on a public health approach to scaling up the testing and antiviral therapy for HBV infection along the continuum of hepatitis prevention, care and treatment. The public health approach seeks to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. High-income countries with more resources and fewer HBV cases favour a more individualized approach to care.

1.4.2 Promoting human rights and equity in access to health care

Access to health care is a basic human right and applies equally to men, women and children, regardless of sex, race, sexual preference, socioeconomic status or behavioural practices, including drug use. The promotion of human rights and equity in access to HBV prevention, treatment, care and support are guiding principles central to these guidelines. People with HBV infection may also come from population groups at higher risk of infection because of low socioeconomic status or poor access to appropriate health care or because they belong to groups that are marginalized or stigmatized such as people who inject drugs, men who have sex with men, migrants, indigenous peoples or prisoners. In general, HBV treatment programmes need to ensure that treatment is accessible to the people with the most advanced disease who need it most; pregnant women; the most severely affected population groups, including the sexual partners, children, other family members and close household contacts of those with

HBV infection; and healthcare workers and that they are provided treatment in an environment that minimizes stigma and discrimination. Informed consent – notably for HBV testing but also for initiating antiviral therapy – should always be obtained. Adequate safeguards must be in place to ensure confidentiality.

The updated guidelines seek to promote equity of access through substantial expansion and simplification of eligibility criteria for treatment that do not depend on access to an HBV DNA test. Each country needs to plan its own approach to ensure that expanded access is fair and equitable.

1.4.3 Person-centred care

People-centred health services are an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants and beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways. This approach acknowledges the experiences and perspectives of health-care providers that may enable or prevent the delivery of people-centred care that is of high quality.

1.4.4 Simplified service delivery to support a public health approach

Chapter 15 provides eight specific approaches for delivering high-quality hepatitis B testing, care and treatment services that were adapted from the 2018 HCV care and treatment guidelines *(12)*. These include: strategies to strengthen linkage from testing to care and treatment; strategies to promote and sustain adherence to long-term antiviral therapy; strategies to promote retention in care and trace and re-engage those disengaged from care; integrating hepatitis testing, care and treatment with other services; decentralized testing and treatment services at primary health facilities or HIV and antiretroviral clinics to promote access to care; task-sharing, supported by training and mentoring of health-care workers and peer workers; a differentiated care strategy to assess level-of-care needs, with specialist referral as appropriate for those with complex problems; and community engagement and peer support to promote access to services and linkage to the continuum of care.

1.4.5 Essential strategies for an enabling environment for key populations

Implementation of the guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need hepatitis services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity. Several populations are subject to structural barriers, including stigma, discrimination, criminalization and violence following a hepatitis B diagnosis. This is especially important for women, young girls and adolescents and key populations, who are subject to these barriers across the HIV and hepatitis care cascade.

The updated WHO consolidated guidelines on HIV services for key populations describe essential strategies for an enabling environment, which include developing supportive legislation and policy, including working towards decriminalizing behaviour, financial commitment, addressing stigma and discrimination, empowering communities and addressing violence against key populations. WHO also supports a strong emphasis on workforce training against stigma, discrimination and strategies to support people subject to violence, to ensure that all populations benefit from accessing better and safer health-care services.

1.4.6 Adapting implementation to the local context

Implementation of the recommendations in these guidelines should be informed by local context, including national HBV epidemiology, health systems and laboratory capacity, supply systems for drugs and other commodities, availability of financial resources, the organization and capacity of the health system and the anticipated cost-effectiveness of the various interventions.

2. Background

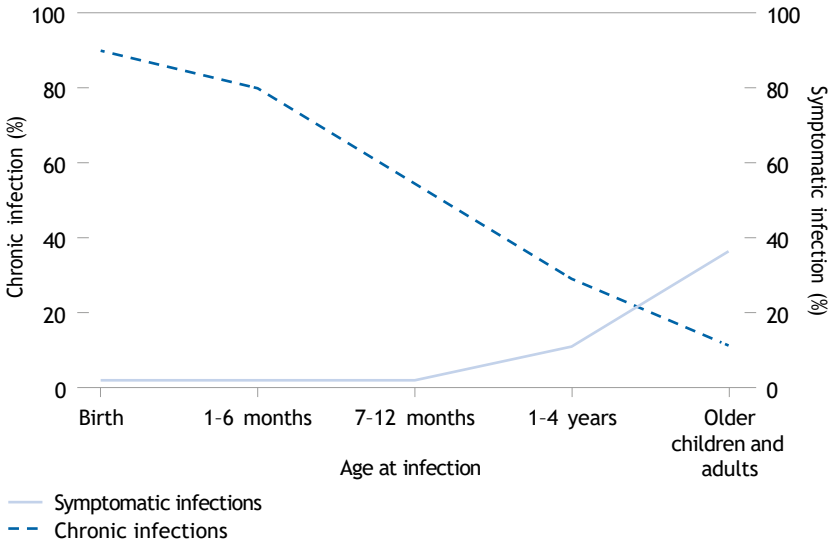
2.1 Epidemiology and burden of hepatitis B infection

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus. HBV infection can be either acute or chronic and may range from asymptomatic infection or mild disease, to severe or rarely fulminant hepatitis *(1,2)*. Acute hepatitis B is usually a self-limiting disease with a case fatality rate of 0.5–1%. CHB is defined by the presence of detectable HBsAg in the blood or serum for longer than six months and encompasses a spectrum of disease. Age of exposure is a key factor in determining the risk of chronic infection (Fig. 2.1). Chronicity is common following acquisition in childhood *(3)*.

Worldwide, an estimated 254 million people are chronic carriers of HBsAg *(4)*. Age-specific HBsAg seroprevalence varies markedly by geographical region *(6)*. Overall, almost half the global population lives in areas of high endemicity. The prevalence of HBeAg-negative disease has been increasing over the past decade as the HBV-infected population ages and accounts for most cases in some regions *(7)*. In 2022, hepatitis B caused an estimated 1.1 million deaths *(4)*. Deaths from HBV infection will continue to rise to a peak of 1.14 million deaths by 2034 without effective intervention *(10)*. In Asia and most other regions, the incidence of hepatocellular carcinoma (HCC) and cirrhosis is low before the age of 35–40 years but then rises exponentially. HCC occurs at a younger age among people infected with genotype F (found in Alaska) and among those infected with subgenotype A1 found in southern Africa and genotype E in western Africa, although aflatoxin exposure may play a role in sub-Saharan Africa.

Although hepatitis B vaccine administered at birth or early childhood has been effective in reducing the incidence and prevalence of hepatitis B in most endemic regions *(11)*, it will not affect the rates of end-stage liver disease or HCC for 20–40 years after the introduction of universal infant immunization *(12)*.

FIGURE 2.1 Outcome of hepatitis B infection by age at infection



2.2 Transmission

HBV is spread predominantly by percutaneous or mucosal exposure to infected blood and various body fluids, including saliva, menstrual, vaginal, and seminal fluids, which have all been implicated as vehicles of human transmission *(13)*. HBV may also be transmitted from accidental inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures or from sharp objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture. Sexual transmission of hepatitis B may occur, particularly in unvaccinated men who have sex with men and heterosexual persons with multiple sex partners or contact with sex workers *(13)*.

Vertical (mother-to-child transmission (MTCT)) has been an important factor in maintaining the reservoir of the infection in some regions, especially in China and South-East Asia but also in sub-Saharan Africa. The greatest risk of developing chronic infection is 90% following MTCT transmission (up to six months of age) but decreases to about 30% between the ages of 0.5 and 5 years (Fig. 2.1) *(14,15)*. Mothers seropositive for HBeAg or who have high HBV DNA levels in blood (>200 000 IU/mL) are at high risk of transmitting the infection to their infants in the absence of prophylaxis *(16-22)*. Although HBV can infect the fetus in utero, this is rare and transmission is generally associated with antepartum haemorrhage and placental tears. HBV also clusters within family groups.

2.3 Natural history of CHB

The natural history of CHB is dynamic and complex. The spectrum of illness varies from asymptomatic infection to severe chronic liver disease and HCC. For some people, CHB does not lead to significant liver disease, but others have progressive liver fibrosis, cirrhosis, end-stage liver disease and a markedly increased risk of HCC *(23)*. Longitudinal studies of untreated people with CHB show an 8–20% cumulative risk of developing cirrhosis over five years *(24-29)*. Those with cirrhosis have an approximately 20% annual risk of hepatic decompensation, and the risk of developing hepatitis B-related HCC ranges from <1% to 5% *(30,31)*. Untreated people with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years *(32-35)*. Several host and viral factors may increase the rate of disease progression and risk of developing HCC *(36)*.

People in endemic regions frequently present for the first time with complications of cirrhosis or even HCC because of late diagnosis.

The infection progresses non-linearly through several of the recognized phases, which are not necessarily sequential (Table 2.1). These stages are delineated by virological, serological, clinical and histological characteristics defined by a combination of serum aminotransferases, HBeAg, serum HBV DNA concentrations and newer biomarkers. Table 2.1 shows the terms given to these phases. However, the nomenclature varies, and although these definitions do not fully describe the molecular or immune pathogenesis of the phase, they serve as indicators of clinical phenotypes and indications for treatment *(37,38)*. Table 2.1 summarizes the definitions and nomenclature.

2.3.1 Phases of CHB (Table 2.1)

1. **HBeAg-positive infection** is characterized by high levels of HBV replication, typically >10^7 IU/mL with normal or near-normal serum aminotransferase (ALT) levels, minimal necroinflammatory change on liver biopsy, no or slow progression to fibrosis and low spontaneous HBeAg loss. This phase of the disease is typically present among children, adolescents and young adults infected at birth or in early childhood. This phase has been previously delineated as the immune-tolerant phase.

   HBeAg-positive disease may be followed in young adulthood by a stage characterized by the continued presence of HBeAg and relatively high serum HBV DNA concentrations (typically between 10^5 and 10^7 IU/mL) but raised serum aminotransferases, indicating active inflammatory disease. Cytolytic T-cell responses directed at infected hepatocytes leads to elevated ALT and reduced HBV DNA levels *(39)*. The intensity of the periodic exacerbations varies.

2. **HBeAg-negative infection** (Table 2.1): Some people (about 10–15% per year) spontaneously seroconvert from HBeAg to anti-HBe and may show a marked decline in HBV DNA and serum ALT concentrations. These individuals (previously referred to as inactive carriers and also as the non-replicative or inactive immune-control phase) typically show near-normal

serum aminotransferases and HBV DNA concentrations of <2000 IU/mL. However, despite low concentrations of HBV DNA, HBsAg concentrations can remain high (>1000 IU/mL). A proportion show little or no necroinflammation or fibrosis, depending on the timing of seroconversion from HBeAg to anti-HBe.

3. **HBeAg-negative disease:** Conversely, HBeAg seroconversion can augur a change to HBeAg-negative disease, with mutations in the precore or basal core promoter downregulating HBeAg despite continued HBV replication *(40)*. HBeAg-negative disease is characterized by fluctuation in serum ALT. HBV DNA concentrations are lower than found among HBeAg-positive people and typically between 10^3 and 10^5 IU per mL but higher than in HBeAg-negative infection. HBsAg concentrations can remain high (>1000 IU/mL) *(41)*. HBeAg-negative disease has a variable course, with abnormal or fluctuating levels of serum ALT and HBV DNA, necroinflammatory changes and more rapid progression to cirrhosis (annual rate of 8–20%). Recurrent exacerbations and bridging fibrosis with severe necroinflammatory change characterizes people who are more likely to progress. Distinguishing between anti-HBe-positive infection and anti-HBe-positive disease is difficult without longitudinal follow-up of serum HBV DNA and serum aminotransferase concentrations.

4. **Occult HBV infection** (Table 2.1): defined as persistence of HBV DNA in the liver or serum among people for whom HBsAg is not detectable in the blood). People who have cleared HBsAg but are anti-HBc positive may reactivate if given potent immunosuppressive drugs. Subjects with occult infection are a potential source of new infections in blood transfusion services when HBsAg is used as the sole marker of infection in donor populations. HBV reactivation may occur spontaneously or may be triggered by cancer chemotherapy and other immunosuppressive therapy and may lead to fatal acute-on-chronic hepatitis, and pre-emptive nucleos(t)ide analogue therapy is therefore used.

Table 2.1 Nomenclature and biomarkers characteristic of the different phases of hepatitis B

Nomenclature		HBeAg-positive infection	HBeAg-positive disease	HBeAg-negative infection	HBeAg-negative disease	Grey zone	Occult hepatitis B
Other terms		Immune tolerant	Immune (re)active	Inactive carrier state	Immune-active or HBeAg-negative disease	Indeterminate	None
Serology	HBsAg	Positive	Positive	Positive	Positive	Positive	Negative
	Quantitative HBsAg	3.5–4.5 log10 IU/mL	3.5–4.5 log10 IU/mL	2.5–3.5 log10 IU/mL	2–3 log10 IU/mL	2–3 log10 IU/mL	Negative
	HBeAg	Positive	Positive	Negative	Negative	Negative	Negative
	Anti-HBe	Negative	Negative	Positive	Positive	Positive	May be positive
	HBV DNA	Typically >10^7 IU/mL	Typically >10^5 to 10^7 IU/mL	<10^3 IU/mL	Typically 10^3 to 10^5 IU/mL	3.3 log10 (2000 IU/mL) to 4.3 log10 (20 000 IU/mL)	Low at detection limit
Biochemistry	ALT	Around ULN	Raised	Around ULN	Raised	Fluctuate around ULN	Around ULN
Histology	Liver biopsy	Minimal necroinflammation or fibrosis	Moderate or severe necroinflammation and varying degrees of fibrosis	Minimal necroinflammation and fibrosis	Moderate to severe necroinflammation or fibrosis	Minimal or low necroinflammation	Usually minimal or low necroinflammation Fibrosis can be present
cccDNA[+]	(Assumed)	Relatively high copy number per cell	Relatively high copy number per cell	Low copy number or transcriptional activity	Lower copy number but transcriptional activity	Low number and transcription variable	Data uncertain
Integrated HBV DNA	Usually assumed	Present	Present	Present and account for majority of HBsAg	Present and account for majority of HBsAg	Present	Present
HBcrAg	Measured	High levels	High levels	Low or undetected	Lower levels	May be detected	Data not available
HBV RNA	Measured	High levels	High levels	Low or undetected	Lower levels	May be detected	Data not available

2.3.2 Extrahepatic manifestations

About 20% of people with hepatitis B develop major extrahepatic manifestations that can influence the quality of life and mortality The extrahepatic manifestations of hepatitis B and their management have been recently reviewed *(42,43)*. Treatment with nucleos(t)ide analogues has improved the management of HBsAg-positive glomerulonephritis, kidney transplant recipients and people on dialysis, resulting in improved survival while not deleteriously compromising renal allograft outcome. It has been reported that arthritis can effectively disappear after reduction of HBV replication.

2.4 Prevention through vaccination

Since 2009, WHO has recommended that all infants receive 3–4 doses of HBV vaccine, with the first dose administered as soon as possible after birth, preferably within 24 hours, and most of WHO Member States include HBV vaccine in their Expanded Programme of Immunization policies. Preventing MTCT from highly viraemic mothers, in the absence of other measures such as hepatitis B immunoglobulin, requires not only birth-dose vaccination but also pre-emptive antiviral therapy for the mother.

In countries with intermediate or low endemicity, a substantial disease burden may result from acute and chronic infection acquired by older children, adolescents and adults. Target groups for catch-up vaccination and other preventive strategies include young adolescents; household and sexual contacts of people who are HBsAg-positive; and people at risk of acquiring HBV infection.

2.5 Screening

WHO *(44)* and most other international guidelines *(45-47)* recommend that high-risk groups be screened for HBsAg and that those at risk and not immune should be offered hepatitis B vaccination. These include: household and sexual contacts of people with CHB, people living with HIV, people who inject drugs, men who have sex with men, sex workers and other groups such as indigenous peoples, people who are incarcerated and transgender people *(48)*. Blood and organ donors should also be screened for HBsAg and other bloodborne pathogens in accordance with WHO recommendations *(49)* to prevent HBV transmission, especially in low- and middle-income countries. Population-based screening is also recommended for migrants from endemic countries *(50)*.

See summary of the WHO recommendations on who to test (testing approaches) and how to test (testing strategies) from the 2017 WHO guidelines on hepatitis B and C testing.

2.5.1 Who to test for HBV infection

WHO guidelines recommend offering focused testing to individuals from populations most severely affected by HBV infection (who are either part of a population with higher seroprevalence or have a history of exposure to or high-risk behaviour for HBV infection). In settings with a ≥2% or ≥5% seroprevalence of HBsAg (based on existing published thresholds for intermediate or high seroprevalence, respectively), it is recommended that all adults have routine access to and be offered testing (a general population testing approach). Routine HBsAg screening of all pregnant women is recommended as part of integrated triple screening for syphilis, hepatitis B and HIV in antenatal clinic services. Overall, these different testing approaches should make use of existing facility-based (such as antenatal clinics, HIV or TB services) or community-based testing opportunities and programmes.

2.5.2 How to test for HBV infection – serological assays and testing strategies

WHO guidelines recommend using a single quality-assured serological in vitro diagnostic test (either a laboratory-based immunoassay (enzyme immunoassay or chemiluminescence immunoassay) or rapid diagnostic test (RDT)) to detect HBsAg that meets minimum performance standards. Using HBV DNA nucleic acid testing (NAT) following a reactive HBsAg serological test result is recommended to help further guide who to treat and to monitor for treatment response. The use of capillary whole-blood dried blood spot specimens for both serological and NAT technologies for HBV infection may be considered for testing in certain settings. Other recommended interventions to promote the uptake of hepatitis testing and linkage to care include peer and lay health worker support in community-based settings, clinician reminders in facilities and testing as part of integrated services within drug treatment and community-based harm-reduction services.

2.6 Diagnosis and staging

HBsAg-positive people need to be routinely assessed to guide management and indicate the need for treatment *(1,2)*. This generally includes assessment of additional serological markers of HBV infection (HBeAg); measuring aminotransferase levels to help determine liver inflammation; quantifying HBV DNA levels; and determining the stage of liver fibrosis by non-invasive tests such as AST-to-platelet ratio index (APRI), transient elastography (FibroScan®) or FibroTest. A full assessment includes clinical evaluation for features of cirrhosis and evidence of decompensation and measurement of serum bilirubin, albumin, ALT, AST, alkaline phosphatase and prothrombin time as well as full blood count, including platelet count. Other routine investigations include ultrasonography and alpha-fetoprotein (AFP) measurement for periodic surveillance for HCC and endoscopy for varices among people with cirrhosis.

Previous HBV infection is characterized by the presence of antibodies (anti-HBs and anti-HBc). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HBs. Recently, quantifying HBsAg has been proposed to determine prognosis *(55–59)*. Use of HBeAg determines whether the person is in the HBeAg-positive or HBeAg-negative phase of infection (Table 2.1) and can also be used to monitor treatment response.

Detection of viral DNA is the optimal method of quantifying hepatitis B viraemia and for monitoring HBV replication before, during or after antiviral therapy. Serum HBV DNA concentrations quantified by real-time polymerase chain reaction (PCR) correlate with disease progression *(27,60)*, and separate HBeAg negative infection from HBeAg negative disease. WHO standards are available for expressing HBV DNA concentrations *(61)*. Serum HBV DNA levels should be expressed in IU/mL to ensure comparability.

Aminotransferase levels may fluctuate with time, and single measurements of ALT and AST do not categorically indicate disease stage. The ALT concentrations are usually higher than those of AST, but with disease progression to cirrhosis, the AST/ALT ratio may be reversed. Tests of liver synthetic function and/or portal hypertension include serum albumin, bilirubin, platelet count and prothrombin time.

Liver biopsy had been used in the past to ascertain the degree of necroinflammation and fibrosis and to help to guide the decision to treat. There are several established methods of scoring histology and measuring activity (necroinflammation) separately from stage (fibrosis). The activity of HBV can vary over time, but the degree of hepatic fibrosis determines the prognosis. Non-invasive methods for assessing the stage of liver disease have largely supplanted liver biopsy and have been validated among adults with CHB (Chapter 4). Blood and serum markers for fibrosis, including APRI and FIB-4 as well as commercial markers such as FibroTest, can be estimated or transient elastography (FibroScan®) performed.

2.7 Newer biomarkers

Quantitative HBsAg

HBsAg concentrations are highest among HBeAg-positive people but can also be detected at relatively high levels among people with anti-HBe-positive infection. However, HBsAg is predominantly expressed from integrated viral genomes among HBeAg-negative people and therefore only weakly correlates with intrahepatic cccDNA. The concentrations of HBsAg differ between genotypes. Low concentrations (<1000 IU/mL) in HBeAg-negative infection among people with an HBV DNA concentration of <2000 IU/mL and normal serum aminotransferases indicate improved outcome *(62,63)*.

Markers of cccDNA transcription

Transition to HBeAg-negative inactive infection, if associated with evidence of reduced cccDNA transcriptional activity, reduces the risk of adverse outcomes. Newer biomarkers such as core-related antigen (HBcrAg), comprising HBeAg, HBcAg and a 22-kDa precore protein, p22cr or hepatitis B RNA (HBV RNA) show potential utility to improve the stratification of risk, since these newer markers better reflect the size of the pool of cccDNA and the transcriptional activity of cccDNA within hepatocytes *(64,65)*. Commercial assays and standardized tests are not currently available, and these new biomarkers remain research assays at present.

2.8 Hepatitis B-related lived experience - stigma and discrimination

People with hepatitis B may encounter multiple barriers in accessing care and treatment services, including the availability of diagnostics, a predominantly hospital-based and specialist care model and out-of-pocket expenses for care and treatment. Adherence to antiviral therapy is often suboptimal, with high loss to follow-up. The importance of provider training is essential to reduce stigma and misinformation and communicate effectively on the importance of disease management and ongoing monitoring.

The reported mental and social consequences of a hepatitis B diagnosis frequently include stigma and discrimination *(66-69)*. Stigma resulting from hepatitis B infection may in turn contribute to subsequent discrimination and reduced quality of life. Hepatitis B discrimination may result in marginalization, social exclusion with relationship instability, difficulties in accessing or loss of employment or educational opportunities, unfair treatment at work, school or home, restrictions on a person's ability to emigrate to certain countries or deportation and denial of opportunity to serve in the military or police forces *(70-75)*. Often people experience discrimination multiple times in their lives. There is a need to better understand the lived experiences of discrimination and stigma as well as the direct effects on those affected, and to consider stigma and discrimination in relation to health-care utilization and outcomes *(69)*.

2.9 Antiviral therapy and the cure agenda

Treatment with nucleos(t)ide analogues has been shown to delay the progression of cirrhosis, reduce the incidence of HCC and improve long-term survival. Therefore, at present, long-term (potentially lifelong) nucleos(t)ide analogue therapy is required in most cases. The development of drug resistance with antiviral drugs with a high genetic barrier to resistance is rare (Table 2.3).

Table 2.3 Antiviral drugs active against HBV infection (in order of potency and barrier to developing resistance)

Antiviral drug	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High
Tenofovir disoproxil fumarate	High	High	High	Low (high in Hong Kong SAR, China and elsewhere in Asia)
Entecavir (ETV)	High	High	Weak	Low
Tenofovir alafenamide fumarate (TAF)	High	High	High	High

New treatment strategies and hepatitis B cure agenda

Research is ongoing to develop and test new agents that can "cure" hepatitis B by eliminating all replicative forms, including cccDNA and thus reduce the need for lifelong treatment. The goal is to achieve "functional" cure, defined as a sustained loss of HBsAg (undetectable <0.05 IU/L) and undetectable HBV DNA after stopping treatment *(76)*. Curing hepatitis B theoretically requires eradication, silencing of cccDNA, silencing of transcription or deletion of integrated viral genomes and overcoming profound T- and B-cell antigen-specific immune dysfunction. Broadly curative antiviral strategies include agents that could directly target infected cells as well as novel immunotherapeutic strategies that boost HBV-specific adaptive immune responses or activate innate intrahepatic immunity. The most advanced investigational treatments include entry inhibitors, RNA interference (small interfering RNA (siRNA)) and HBsAg assembly agents, capsid assembly modulators and immunomodulatory approaches. Progress has been slow in identifying optimal combinations of novel antiviral drugs and immunomodulatory strategies to achieve functional cure.

Early data suggest that new direct antiviral drugs alone are insufficient to restore effective immune control. Therefore, immunomodulatory strategies to restore or replenish exhausted, HBV-specific T- and B-cell responses are being researched. Pegylated interferon-alpha (PEG-IFNα) is being added to siRNA and nucleic acid polymers in current clinical trials. Several oral selective toll-like receptor agonists are also being evaluated *(77)*.

2.10 Management considerations for specific populations

Chapter 20 addresses management considerations in various special populations. These include those coinfected with HIV, HDV, HCV and TB, other populations including pregnant women, children and adolescents (see Chapter 8), people who inject drugs, dialysis and renal transplant recipients, health-care workers and indigenous peoples.

3. Methods and process of developing the guidelines

3.1 WHO guideline development process

The WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes led the development of these updated guidelines on priority areas on hepatitis B testing, care and treatment in accordance with the WHO procedures and reporting standards laid out in the WHO handbook for guideline development *(1-4)*. The recommendations in the guidelines are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations.

3.2 Roles

A WHO Steering Group was constituted, which included individuals with relevant expertise from units within the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes and other WHO departments, and oversaw the guidelines development process. A Guidelines Development Group was constituted to ensure representation from various stakeholder groups, including members of organizations that represent patients' groups, advocacy groups, researchers and clinicians. Group members were also selected to achieve geographical representation and gender balance. There were four representatives from civil society, of whom two were directly affected by hepatitis B. The Guidelines Development Group was further enriched with two additional subgroups to provide specific expertise in HDV coinfection and in HBV infection among children and adolescents. These individuals joined the core Guidelines Development Group for sessions on these topics to help to consider the evidence and formulate recommendations.

There was an initial scoping and planning process and virtual meeting in December 2022 to formulate questions to guide the systematic reviews used to inform the guidelines, with a particular focus on questions most relevant to low- and middle-income countries, and to define patient-important outcomes (see Web annex B for all population, intervention, comparison, outcomes (PICO) questions). The Guidelines Development Group helped formulate the questions using the PICO framework, reviewed the evidence profiles and decision-making tables, composed and agreed on the wording of the recommendations and reviewed drafts of the guidelines document.

The guidelines methodologist ensured that the GRADE framework was appropriately applied throughout the guideline development process. This included formulating the PICO questions, ensuring the comprehensiveness and quality of the systematic reviews and preparing evidence profiles and decision-making tables. The methodologist also provided guidance to the Guidelines Development Group in formulating the wording and strength of the recommendations. The External Review Group reviewed the draft guidelines document and provided critical feedback.

3.3 Evidence that informed the recommendations

To complement the systematic reviews addressing the PICO questions, modelling and cost-effectiveness analyses, acceptability, values and preferences surveys were undertaken among various constituencies and end-users of guidelines. These included affected communities, health-care workers, paediatricians and hepatitis focal points in national health ministries., which were utilized to support the process of formulating recommendations and identifying patient-important outcomes. Landscaping reports were also commissioned to inform price, access and availability considerations for relevant treatments and diagnostics for hepatitis B and D coinfection.

3.3.1 Systematic reviews and meta-analyses (Web annex C)

Fifteen systematic reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and patient-important outcomes. The Guidelines Development Group ranked the outcomes based on their importance to the patient population (Web annex C).

These included:

- an updated 2015 systematic review on using non-invasive tests to stage liver disease among people with CHB;
- two new systematic reviews to inform criteria for treating adults, adolescents and children with CHB to provide *(1)* estimates of incidence of clinical outcomes without treatment; and *(2)* efficacy of antiviral therapy for preventing clinical outcomes among adults, adolescents and children without cirrhosis, stratified by HBV DNA and ALT levels;
- a new systematic review on using alternative antiviral drugs to existing recommended tenofovir disoproxil fumarate (TDF) or ETV, including dual therapy: TDF + lamivudine (3TC), TDF + emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF);
- a new systematic review on the diagnostic accuracy and clinical outcomes with use of HBV DNA POC viral load assays;

- a new systematic review on using HBV DNA reflex testing: for those with CHB, as well as reflex hepatitis D serology for those with CHB and reflex hepatitis D molecular RNA testing for those with positive hepatitis D serology;
- a new narrative review on who to test and how to test for hepatitis D coinfection for those with CHB;
- a new systematic review of the effectiveness of different hospital-based, primary care-based, co-managed and integrated service delivery models for for CHB. Existing HIV systematic reviews on adherence support, retention in care and person-centred interventions were also used to inform the 2021 WHO consolidated HIV guidelines; and
- Three commissioned market landscaping reports on HBV DNA diagnostics, hepatitis delta diagnostics, and on access and cost of TAF and dual therapy.

Search strategies, summaries of evidence and GRADE tables are reported in Web annex C. The glossary of terms provides full definitions for diagnostic and analytical test performance.

3.3.2 Modelling and cost-effectiveness analysis (Web annex C)

WHO commissioned 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 PMTCT to include all HBsAg-positive women versus the existing recommendation for only those with a high HBV DNA level.

3.3.3 Values and preferences and acceptability surveys (Web annex D)

WHO commissioned four key surveys among populations affected by hepatitis B (including pregnant women); health-care workers and an additional survey among paediatricians and national hepatitis programme managers to inform the WHO 2024 hepatitis B guidelines through understanding the values, preferences and acceptability of potential recommendations relating to topics covered in the guidelines.

- Patients' lived experience for the hepatitis B treatment preferences survey: An anonymous online survey was distributed to patient-focused and civil society networks by the Hepatitis B Foundation, World Hepatitis Alliance and partner organizations working directly with people living with hepatitis B globally. Individuals were eligible to participate if they self-reported being at least age 18 years and living with hepatitis B. A total of 550 eligible respondents from 76 countries completed the survey.
- National hepatitis programme managers were surveyed across 30 countries to understand their perspectives on new directions in hepatitis B care and treatment and HBV PMTCT.

- A global online survey was performed among health-care workers to better understand the challenges in delivering hepatitis B care in resource-limited settings. The 53-item survey addressed the accessibility of diagnostic tests and therapies and the priorities to reach the goal for hepatitis B elimination.
- An online survey was conducted among nine networks of paediatricians providing care to children and adolescents with hepatitis B: PENTA Child Health network, FISPGHAN – Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition; Asia Pacific – APPSPGHAN; Commonwealth – CAPGAN; Europe – ESPGHAN; Latin America – LASPGHAN; North America – NASPGHAN; and Pan Arab – PASPGHAN.

3.4 Grading the quality of the evidence and the strength of the recommendations (Web annex B)

The certainty of the evidence was assessed based on criteria specified in GRADE methods, modified for diagnostic tests and test strategies *(5,6)*. Summaries of the certainty of evidence to address each outcome were entered into the GRADE profiler software (GRADE pro 3.6). The certainty of evidence was categorized as high, moderate, low or very low (Box 3.1 and Table 3.1).

Box 3.1 **Standard approach to rating the certainty of evidence and strength of recommendations using the GRADE system**

The GRADE system separates the rating of the certainty of evidence from the rating of the strength of the recommendation.

The certainty of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the certainty of evidence as high, moderate, low or very low. For studies of interventions, randomized controlled trials (RCTs) are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies of interventions are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose-response relationship or if all plausible biases would underestimate the effect. The higher the certainty of evidence, the more likely a strong recommendation can be made.

The strength of a recommendation reflects the extent to which the Guidelines Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The GRADE system classifies the strength of a recommendation in two ways: "strong" and "conditional" *(5–8)*. The strength is influenced by the following factors: the balance of benefits to harm, the quality of the evidence, values and preferences regarding outcomes, resource use, the feasibility of carrying out the intervention, acceptability of the intervention among impacted stakeholders and impact on equity (Table 3.2).

A strong recommendation is one for which the Guidelines Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects, based on higher-quality evidence indicating that benefits clearly outweigh harm. Other factors that support a strong recommendation are low resource requirements and/or high cost-effectiveness, insensitivity to preferences regarding outcomes, high acceptability, high feasibility and positive impact on equity. The implications of a strong recommendation are that people and settings will generally adopt the recommendation.

A conditional recommendation is one for which the Guidelines Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the benefits are relatively small relative to harm and/or the Guidelines Development Group is not confident about these trade-offs. Other factors that make a conditional recommendation more appropriate are high costs and/or low cost-effectiveness, sensitivity to preferences regarding outcomes, low or variable acceptability or feasibility and negative or variable impact on equity. The implications of a conditional recommendation are that, although most people or settings would adopt the recommendation, many would not or would do so only under certain conditions. The reasons for making a conditional recommendation include the absence of high-quality evidence, imprecision in outcome estimates, uncertainty regarding how individuals value the outcomes, small benefits relative to harm and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Table 3.1 GRADE categories of the certainty of evidence

Certainty of evidence	Rationale
High	We are very confident that the true effect lies close to the estimate of effect.
Moderate	We are moderately confident in the estimate of effect. The true effect is likely to be close to the estimate of effect, but it could differ substantially.
Low	Our confidence in the estimate of effect is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the estimate of effect. Any estimate of effect is very uncertain.

Table 3.2 Key domains considered in determining the strength of recommendations

Domain	Rationale
Benefits and harm	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks or harm), considering any previous recommendation or an alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Certainty of evidence	High certainty of evidence is likely to lead to a strong recommendation.
Values and preferences (of providers and stakeholders)	If the recommendation is likely to be widely accepted or highly valued, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted, it is more likely that a conditional recommendation will be made.
Cost and financial implications	Lower costs (monetary, infrastructure, equipment or human re-sources) or greater cost-effectiveness contribute to a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.
Equity and human rights	If the recommendation is likely to increase access to an intervention for those most in need, a strong recommendation is likely.
Acceptability	The greater the acceptability to all or most stakeholders, the greater the likelihood of a strong recommendation

3.5 Formulating recommendations

At the Guidelines Development Group meeting, the results of the systematic reviews, meta-analyses and complementary information were presented, and the evidence profiles and decision-making tables were reviewed to ensure that there was understanding and agreement on the scoring criteria. See Web annex B for the decision making tables, Web annex C for the systematic reviews and modelling reports and Web annex D for the values and preferences and acceptability surveys. The GRADE method was used to rate the certainty of the evidence and determine the strength of the recommendations. The strength of the recommendations was rated as either strong or conditional. The certainty of evidence supporting each recommendation was graded as high, moderate, low or very low. The methodologist provided guidance on methodological issues and grading of evidence to the systematic review teams, WHO and the Guidelines Development Group members. Recommendations were then formulated by members of the Guidelines Development Group through discussions based on the balance of benefits and harm and overall quality of the evidence, in addition the other factors described above. The Chairs and methodologist worked to reach consensus during the meeting. After addressing all comments and questions from members of the Group, the Chairs asked Group members whether they agreed with the recommendations to document consensus. Voting was not required since consensus was reached for all recommendations. Following the development of recommendations, implementation needs were evaluated, and areas and topics requiring further research identified. The draft guidelines were reviewed by the Guidelines Development Group and the External Review Group.

3.6 Declarations of interest and managing conflicts of interest (Web annex A)

Conflicts of interest were managed as follows.

1. In accordance with WHO Compliance, Risk Management and Ethics (CRE) policy, all external contributors to the guidelines, including members of the Guidelines Development Group and the External Review Group, completed a WHO declaration of interests form, including participation in consulting and advisory panels, research support and financial investment.

2. A brief biography of each member of the Guidelines Development Group was posted on the WHO website with a description of the objective of the Guidelines Development Group meeting. No public comments or objections were received concerning the Groups' membership.

3. The WHO Steering Group reviewed and assessed the declarations submitted by each member and agreed on an approach to assess potential conflicts of interest. At the meeting, declarations of interest were reported according to WHO standard requirements. Individuals from organizations that had received significant funding from private (primarily pharmaceutical) companies and individual researchers or clinicians who had received

payments above US$ 5000 from pharmaceutical companies were considered to have a conflict of interest if it was related to the guideline topic addressed in a recommendation. When any conflict of interest was declared, the WHO Steering Group determined whether such conflicts could potentially affect the experts objective judgement on the guideline development process and recommendations. To ensure consistency, the Group applied the criteria for assessing the severity of conflict of interests in the WHO handbook for guideline development.

4. Most of the participants of the Guidelines Development Group did not declare significant conflicts of interest. Six Guidelines Development Group and two hepatitis D subgroup and two paediatric group members declared a conflict with a public disclosure statement. Their participation was designated as conditional, with continued involvement in the meeting following public disclosure of their interests at the start of the meeting. Significant financial institutional or personal research support was identified for six other individuals (Chari Cohen, Jordan Feld, Jin-Lin Hou, Patrick Kennedy, Janus Ong, Lewis Roberts and Su Wang), and their participation was restricted for the topics of antiviral drugs and who to treat. These individuals were permitted to contribute their technical expertise in reviewing the evidence summaries and to the discussion but were excluded from participation in voting on topics of antiviral drugs and who to treat. No individual was excluded from participated in the Guidelines Development Group altogether (see Web annex A).

5. Declared interests were shared with all participants at the meeting of the Guidelines Development Group so that all participants were aware of any existing interests among the members.

6. The Guidelines Development Group meeting achieved consensus and support for all these recommendations. On the topic of who to treat (Chapter 5), although there was consensus and support for the four recommendations on treatment eligibility, the Guidelines Development Group specifically requested further discussion on two issues:

   - the need for additional language on person-centred shared decision-making, especially for those who do not meet treatment eligibility criteria; and
   - to clarify further strategies for preventing mother-to-child transmission among pregnant women (Chapter 7) on how recommendations on using antiviral prophylaxis for PMTCT versus long-term antiviral therapy for the mother's own health could be more clearly aligned.

   An additional half-day meeting was scheduled with the Guidelines Development Group on 8 June 2023 – one month after the main guidelines meeting. A short draft document was prepared and shared in advance with the Guidelines Development Group that addressed these two issues. Each Guidelines Development Group member was asked to individually comment on the who to treat recommendations alongside the new remarks text to ensure an equal voice. There was strong endorsement and complete consensus among all the Guidelines Development Group members. As a result, voting was not required.

7. WHO drafted the recommendations and guidelines. Several Guidelines Development Group members provided additional input on referencing and citations to ensure accuracy, and their contributions are acknowledged.

8. The declarations of interest forms from members of the External Review Group were reviewed in accordance with the WHO guidelines development policy. For the external peer review group, WHO was satisfied that no case necessitated exclusion from the review process. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process. The external reviewers could not and did not make changes in the recommendations (see Web annex A).

3.7 Disseminating and updating the guidelines

The guidelines, web annexes and a policy brief will be disseminated electronically on the WHO website, through WHO regional offices to WHO country offices and health ministries, webinar series and made available as a print publication on demand. Dissemination will be further supported through conference presentations, webinars on specific guideline topics and through publishing the systematic reviews and evidence in peer-reviewed journals as well as topic specific policy briefs and web- and mobile phone-based applications.

The successful implementation of the recommendations in these guidelines depends on a well-planned and appropriate process of adaptation and integration into relevant regional and national strategies. The implementation of these guidelines can be measured by the number of countries that incorporate them into their national treatment programmes and data on uptake of hepatitis B DNA testing and treatment, which is part of the monitoring and evaluation framework. This approach will be instrumental in measuring the impact of these guidelines at the country level.

These guidelines will be updated in full or in part based on regular scoping exercises of available evidence and experience from country implementation that will guide and trigger the need for new guidance. As the evidence base or user needs change, consideration will be given to producing technical updates on specific subjects.

Expanded treatment eligibility

Chapter 4: Non-invasive assessment of liver disease stage

Chapter 5: Who to treat among people with CHB

Chapter 6: First-line antiviral therapies for CHB

Chapter 7: Preventing mother-to-child transmission of HBV using antiviral prophylaxis

Chapter 8: Who to treat and what antiviral drugs to use for adolescents and children

Chapter 9: Second-line antiviral therapies for managing treatment failure

4. Non-invasive assessment of liver disease stage

4.1 Recommendations

Existing and maintained recommendation *(1)*

APRI (aspartate aminotransferase-to-platelet ratio index) is recommended as the preferred non-invasive test to assess for the presence of significant fibrosis or cirrhosis among adults in resource-limited settings. Transient elastography (FibroScan®) may be a preferable non-invasive test in settings where it is available and cost is not a major constraint. *(strong recommendation, moderate-certainty evidence)*

New recommendation (for non-invasive test thresholds (APRI and transient elastography) to establish the presence of significant fibrosis (≥F2) or cirrhosis (F4))

Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 or transient elastography value of >7.0 kPa,[a] and cirrhosis (F4) should be based on clinical criteria[b] (or an APRI score of >1.0 or transient elastography (FibroScan®) value of >12.5 kPa[a]). *(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)*

a These cut-offs apply to FibroScan® – other elastography techniques do not necessarily have the same cut-offs.
b Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema or oedema.

4.2 Background

The spectrum of liver disease among people with CHB ranges from no or only minimal fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis, which is associated with potentially life-threatening complications of ascites, oesophageal varices and bleeding, and hepatic encephalopathy *(2)*. People with significant fibrosis may also progress to cirrhosis with its associated complications *(3)*. Although decompensated cirrhosis is diagnosed based on distinct clinical features, this is not always the case for compensated cirrhosis or lesser fibrosis stages. Identifying people with less advanced CHB who need treatment is generally based on a combined assessment of level of transaminases, HBV viral load and degree of fibrosis and/or necroinflammation *(3)*.

Liver biopsy had previously been considered the gold standard method to stage liver disease and for assessing fibrosis, but it is not widely used because of its high cost, invasiveness, discomfort, risk of complications and the need for expert histological interpretation. Several liver biopsy scoring systems have been developed, of which the METAVIR system and Knodell and Ishak scores *(4,5)* are the most commonly used (Table 4.1).

Table 4.1 METAVIR liver-biopsy scoring system

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Several non-invasive fibrosis tests, using serum indices (APRI *(6)* and FIB-4 *(7)*) or ultrasound that measure liver stiffness (transient elastography (FibroScan®) *(8)*) are increasingly employed to assess liver fibrosis, reducing reliance on liver biopsy for individuals with an established underlying cause of liver disease (Box 4.1 and Table 4.2). Low-cost serum tests such as APRI and FIB-4 offer cost-effective and easily interpretable indirect markers of fibrosis in outpatient settings, whereas others such as FibroTest are less accessible because of patent protection and stringent laboratory requirements. The tests vary in their ability to assess all fibrosis stages, For example, FIB-4 was originally validated for advanced fibrosis (≥F3), and APRI has been validated for diagnosing both significant fibrosis (≥F2) and cirrhosis.

Transient elastography has been the most widely evaluated and used method in high-income settings. It is non-invasive, takes less than 10 minutes to perform and can be undertaken easily in outpatient or community settings by trained health-care personnel. However, challenges include high equipment costs, the need for regular maintenance, reduced accuracy in specific conditions and inapplicability to certain populations. Other more recent ultrasound-based techniques like 2D ARFI imaging and shear-wave elastography combine ultrasound examination with measurement of liver stiffness and thus provide a one-stop shop for HCC surveillance and evaluation of liver fibrosis but require more operator expertise *(8)*. The use of accurate and validated non-invasive fibrosis tests in resource-limited settings can help with the optimal selection of people with hepatitis B for antiviral therapy.

Table 4.2 Selected non-invasive tests to assess liver fibrosis

Test	Components	Requirements	Cost
APRI	AST, platelets	Simple blood tests	+
FIB-4	Age, AST, ALT, platelets	Simple blood tests	+
FibroScan®	Transient elastography	Dedicated equipment	+++

Box 4.1 APRI and FIB-4 calculations

APRI = * ((AST/ULN) Í 100)/platelet count (10^9/L)

FIB-4 = (age (years) Í AST (IU/L))/(platelet count (10^9/L Í [ALT (IU/L)$^{1/2}$])

ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken.

For APRI, an online calculator can be accessed at https://www.hepatitisc.uw.edu/page/clinical-calculators/apri.

For FIB4, an online calculator can be accessed at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

In the 2015 hepatitis B guidelines, the cut-off of >2 for APRI was used for diagnosing cirrhosis *(1)*. This cut-off had a sensitivity of 35% and a specificity of 89%. Although, the choice of a high cut-off was to reduce false-positive results, it was recognized that at least 50% of those who had cirrhosis were being missed by such a high cut-off. However, APRI was not the only criterion for treatment, and some of these people would have been treated based on the presence of raised transaminases and/or high viral load. The cost and availability of antiviral therapy is now a lesser concern, and the focus has shifted to diagnosing at lesser fibrosis stages and expanding treatment, since this can prevent the progression to cirrhosis and complications. It was also recognized that the previous systematic review used in the 2015 hepatitis B guidelines had no data on the use of non-invasive tests for children and adolescents and no data from sub-Saharan Africa.

4.3 Summary of the evidence (Web annex C 4.1)

A systematic review and meta-analysis compared the diagnostic accuracy of non-invasive fibrosis assessment tests (APRI, FIB-4 and transient elastography (FibroScan®) for diagnosing and staging liver fibrosis among adults, adolescents and children with CHB versus liver biopsy as the reference standard. These tests were chosen because of their potential for ready access and use in low- and middle-income countries. The outcomes of interest were the sensitivity and specificity of non-invasive tests using a defined index test cut-off point for detecting significant fibrosis (METAVIR stage ≥F2), advanced fibrosis (≥F3) and cirrhosis (F4) based on the METAVIR staging system. Only the results for significant fibrosis (≥F2) and cirrhosis (F4) are reported. Eligible studies had an interval of less than six months between liver biopsy and index test. Meta-analysis was performed separately for each non-invasive test and for each METAVIR stage (F2 to F4). Studies were included in the meta-analysis if they reported diagnostic accuracy of non-invasive tests within a predetermined range of cut-offs, as shown in Tables 4.3, 4.4 and 4.5.

Data on people with hepatitis B were extracted from 264 studies, of which 219 studies reported diagnostic accuracy across the predetermined range of cut-offs and were included in the meta-analysis. Five studies reported on non-invasive fibrosis tests performed in adolescents and children. One study specifically reported on the performance of non-invasive fibrosis tests in adolescents. Tables 4.4 and 4.5 summarize the sensitivity and specificity results. Overall, the certainty of evidence was graded as moderate, downgraded mainly for risk of bias due to the absence of predetermined index test cut-offs.

Non-invasive test cut-off values for detecting significant fibrosis and cirrhosis

Optimal thresholds for non-invasive test values that correlate with specific histological stages have been derived and the cut-offs validated for APRI and FIB-4. APRI and FIB-4 use two cut-off points for diagnosing specific fibrosis stages, since using a single cut-off would result in suboptimal sensitivity and specificity. These are either a high cut-off with high specificity (fewer false positives) or a low cut-off with high sensitivity (fewer false negatives). A combined approach for APRI and FIB-4 uses the low cut-off to rule out the presence of a particular stage of fibrosis and the high cut-off to confirm that the person has a particular stage of fibrosis. Meta-analyses were performed for similar low and high cut-offs used in studies. Transient elastography uses a single cut-off, although there are no uniformly established and validated cut-offs for specific fibrosis stages. Table 4.3 shows the established high and low cut-off values of the APRI (high and low) and a range of the most reported cut-offs of transient elastography (FibroScan®) for diagnosing ≥F2 and cirrhosis.

Table 4.3 Cut-off values for detecting significant fibrosis (≥F2) and cirrhosis (F4)

	APRI (low cut-off)	APRI (high cut-off)	Transient elastography (FibroScan®)[a]
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	>6-8 kPa
Cirrhosis (METAVIR F4)	1.0	2.0	>11-14 kPa

a Transient elastography (FibroScan®) has no validated exact cut-off for specific fibrosis stages. This table presents the range of the most used cut-offs for ≥F2 and F4 in CHB. "Mean" cut-offs of 7 and 12.5 kPa could be used for treatment decisions in significant fibrosis and cirrhosis, respectively.

Diagnostic accuracy of non-invasive tests (Tables 4.4 and 4.5)

Tables 4.4 and 4.5 presents the summary sensitivity and specificity for detecting significant fibrosis (≥F2 stage) and cirrhosis (F4 stage) of APRI and transient elastography (FibroScan®). The FIB-4 results are not shown, since this test has been developed for advanced fibrosis (≥F3 stage) and is also less validated for people younger than 35 years. For diagnosing ≥F2, the summary sensitivity (low cut-off) was 72% for APRI and 75% for transient elastography, and the summary specificity (high cut-off) was 94% for APRI and 79% for transient elastography. For diagnosing cirrhosis (F4), the summary sensitivity (low cut-off) was 54% for APRI and 83% for transient elastography, and specificity (high cut-off) was 90% for APRI and 89% for transient elastography. For diagnosing ≥F2, the low cut-off for APRI had similar sensitivity to transient elastography and the APRI high cut-off had significantly better specificity than transient elastography. For diagnosing cirrhosis, transient elastography had significantly better sensitivity than APRI but a similar specificity.

Table 4.4 Summary sensitivity and specificity for APRI and transient elastography (FibroScan®) for detecting significant fibrosis (fibrosis stage ≥F2)

Test	Cut-off	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)
APRI - F2	0.3-0.7	120	72.7% (70.0-75.2%)	65.1% (61.3-68.7%)
APRI - F2	0.5 (low)	49	71.7% (67.1-75.8%)	64.8% (58.6-70.5%)
APRI - F2	1.3-1.7	45	29.3% (23.0-36.6%)	93.6% (90.8-95.6%)
APRI - F2	1.5 (high)	42	28.2% (21.8-35.6%)	93.5% (90.5-95.6%)
Transient elastography FibroScan® - F2	6.0-8.0 kPa	53	75.1% (72.2-77.7%)	79.3% (76.2-82.2%)

Table 4.5 Summary sensitivity and specificity for APRI and transient elastography (FibroScan®) for detecting cirrhosis (F4) (fibrosis stage ≥F2)

Test	Cut-off	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)
APRI – F4	0.8–1.2	47	57.8% (51.9–63.5%)	75.9% (71.6–79.7%)
APRI – F4	1 (low)	27	54.3% (47.7–60.8%)	76.9% (71.7–81.4%)
APRI – F4	1.8–2.2	32	28.9% (23.2–35.5%)	89.9% (86.5–92.5%)
APRI – F4	2 (high)	31	28.1% (22.5–34.5%)	90.3% (87.2–92.8%)
Transient elastography FibroScan® – F4	11.0–14.0 kPa	37	82.6% (77.8–86.5%)	89.0% (86.3–91.2%)

Positive and negative predictive value of non-invasive tests (Table 4.6)

The comparative performance of the non-invasive tests was assessed (number of true-positive, false-positive, true-negative and false-negative results) according to the prevalence of significant fibrosis and cirrhosis in a population, which can strongly determine the predictive value of these tests in practice. Two different hypothetical scenarios for using non-invasive tests were evaluated, with projection of the number of true-positive, false-positive, true-negative and false-negative results for 1000 people with CHB for each non-invasive test based on: *(1)* a median prevalence of 52% for significant fibrosis and 16% for significant cirrhosis, similar to the median prevalence reported in the studies included in the meta-analysis (assumes preselection based on ALT and/or viral load) and *(2)* a prevalence of 25% for ≥F2 and 5% for F4. For scenario 2, in a hypothetical population of 1000 people with CHB infection and a 25% prevalence of ≥F2 fibrosis, using an APRI cut-off of >0.5 would result in 183 true positives, 263 false positives, 68 false negatives and 488 true negatives for ≥F2 fibrosis. Using a transient elastography cut-off of >7.0 kPa would provide similar results (188 true positives, 158 false positives, 63 false negatives and 593 true negatives). Using a high APRI cut-off (>1.5) would result in more true negatives (705) but also fewer true positives *(73)*.

Table 4.6 Test outcomes of APRI and transient elastography (FibroScan®) based on a hypothetical population of 1000 people with a 25% prevalence of ≥F2 (unselected HBsAg-positive people with CHB)

	True positive	False positive	False negative	True negative
APRI low cut-off (>0.5)	183	263	68	488
APRI high cut-off (>1.5)	73	45	178	705
APRI combined cut-off	73	45	68	488
Transient elastography of 7 kPa	188	158	63	593

4.4 Rationale for the recommendations

In the 2015 hepatitis B guidelines *(1)* and again in 2024, the Guidelines Development Group recommended using non-invasive tests (APRI or transient elastography) in preference to liver biopsy, especially in low- and middle-income countries, to assess the stage of liver disease and the presence of advanced disease as a priority for antiviral therapy. Over the past decade, the use of non-invasive tests has emerged as the gold standard for staging of liver disease globally, and with ready access to APRI score in low- and middle-income countries, it is now a strong recommendation supported by a substantive moderate-certainty evidence base.

In the 2024 guidelines, the focus is now on detecting the presence of significant fibrosis (≥F2) as well as cirrhosis (F4) using non-invasive tests since this is now a priority criteria for treatment eligibility (Chapter 5: Who to treat for CHB). In selecting the cut-offs for treatment eligibility, a high priority was given to minimizing false-negative results and accepting more false-positive results.

Based on evidence from the systematic review, the Guidelines Development Group considered that APRI and transient elastography (FibroScan®) provide useful diagnostic information for identifying people with significant fibrosis and cirrhosis. An APRI score using a low cut-off of >0.5 was associated with a sensitivity of 71.7% (95% CI 67.1–75.8%) and a specificity of 64.8% (95% CI 58.6–70.5%) for identifying ≥F2 among people with CHB infection based on 49 studies, sensitivity was much lower when a higher cut-off was used of >1.5 (sensitivity 28.2% [95% CI 21.8–35.6%] and specificity 93.5% [95% CI 90.5–95.6%]), based on 42 studies. Transient elastography using a cut-off of >6.0 to 8.0 kPa was associated with a sensitivity of 75.1% (95% CI 72.2–77.7%) and a specificity of 79.3% (95% CI 76.2–82.2%) based on 53 studies. Overall, the evidence was graded as moderate certainty (downgraded for risk of bias).

An APRI score >0.5 or transient elastography value of >7.0 kPa identifies most adults with significant fibrosis and an APRI score of >1.0 or transient elastography value of >12.5 kPa alongside clinical criteria identifies most adults with cirrhosis (F4) and in priority need of antiviral therapy.

Therefore, an APRI score >0.5 is recommended in these guidelines as a key criterion for giving priority to initiating antiviral therapy in resource-limited settings. Conversely, treatment can be deferred for those with an initial APRI score ≤0.5, who can be re-evaluated at subsequent visits.

Evidence on the diagnostic accuracy of non-invasive tests for adolescents was extremely limited. However, the Guidelines Development Group judged that the evidence on adults could be extrapolated to adolescents, albeit with decreased (low) certainty, due to indirectness.

4.4.1 Balance of benefits and harm

Potential harm includes treatment decisions based on either false-positive or false-negative APRI results. A false-negative result would mean that a person with significant fibrosis would not be identified by non-invasive tests and would be delayed in receiving prompt antiviral therapy, which might have prevented progression to cirrhosis or reduced the risk of developing HCC. However, people with CHB infection may meet other eligibility criteria for antiviral therapy (such as elevated HBV DNA viral load). A false-positive test result may lead to unnecessary or premature treatment, exposing people to the inconvenience of long-term treatment, potential drug resistance and a small risk of drug toxicity. The Guidelines Development Group concluded that concerns regarding false positives were significantly less than potential false-negatives, given the overall goals for earlier treatment and a significant expansion in treatment eligibility and relatively minor harm of earlier treatment.

Transient elastography (FibroScan®) is no longer contraindicated in pregnancy (United States Food and Drug Administration 2023 clearance), but a specific probe is required for children. The cut-offs used need further validation for children and adolescents. In addition, accuracy is reduced for people with obesity and intercurrent diseases may also affect the results of non-invasive tests by may falsely increasing or decreasing the values of each parameter. For example, people with hepatitis flares or acute hepatitis will have falsely high liver stiffness measurements *(9)*. APRI has not been evaluated among people with flares but will likely result in falsely high scores as well.

4.4.2 Values and preferences

From the perspective of people with hepatitis B, the Guidelines Development Group considered that the APRI test was acceptable, since it only requires phlebotomy, and is routinely available and can be undertaken by untrained personnel. Similarly, transient elastography (FibroScan®) is non-invasive, takes less than 10 minutes to perform and can be undertaken in outpatient or community settings. Medical, nursing and other health-care personnel can be easily trained to use FibroScan®.

4.4.3 Resource use

The lower cost of the blood-based non-invasive tests remained a key factor in continuing to recommend APRI as the preferred non-invasive test. The blood tests that are needed to calculate APRI score are inexpensive (less than a few US dollars per test) and are routinely available at most health-care facilities, even in resource-limited settings. Interpreting APRI results is also relatively straightforward.

Characteristics that may limit the use of transient elastography in contrast to APRI include the high cost of the equipment and the need for regular service and recalibration and trained operators. The machine costs US$ 50 890 (US$ 28,585 for the portable machine), and yearly maintenance is about US$ 8500/year. However, consumable costs are minimal, and the cost per test is therefore less than US$ 9. Carrying out transient elastography requires a trained operator, and interpreting the results requires understanding the indications and limitations of the method. However, the training process is simple and the inter- and intraobserver variability is low. For these reasons, the use of transient elastography has been considered less feasible in most low- and middle-income countries. The cost of alternative elastography methods, such as ARFI imaging and shear-wave elastography, is slightly higher but will depend on whether this is used for liver stiffness only or as ultrasound for HCC screening.

4.5 Research gaps

- Further evaluation of the performance of non-invasive tests in under-researched populations, including people with HBV and HIV coinfection, HBV and HDV coinfection, pregnant women, children and adolescents, in the presence of metabolic dysfunction–associated steatotic liver disease *(10)* and in populations from sub-Saharan Africa and Latin America.
- Evaluation in resource-limited settings of alternative elastography methods, such as ARFI imaging and shear-wave elastography, which are similar in principle to transient elastography and are incorporated into ultrasound imaging machines.

5. Who to treat among people with CHB

5.1 Recommendations

New recommendations – who to treat

Treatment is recommended for all adults and adolescents (aged ≥12 years) with CHB[a] (including pregnant women and girls and non-pregnant women of reproductive age) with:

1. Evidence of significant fibrosis (≥F2)[b] based on an APRI score of >0.5 or transient elastography[c] value of >7 kPa or evidence of cirrhosis (F4) (based on clinical criteria (or an APRI score of >1 or transient elastography value of >12.5 kPa[b]), regardless of HBV DNA or ALT levels.

(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)

OR

2. HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period.[d]

(adults: strong recommendation, high-certainty evidence [HBV DNA >20 000 IU/mL] and low-certainty evidence [HBV DNA 2000-20 000,]; adolescents: conditional recommendation, low-certainty evidence)

OR

3. Presence of **coinfections** (such as HIV, hepatitis D or hepatitis C); **family history** of liver cancer or cirrhosis; **immune suppression** (such as long-term steroids, 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 the APRI score or HBV DNA or ALT levels.

(adults: strong recommendation, moderate-certainty evidence; adolescents: conditional recommendation, low-certainty evidence)

OR

In the absence of access to an HBV DNA assay:

4. Persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score.[e]

(adults and adolescents: conditional recommendation, very-low-certainty evidence)

a Defined as the presence of HBsAg on at least one occasion, and for adolescents and children, persistence of HBsAg for six months or more.

b The thresholds of non-invasive tests (APRI and transient elastography) for diagnosis of significant fibrosis or cirrhosis and treatment recommendation are based on extrapolating data from adults and have not yet been fully validated for adolescents or children.

c Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

d The ULN for ALT have been defined as <30 U/L for men and boys and <19 U/L for women and girls for consistency. Some guidelines use different ULN ALT levels for adolescents and children (<22 U/L for girls and <25 U/L for boys). Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.

e Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

ALGORITHM FOR ASSESSMENT, TREATMENT AND MONITORING OF PEOPLE WITH CHRONIC HEPATITIS B INFECTION[a]

HBsAg positive

INITIAL ASSESSMENT

ASSESSMENT FOR TREATMENT ELIGIBILITY

1. **Severity of liver disease** using non-invasive tests (APRI or transient elastography)
2. **ALT and HBV DNA level**
3. **Medical history:** Screening for presence of coinfections (eg. HIV, HDV or HCV), comorbidities (eg. diabetes, steatotic liver disease) immune suppression (eg. long term steroids, transplant), extrahepatic manifestations (eg. glomerulonephritis, vasculitis), or family history of liver cancer or cirrhosis

GENERAL CARE MEASURES

1. **Counselling on lifestyle** eg. alcohol consumption, diet and physical activity
2. **Preparation for starting treatment** eg. adherence support, risk factors for renal dysfunction[b] and baseline renal function (as indicated)
3. **Preventive measures** eg. HBsAg screening of family and household members and sexual contacts, with HBV vaccination of those negative

TREATMENT ELIGIBILITY

TREAT ALL ADULTS and ADOLESCENTS (aged ≥12 years[c]) (including pregnant and non-pregnant women and girls of reproductive age) **WITH:**

1. **SIGNIFICANT FIBROSIS (≥F2) or CIRRHOSIS (F4)** (regardless of HBV DNA or ALT levels
   - Clinical criteria for cirrhosis[d]
   - Non-invasive tests: **APRI >0.5** or **transient elastography>7 kPa** (adults)[e]

OR

2. **HBV DNA>2000 IU/mL AND ALT level > ULN**[f]

OR

3. **PRESENCE OF of any of following** (regardless of APRI score, HBV DNA or ALT level)
   - **Coinfection** (eg. HIV, HDV, HCV)
   - **Family history** of liver cancer or cirrhosis
   - **Immune suppression**
   - **Comorbidities** (eg. diabetes, metabolic dysfunction-associated steatotic liver disease)
   - **Extrahepatic manifestations** (eg. glomerulonephritis or vasculitis)

OR

In absence of access to HBV DNA assay

4. **PERSISTENTLY ABNORMAL ALT LEVELS ALONE**[f,g]

ALT
Persistently normal[f,g]

AND

HBV DNA
<2000 IU/mL

AND

Absence of coinfections, comorbidities, immune suppression, extrahepatic manifestations family history of liver cancer or cirrhosis

ANTIVIRAL TREATMENT REGIMEN

INITIATE ANTIVIRAL THERAPY AND MONITOR[h]

- **TDF or ETV**
- **TDF +3TC or TDF + FTC** (if no access to TDF monotherapy)
- **ETV or TAF** in persons with osteoporosis or impaired kidney function or in children and adolescents

DEFER TREATMENT AND MONITOR

MONITORING[h]

Every 6 months	**SURVEILLANCE FOR** (AFP and ultrasound)[h] (persons with cirrhosis or family history of liver cancer or cirrhosis)
Every 12 months	**TREATMENT RESPONSE AND/OR DISEASE PROGRESSION**[h] • Adherence at each visit, if on treatment • Non-invasive tests (APRI or transient elastography) • ALT and HBV DNA level • Monitoring of renal function (creatinine), as indicated

ALT: alanine aminotransferase, APRI: aspartate aminotransferase-to-platelet ratio index

a Defined as the presence of HBsAg for adults and persistence of HBsAg for six months or more for adolescents and children.

b Before initiation, consider assessing renal function: serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria and risk factors for renal dysfunction (decompensated cirrhosis, creatinine clearance <50 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, solid organ transplantation, older age, BMI <18.5 kg/m2 (or body weight <50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV). Monitoring should be more frequent for those at higher risk of renal dysfunction.

c Age groups: these guidelines use the following definitions for the purpose of implementing treatment recommendations for adolescents and children aged two years and older. An adult is a person aged 18 years or older; an adolescent 12–17 years old inclusive; and a child is 2–11 years old. Countries may have other definitions under national laws.

d Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

e Non-invasive tests including APRI and transient elastography have not yet been validated for children and adolescents.

f The ULN for ALT has been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

g Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.

h All people with CHB should be monitored regularly for disease activity and progression and surveillance for HCC and after stopping treatment for evidence of reactivation. More frequent monitoring may be required for those with more advanced liver disease, during the first year of treatment or if adherence is a concern.

Key remarks

The four new recommended options for meeting treatment eligibility will substantially expand treatment access to most individuals testing positive for HBsAg. There may also be individual circumstances in which, although individuals may not meet any of the four options for treatment eligibility, there are specific individual concerns regarding infectivity, transmission, associated stigma, the risk of oncogenicity and progressive liver fibrosis and a strong individual motivation to consider treatment, despite the lack of direct evidence. In such cases, a patient-centred approach with discussion between individuals and their health-care provider will be key in helping them make informed decisions about whether to begin treatment or not. This should consider the uncertainties resulting from lack of direct evidence for treatment benefit and low risk of transmission for those with HBV DNA <2000 IU/mL, overall lower benefit-to-risk ratio, the financial implications associated with long-term treatment and importance of sustained treatment adherence.

Regardless of the criteria guiding the initiation of treatment, WHO recommends that all individuals starting treatment should undergo annual monitoring involving HBV DNA, ALT and APRI score assessments, with continuous support to ensure adherence. Individuals who have not yet initiated treatment should also undergo close monitoring (see Chapters 16–18).

5.2 Background

The objective of treatment is to prevent the adverse outcomes of CHB. The decision to treat is usually based on a combined assessment of the stage of liver disease (from clinical features alongside blood- or ultrasound-based non-invasive tests) together with levels of serum ALT and HBV DNA. Those who present with advanced liver disease, such as cirrhosis or acute liver failure, require immediate treatment. Prospective studies have identified several predictors of progression of HBV-related liver disease, including cirrhosis and HCC and likelihood of exacerbations of CHB. These include age, male sex, mode of HBV transmission, serum ALT levels, viral factors (including ongoing HBV replication measured by serum HBV DNA level, HBV genotype and HBV pre-core and core promoter variants), a family history of HCC and accompanying factors such as alcohol use, obesity, steatotic liver disease, HIV infection and diabetes *(1–3)*.

In 2015, WHO launched the first global guidelines on hepatitis B treatment to simplify treatment decisions, especially in resource-limited settings. WHO recommended using simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment, giving priority to antiviral therapy for those with CHB and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on an APRI score >2 in adults), regardless of ALT levels, HBeAg status or HBV DNA levels. WHO also recommended treatment for adults (especially people older than 30 years of age) without clinical evidence of cirrhosis (or based on APRI score ≤2 for adults) and persistently elevated ALT levels and HBV DNA >20 000 IU/mL, regardless of HBeAg status. Antiviral therapy was assessed to have minimal harm. The evidence was graded as moderate certainty. However, at the time the guidelines were developed, the data to inform decisions were limited, especially for sub-Saharan Africa and for lower HBV DNA levels. There were also no studies of pregnant women, adolescents or children with CHB.

Based on additional evidence on the longer-term impact of treatment on key clinical outcomes and the strong request from health-care providers and civil society to simplify treatment criteria and remove other potential barriers to scaling up antiviral therapy, several criteria were given priority for re-evaluating treatment indications. These include lowering the HBV DNA threshold for treatment from the current WHO recommendation of ≥20 000 IU/mL and treating those with significant fibrosis, coinfections and comorbidities *(4–7)*. Nevertheless, it is recognized based on available studies that significant subset of people with HBeAg-negative CHB and persistently normal ALT, low HBV DNA levels (<2000 IU/mL) and no or mild liver fibrosis have a very low risk of hepatitis B–related morbidity and mortality and may not benefit significantly from antiviral therapy.

Chapter 8 addresses treatment recommendations and considerations for adolescents and children.

5.3 Summary of the evidence (Web annex C 5.1 and 5.2)

To inform the 2024 guidelines, two key new systematic reviews and meta-analyses were performed.

- Incidence of clinical outcomes according to baseline HBV DNA and ALT levels among adults (Table 5.1 and Web annex C 5.1): to provide a summary estimate of the incidence of key clinical outcomes (HCC, cirrhosis, liver-related mortality and fibrosis progression) in the absence of treatment among people with hepatitis B without cirrhosis, stratified by HBV DNA levels (<2000, 2000–20 000, 20 000–200 000 and ≥200 000 IU/mL) and ALT levels (<1, 1–2 and ≥2 times the ULN).
- Effectiveness of treatment according to baseline HBV DNA and ALT levels among adults, adolescents and children (Table 5.2 and Web annex C 5.2): to provide a summary estimate of the efficacy of antiviral therapy for preventing key clinical outcomes (HCC, ALT normalization, HBeAg loss and HBsAg loss) among adults with hepatitis B without cirrhosis, stratified by both HBV DNA levels (<2000, 2000–20 000, 20 000–200 000 and ≥200 000 IU/mL) and ALT levels (<1, 1–2 and ≥2 times the ULN) at baseline. The same question was also addressed for children and adolescents.

Chapter 8 summarizes the evidence, treatment recommendations and rationale for adolescents and children.

5.3.1 Incidence of clinical outcomes according to baseline HBV DNA and ALT levels among adults (Table 5.1 and Web annex C 5.1)

A systematic review and meta-analysis examined aggregated data from 78 longitudinal cohort studies among people with CHB without cirrhosis and in absence of treatment. Most studies were from the WHO Western Pacific Region (61%), followed by the European Region (16%), Region of the Americas (5%), Eastern Mediterranean Region (4%), African Region (4%) and South-East Asia Region (1%). Most studies focused on adults (85%), 12.5% (n = 10) focused on adolescents and children and 2.5% (n = 2) included both. Half the studies were conducted before 2015 and the remaining half after the 2015 hepatitis B guidelines were published. For adults, many estimates were available for different HBV DNA and ALT strata, especially for the risk of HCC and cirrhosis (Table 5.1).

Incidence of clinical outcomes according to baseline HBV DNA levels among adults (Table 5.1)

HCC: The pooled incidence of HCC among adults (per 100 person-years) were similarly low for HBV DNA <200 IU/mL (0.13, 95% CI: 0.09–0.18), <2000 IU/mL (0.16, 95% CI: 0.10–0.25) and 2000–20 000 IU/mL (0.27, 95% CI: 0.21–0.33), with overlapping confidence intervals. However, for HBV DNA strata above 2000 IU/mL, there was a clear dose–response relationship between HBV DNA levels at baseline and the incidence of HCC: 2000–20 000 IU/mL: 0.27 (95% CI: 0.21–0.33); 20 000–200 000 IU/mL: 0.73 (95% CI: 0.59–0.91); and ≥200 000 IU/mL: 0.92 (95% CI: 0.68–1.26) (P < 0.01). The meta-analysis of studies with repeat HBV DNA assessments was more limited, since few studies included high HBV DNA strata. However, individuals with persistently low viraemia of <2000 IU/mL had a low pooled incidence of HCC (0.10, 95% CI: 0.07–0.13).

Cirrhosis and liver-related mortality: Similarly, the pooled incidence of cirrhosis (per 100 person-years) was similar between the <200 IU/mL HBV DNA stratum (0.31, 95% CI: 0.22–0.43) and <2000 IU/mL (0.30, 95% CI: 0.15–0.62). However, there was a clear dose–response relationship between HBV DNA levels at baseline and the incidence of cirrhosis: <2000 IU/mL (0.30, 95% CI: 0.15–0.62); 2000–20 000 IU/mL (0.72, 95% CI: 0.63–0.82); 20 000–200 000 IU/mL (1.46, 95% CI: 0.99–2.16); and ≥200 000 IU/mL (2.24, 95% CI: 1.70–2.94) (P < 0.01 for subgroup differences). Analysis of a group of individuals with persistently low viremia of <2000 IU/mL confirmed the relatively low incidence of cirrhosis (0.29, 95% CI: 0.13–0.62). A dose–response relationship was also found for liver-related mortality <2000 IU/mL (0.08, 95% CI: 0.05–0.13); 2000–20 000 IU/mL (0.22, 95% CI: 0.14–0.35); 20 000–200 000 IU/mL (0.82, 95% CI: 0.56–1.14, only one study); and ≥200 000 IU/mL (1.06, 95% CI: 0.85–1.31, only one study).

Other intermediate endpoints: In contrast with the hard clinical endpoints, there was no clear dose–response relationship with baseline HBV DNA levels for outcomes such as progression of fibrosis, HBeAg loss and HBsAg loss. This may result from the small number of available estimates for these outcomes and important heterogeneity across the studies within the same HBV DNA stratum.

Incidence of clinical outcomes according to the baseline ALT levels among adults (Table 5.1)

For adults, the pooled incidence of HCC (per 100 person-years) was slightly higher for those with raised ALT levels: serum ALT 1–2 times the ULN (0.74, 95% CI: 0.43–1.29) and ALT >2 times the ULN (0.66, 95% CI: 0.40–1.1) than for those with a normal ALT level (0.26, 95% CI: 0.13–0.54) (P = 0.06). Nevertheless, there was high heterogeneity across the studies within the normal ALT level stratum and the stratum with ALT 1–2 times the ULN. Importantly, the individuals with persistently normal ALT levels had a consistently low incidence of HCC per 100 person-years.

Table 5.1 Summary table of unadjusted incidence (per 100 person-years) for HCC, cirrhosis, all-cause mortality or liver-related mortality among adults

Stratum	HCC	Cirrhosis	All-cause mortality	Liver-related mortality
HBV DNA <200 IU/mL	0.13 (0.09-0.18) (n = 4)	0.31 (0.22-0.43) (n = 2)	0.65 (0.52-0.82) (n = 1)	0.08 (0.04-0.15) (n = 1)
HBV DNA <2000 IU/mL	0.16 (0.10-0.25) (n = 16)	0.30 (0.15-0.62) (n = 8)	0.56 (0.50-0.62) (n = 5)	0.08 (0.05-0.13) (n = 4)
HBV DNA 2000-20 000 IU/mL	0.27 (0.21-0.33) (n = 7)	0.72 (0.63-0.82) (n = 5)	0.60 (0.46-0.78) (n = 4)	0.22 (0.14-0.35) (n = 3)
HBV DNA 20 000-200 000 IU/mL	0.73 (0.59-0.91) (n = 4)	1.46 (0.99-2.16) (n = 3)	1.44 (1.13-1.85) (n = 1)	0.82 (0.59-1.14) (n = 1)
HBV DNA ≥200 000 IU/mL	0.92 (0.68-1.26) (n = 8)	2.24 (1.70-2.94) (n = 3)	0.88 (0.38-2.08) (n = 3)	1.06 (0.85-1.31) (n = 1)
ALT <1 times ULN	0.26 (0.13-0.54) (n = 17)	0.24 (0.15-0.37) (n = 4)	0.90 (0.45-1.82) (n = 2)	0.03 (0.01-0.20) (n = 4)
ALT 1-2 times ULN	0.74 (0.43-1.29) (n = 5)	N/A	0.30 (0.19-0.47) (n = 1)	N/A
ALT >2 times ULN	0.66 (0.40-1.10) (n = 2)	N/A	N/A	N/A

5.3.2 Effectiveness of treatment according to baseline HBV DNA and ALT levels among adults (Table 5.2 and Web annex C 5.2)

This systematic review and meta-analysis aggregated data from RCTs or non-randomized studies of interventions to provide estimates of the efficacy of antiviral therapy for preventing clinical outcomes among people with CHB without cirrhosis, stratified by HBV DNA (<2000, 2000-20 000, 20 000-200 000 and ≥200 000 IU/mL) or ALT levels (<1, 1-2 and ≥2 times the ULN) at baseline. A total of 43 studies (31 RCTs and 12 observational studies) met the inclusion criteria; 22 (52%) studies were from Asia, 7 (17%) from Europe, 2 (5%) from North America and none from Africa. A total of 21 studies (50%) focused on adults aged ≥18 years and 13 (31%) on those <18 years. Most studies (86%) only reported outcomes for groups with HBV DNA >20 000 IU/mL. Only one RCT and five observational studies (14%) reported results for groups with HBV DNA <20 000 IU/mL (five for <2000 IU/mL and one for 2000-20 000 IU/mL). Only one RCT focused on HBV DNA <2000 IU/mL.

Table 5.2 summarizes the outcomes. Based on studies that were mostly conducted on groups with higher baseline HBV DNA levels (>20 000 IU/mL), antiviral therapy was associated with improved biochemical (ALT normalization) and some viral outcomes (undetectable viral load), with increasing HBV DNA levels at baseline. Treatment efficacy also tended to be greater at higher baseline treatment HBV DNA levels for key clinical (HCC) and histological (fibrosis and

necroinflammation) outcomes. Overall, the hazard ratios for HCC for treated versus untreated groups according to baseline viral load were: <2000 IU/mL: 0.72 (95% CI 0.43–1.20; only one study); 2000–20 000 IU/mL: 0.45 (95% CI 0.14–1.46; only one study); 20 000–200 000 IU/mL: 0.17 (95% CI 0.06–0.50; only one study); 200 000–2 million IU/mL: 0.48 (95% CI 0.26–0.91; three studies); 2 million–20 million IU/mL: 0.44 (95% CI 0.19–1.03; only one study); and 20 million–200 million IU/mL: 0.40 (95% CI 0.17–0.9; two studies). The certainty of evidence supporting treatment efficacy was very low or low for the lower HBV DNA strata (<2000 and 2000–20 000 IU/mL) and ranged from very low to high for the higher HBV DNA strata.

Table 5.2 Summary estimates of the efficacy of antiviral therapy at reducing clinical outcomes among adults with CHB without cirrhosis, stratified by HBV DNA levels

HBV DNA stratum (IU/mL)	Outcome	Number of studies	Type of studies	RR or adjusted hazard ratio (aHR)	95% CI
<2000	HCC	1	Cohort	aHR 0.72	0.43–1.20
	HBsAg seroconversion	1	RCT	RR 3.72	0.30–45.8
		4	Cohort	RR 36.21	8.74–149.4
	HBsAg loss or reduction	6	Cohort	RR 5.88	1.37–33.0
2000–20 000	HCC	1	Cohort	aHR 0.45	0.14–1.46
20 000–200 000	HCC	1	Cohort	aHR 0.17	0.06–0.52
	Worsening of fibrosis	2	RCT	RR 0.56	0.25–1.15
	Improvement of fibrosis	2	RCT	RR 1.23	0.48–8.12
	Worsening of necroinflammation	2	RCT	RR 0.38	0.13–1.01
	Improvement of necroinflammation	2	RCT	RR 1.42	0.76–4.41
	ALT normalization	1	RCT	RR 1.49	1.13–1.97
	HBeAg loss	1	RCT	RR 0.40	0.05–3.13
	HBsAg loss or reduction	1	RCT	RR 0.34	0.01–8.16
	Undetectable viral load	2	RCT	RR 6.86	2.65–15.15
200 000–2 million	HCC	1	Cohort	aHR 0.37	0.15–0.91
	Improvement of necroinflammation	1	RCT	RR 0.86	0.40–1.82
	ALT normalization	1	RCT	RR 3.64	2.43–5.45
	HBeAg loss	1	RCT	RR 6.88	0.38–124.5
	HBeAg seroconversion	2	RCT	RR 17.04	3.33–50.2
	Undetectable viral load	3	RCT	RR 14.02	5.25–31.9

Data for studies with HBV DNA >2 million IU/mL (2 million–20 million, 20 million–200 million and >200 million IU/mL) are not shown.

5.3.3 Effectiveness of treatment according to baseline HBV DNA and ALT levels among children and adolescents (age <18 years)

Chapter 8 addresses this review.

5.3.4 Numbers needed to treat to prevent one case of HCC, cirrhosis or liver-related death according to HBV DNA level (Web annex C 5.2)

The number needed to treat for an additional beneficial outcome was estimated at each HBV DNA stratum based on natural history studies and the efficacy of antiviral therapy from the systematic reviews.

For the lowest HBV DNA stratum of <2000 IU/mL, assuming a relative risk of 0.72 (95% CI: 0.43–1.20) for preventing clinical outcomes with treatment, the numbers needed to treat for an additional beneficial outcome were 210 (range 103–294) to prevent one case of HCC after a median of 12.2 years, 119 (range 58–167) to prevent one case of cirrhosis after a median of 10.0 years and 1190 (range 585–1667) to prevent one case of liver-related death after a median of 10.0 years.

For a baseline HBV DNA stratum of 2000–20 000 IU/mL, assuming a relative risk of 0.45 (95% CI: 0.14–1.46) for preventing clinical outcomes with treatment, the numbers needed to treat for an additional beneficial outcome were 59 (range 38–70) to prevent one case of HCC after a median of 10.6 years, 21 (range 14–25) to prevent one case of cirrhosis after a median of 11.3 years and 182 (range 116–217) to prevent one case of liver-related death after a median of 10.6 years.

For a baseline HBV DNA stratum of 20 000–200 000 IU/mL, assuming a relative risk of 0.17 (95% CI: 0.06–0.50) for preventing clinical outcomes with treatment, the numbers needed to treat for an additional beneficial outcome were 14 (range 13–24) to prevent one case of HCC after a median of 13.6 years, 7 (range 6–11) to prevent one case of cirrhosis after a median of 10.4 years and 12 (range 11–20) to prevent one case of liver-related death after a median of 12.3 years.

5.3.5 Modelling the impact of eligibility for hepatitis B treatment (Web Annex C 5.3)

The impact of changing hepatitis B treatment eligibility criteria was modelled across WHO regions, based on key assumptions about how treatment affects clinical outcomes and treatment adherence. Removing ALT>ULN had the greatest impact on the total number of individuals with CHB eligible for treatment (75–100% increase). The second largest factor was lowering the HBV DNA cut-off from ≥20 000 IU/mL to ≥2000 IU/mL. Lowering the age eligibility cut-off for HBV treatment to 15 years (and also 11 years) had the greatest impact in expanding treatment eligibility in the African Region (from 16% to 26%) and Eastern Mediterranean Region (from 22% to 29%) among those with HBV DNA ≥2000 IU/mL and ALT≥ULN) because of the age structures of these regions (much of the population is younger than 18 years) and higher prevalence of CHB in younger age cohorts. Lowering the eligibility age for treatment also had a notable impact on lowering mother-to-child transmission (when the eligible age was lowered to 20 years old), especially in the African Region, because of lower levels of hepatitis B birth-dose and three-dose vaccination and later initiation of HBV vaccination programmes in these regions.

The impact of changing the guidelines on the key outcomes of incidence, morbidity and mortality was forecasted in three countries representative of different WHO regions (China, Ethiopia and Pakistan), with very different mother-to-child prevention programmes. The impact of expanding eligibility criteria on the outcomes of HCC, decompensated cirrhosis and deaths averted was modest across all the treatment scenarios considered (suggesting that even the most conservative guidelines may already treat those most likely to progress to advanced liver disease).

5.4 Rationale for the recommendations among adults

5.4.1 Summary of implications of expanded and simplified treatment eligibility criteria

The updated recommendations prioritise who to treat rather than on who not to treat. The four new recommended options for meeting treatment eligibility will capture a much higher proportion (at least 50%) of all HBsAg-positive people versus about 20% previously *(8)* and include options for those without access to an HBV DNA assay.

- The flexible and inclusive approach with four options for meeting treatment eligibility is applicable to all settings, including where there is ready access to or no access to HBV DNA. Most HBsAg-positive people will meet criteria for treatment without the need for HBV DNA assay. Only one of the four recommendations requires access to HBV DNA.
- Many of these treatment criteria overlap: a proportion of those with ≥F2 may also have a viral load >2000 IU/mL or a comorbidity or persistently abnormal ALT.
- All four recommendations on who to treat apply to adults and adolescents aged 12 years or older, including those of reproductive age and pregnant women, which enables a common entry point for assessment and treatment across age groups.

- This will enable significant expansion of treatment to adolescents, especially by including treatment for everyone with HBV DNA >2000 IU/mL and ALT persistently above the ULN (see Chapter 8). Importantly, this will include expanded treatment for adolescent girls of reproductive age, which will complement the recommendations for expanded use of antiviral prophylaxis to reduce mother-to child transmission. This represents a major opportunity to further reduce new HBV infections among children, especially in sub-Saharan Africa, where coverage of birth-dose HBV vaccination remains low. The recommendation also offers both pregnant and non-pregnant adolescent girls and women both treatment for their own health and a reduction in maternal infectivity.
- Although only one of the four criteria for treatment eligibility requires access to HBV DNA level, it is strongly encouraged to have at least one HBV DNA test if available to provide full assessment before treatment. HBV DNA level will also be required for monitoring the treatment response.
- The presentation of the level of certainty of evidence (high, moderate, low or very low) for each recommendation for adults and adolescents (Chapter 8) is important to inform discussion and shared decision-making between health-care workers and patients.

5.4.2 Summary of rationale and balance of benefits and harm for four treatment eligibility options

For this updated 2024 guideline, WHO commissioned two systematic reviews to inform recommendations on who to treat among people with CHB infection. One review focused on the natural history of CHB infection with the incidence of clinical progression (development of liver-related morbidity [fibrosis, cirrhosis, end-stage liver disease and HCC]; progression of liver disease; or mortality) and the other review on the efficacy of antiviral therapy. In both systematic reviews, the estimates need to be stratified by the baseline HBV DNA levels or ALT levels.

Overall, the first systematic review found evidence of higher progression rate of clinical outcomes (HCC, cirrhosis and liver-related mortality) with higher baseline HBV DNA level. HCC incidence was low for individuals with persistently normal ALT levels. Based on the second systematic review, the magnitude of treatment benefit was highest for people with HBV DNA level >20 000 IU/mL and elevated ALT level (>30 U/L for men and >19 U/L for women). The overall certainty of evidence was assessed in adults as moderate; low to moderate (depending on outcome) for HBV DNA level 20 000 to 200 000 IU/mL; and very low for people with HBV DNA levels 2000 to 20 000 IU/mL. For adolescents, the certainty of evidence was also assessed as low.

A previous review had idenfied that treatment benefit was greatest in those with cirrhosis or significant fibrosis. Chapter 8 addresses treatment recommendations and considerations among adolescents and children in more detail.

1. Treatment of those with significant fibrosis or cirrhosis

- The recommendation for treating everyone with early (METAVIR F2) stage of fibrosis and cirrhosis based on APRI score >0.5 or transient elastography >7.0 kPa is based on re-evaluation of the sensitivity of APRI and transient elastography thresholds to detect early or moderate fibrosis in various populations (Chapter 4). This recommendation alone may capture an estimated 20–25% of all HBsAg-positive people.

The Guidelines Development Group supported giving priority to initiating antiviral therapy for those with more advanced liver disease for several reasons.

- Evidence from a previous systematic review demonstrating that those with advanced fibrosis have a much higher risk of developing life-threatening complications of liver disease (death, acute-on-chronic liver failure due to reactivation and flares (ALT flare with jaundice and/or coagulopathy and HCC) than people without advanced fibrosis or cirrhosis.
- Previous studies reported in 2015 HBV guidelines demonstrated that antiviral therapy in this group can halve disease progression (including hepatic decompensation, HCC or liver-related death) and may also lead to regression of fibrosis and cirrhosis over the long term. Treating this group will also have the greatest impact on achieving reduction in morbidity and mortality. Therefore, targeting people with significant fibrosis and cirrhosis for treatment would effectively use resources.

2. Treatment of those with HBV DNA >2000 IU/mL and ALT >ULN

- The treatment recommendation for those with HBV DNA >2000 IU/mL and ALT>ULN is estimated to capture 20–35% of all HBsAg-positive people, depending on the region. The Guidelines Development Group considered the evidence base from natural history studies and trials of antiviral therapy, and overall benefits and harm of initiating antiviral therapy at different HBV DNA levels and different thresholds of ALT ULN, balancing potential benefits with clinical outcomes with the requirement for long-term adherence to nucleos(t)ide analogue therapy and the potential risks for developing renal or bone toxicity.
- Overall, evidence indicates much higher progression for people with HBV DNA >2000 IU/mL or ALT>ULN versus people with HBV DNA <2000 IU/mL or normal ALT. Evidence also indicates that the benefits of antiviral therapy will be greater in this group, as demonstrated in the estimates of numbers needed to treat (see subsection 5.3.4 and Web annex 5.2).
- The systematic review identified only one RCT that had evaluated the efficacy of antiviral therapy among those with viral load <2000 IU/mL *(9)* and five non-randomized studies among those with HBV DNA 2000– 20 000 IU/mL (see section 5.3). The limited evidence available suggests some benefit of antiviral therapy in this group

3. Treatment of those with coinfections, family history, comorbidities, extrahepatitic manifestations

- The recommendation to include the presence of coinfections, family history of HCC or cirrhosis, immune suppression, comorbidities and extrahepatic manifestations as criteria for antiviral therapy will capture an estimated 5–8% of HBsAg-positive people.

Coinfections

HIV and HBV coinfection. HIV coinfection profoundly affects almost every aspect of the natural history of HBV infection and includes more rapid progression to cirrhosis and HCC, higher liver-related mortality, less spontaneous clearance, higher levels of HBV replication and rate of reactivation, higher rates of occult HBV (HBV DNA positivity in the absence of HBsAg-positivity) and reduced treatment response compared with people without HIV coinfection. Treating HIV and HBV coinfection with ARV drug regimens that include TDF or TAF active against hepatitis B have substantially improved outcomes *(10–13)*.

HCV and HBV coinfection. People with both HBV and HCV coinfection have a much higher risk of developing an infiltrating and aggressive form of HCC and at a younger age than those with nodular HCC, suggesting accelerated hepatocarcinogenesis. Treatment for both HBV and HCV infections is generally required. Treating HBsAg-positive people with a nucleos(t)ide analogue during and after HCV direct-acting antiviral therapy is advisable because of the moderate risk of HBV reactivation for HBsAg-positive people *(14–18)*.

HDV and HBV coinfection. Chronic HDV infection among people with established CHB is considered to be the most aggressive form of viral hepatitis because of its accelerated progression to liver cirrhosis or liver cancer compared with CHB monoinfection. Longitudinal studies also show increased disease progression, with male sex, older age, concomitant HIV infection or HCV infection, persistent HDV viraemia, HBV replication, diabetes and obesity *(19–23)*. Until recently, PEG-IFNα had been used off licence for the past three decades as the only treatment option for HDV infection alongside treatment of CHB with nucleos(t)ide analogues, although its use was limited by poor treatment outcomes, side-effects and contraindications. The HDV treatment landscape is now rapidly evolving, with novel agents showing favourable results in Phase 2 and 3 clinical trials *(24,25)*.

Comorbidities

The prevalence of steatotic liver disease among the general population and people with CHB has increased worldwide. Diabetes, obesity or dyslipidaemia are key components of metabolic dysfunction–associated steatotic liver disease and also well-established risk factors of fibrosis progression and HCC development among people with CHB *(26–31)*. Although the aggressive correction of metabolic dysfunction (diabetes, obesity and dyslipidaemia) alongside lifestyle modification is the priority to improve clinical outcomes, earlier initiation of antiviral therapy among those with concomitant CHB may also play a role, though direct evidence is lacking *(25,32)*

Immune suppression

Using a wide array of immunosuppressant agents can induce HBV reactivation. This includes cancer chemotherapy, checkpoint inhibitors, immunosuppressive therapies, bone marrow and stem cell treatment, newer anti-tumour necrosis factor immunobiologics, chimeric antigen receptor T-cell treatment and after treatment for coexistent hepatitis C. Rituximab treatment also poses a particular risk, and reactivation may occur months after chemotherapy ends. Pre-emptive antiviral use is therefore recommended.

Extrahepatic manifestations

Although rare, extrahepatic manifestations of hepatitis B, including glomerulonephritis, vasculitis or arthritis, also represent indications for antiviral therapy. Effective antiviral therapy for the primary liver disease can improve extrahepatic signs or symptoms.

4. Treatment of those with persistently abnormal ALT levels >ULN

- The conditional recommendation for treatment based on persistently abnormal ALT levels regardless of APRI score is intended for settings where HBV DNA testing is not available and other treatment criteria have not been met. This will capture an estimated 20% of all HBsAg-positive people. This recommendation is retained from the 2015 WHO hepatitis B guidelines. The evidence base remains very limited to guide treatment in the absence of HBV DNA levels, and only a conditional recommendation was therefore made. Other common causes of persistently abnormal ALT such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.

Treatment in those not meeting any of the four options for treatment eligibility

- Key remarks linked to these recommendations capture the importance of a person-centred approach to address individual circumstances and concerns, with the flexibility to consider treatment for some people who do not meet current treatment criteria. Most of those not meeting the treatment criteria will have an HBV DNA viral load <2000 IU/mL (about 75% of all HBsAg-positive people in sub-Saharan Africa and 50% in Asia). This group will require continued monitoring whether they are treated or not (see Chapter 16).
- Regardless of the criteria used for treatment initiation, everyone initiating treatment should be monitored annually with HBV DNA, ALT and APRI score, with ongoing adherence support and retention in care (Chapter 16). Those not yet meeting the treatment criteria will also require continued monitoring (Chapter 16).

5.4.2 Acceptability, values and preferences (Web annex D)

Patient preferences

Of 550 individuals with CHB representing 76 countries, the main reasons given for starting treatment were: recommended by their doctor (30%); raised hepatitis B DNA level (38%) and desire to reduce the risk of liver cancer or liver damage (11%). The main reasons for not starting treatment were: not recommended by their doctor (42%), high cost of medication (23%) and feeling well (11%). Only 4% expressed concerns regarding the side-effects of treatment (4%). Other priorities expressed were knowledgeable health-care providers to ensure accurate and appropriate management of their condition with confidentiality of test results and the desire for shared decision-making with their provider regarding treatment initiation and management plans. One third of respondents were open to receiving treatment on the same day of diagnosis (30%) or whenever their doctor recommends it (50%).

Health-care worker preferences

A 2022 International Coalition to Eliminate Hepatitis B global online survey of 178 health-care workers (37% from the WHO African Region) found that 79% (of 159) agreed or strongly agreed with giving priority to antiviral therapy for people with CHB with advanced hepatic fibrosis (stage 3 or 4), and 55% (of 160) agreed or strongly agreed with treating people with CHB with elevated ALT, regardless of HBV DNA level, in the absence of other liver conditions. Only 31% (of 151) agreed or strongly agreed with treating HBeAg-positive people with CHB with normal ALT, and 30% (of 155) agreed or strongly agreed with treating HBsAg-positive adults older than 40 years regardless of HBV DNA level, HBeAg and ALT level. Only 19% (of 159) agreed or strongly agreed with treating all HBsAg-positive adults regardless of HBV DNA level, HBeAg and ALT levels.

National hepatitis programme manager preferences

A 2023 WHO survey of 32 national hepatitis programme managers from all WHO regions found that 55% agreed or strongly agreed with treating all HBsAg-positive adults 30 years or older with HBV DNA >2000 IU/mL regardless of ALT level; 45% agreed or strongly agreed with treating all HBsAg-positive adults 20 years and older with HBV DNA >2000 IU/mL regardless of ALT. In addition, 26% agreed with treating all HBsAg-positive adults with HBV DNA >2000 IU/mL, and 45% agreed with treating all HBsAg-positive adults with abnormal ALT.

5.4.3 Resource and access considerations (Web annex C 5.3)

The cost implications of expanding treatment eligibility in various countries have not yet been fully examined, and further modelling work is underway to explore the cost implications of expanded treatment eligibility in different regions, comparing the costs of treatment and monitoring and different scenarios of treatment expansion. This may be substantial for the few governments that support a public sector hepatitis programme and for individuals in the majority of low- and middle-income countries with no public sector funding for viral hepatitis.

In general, the annual costs of treatment with generic TDF (and to a lesser extent, ETV) are low (US$ 30 annually), even over a lifetime of treatment, although prices vary in low- and middle-income countries. Long-term treatment with TDF (or ETV) also requires laboratory infrastructure for monitoring the response to treatment with ALT and, if possible, annual HBV DNA levels (about US$ 15–60 annually). Access to HBV DNA testing is increasing in low- and middle-income countries but remains a major impediment outside urban settings and referral facilities.

5.5 Implementation considerations

- Key points in the initial assessment of people with CHB before therapy and in counselling and preparing people before initiating antiviral therapy (Box 5.1).
- A key initial step will be expanding and scaling up testing and case finding. This includes promoting existing recommendations on routine testing of all pregnant mothers and testing family members and children, with vaccination of HBsAg-negative household and family members and contacts. Note that everyone being considered for pre-exposure prophylaxis (PrEP) should be first tested for HBV and HIV infection to ensure appropriate long-term treatment of HIV, CHB or both, as appropriate *(33)*.
- Although only one of the four criteria for treatment eligibility requires access to HBV DNA level, having at least one HBV DNA test is strongly encouraged to provide full assessment before treatment. HBV DNA level will also be required for monitoring treatment response.
- Regardless of the criteria used for treatment initiation, everyone initiating treatment should be monitored annually with HBV DNA, ALT and APRI score and HCC surveillance, with ongoing adherence support and retention in care.
- There are currently few models or country examples of the adoption of expanded treatment eligibility from low- and middle-income countries. Experience in Uzbekistan showed that removing treatment restrictions does not necessarily result in increased treatment uptake, especially in areas of low awareness and acceptance *(34)*.
- Implementing expanded treatment eligibility poses major challenges, especially in low-and middle-income countries, and will require more awareness and community education, expanded access to testing, HBV DNA assays and non-invasive tests, trained health-care personnel and appropriate monitoring tools, especially HBV DNA assays and lifelong antiviral therapy.

Box 5.1 Key items in the initial assessment of people with CHB before therapy and in counselling and preparing people before initiating antiviral therapy

Assessment of the severity of liver disease should include history; physical examination, including for the presence of hepatomegaly and splenomegaly; measurement of ALT, AST, ALP and total bilirubin; and full blood count, including platelet count and white cell count. AST and platelet count measurements enable calculation of APRI for staging of liver disease. The synthetic function of the liver should be assessed with serum albumin and prothrombin time or international normalized ratio. People with CHB should also be questioned about the presence of liver-related symptoms, although even advanced disease may be asymptomatic.

The level of viral replication should be assessed by quantifying serum HBV DNA (if HBV DNA testing is available) and through HBeAg and anti-HBe serostatus.

Assessment for the presence of comorbidities should include coinfection with HIV, HCV (see Chapter 19) or HDV (see Chapters 12–14), impaired glucose tolerance, dyslipidaemia, metabolic dysfunction–associated steatotic liver disease, alcoholic liver disease and drug- or toxin-induced injury. All people with cirrhosis should be screened for the presence of HCC. Family history of HCC and medication history should also be reviewed.

Household screening and preventive measures should include HBsAg screening with HBV vaccination of non-immune family and household members and sexual contacts and other general measures to reduce HBV transmission.

Counselling on lifestyle should assess alcohol consumption and provide advice on lifestyle, including alcohol reduction (WHO ASSIST package [Alcohol, Smoking and Substance Involvement Screening Test]), diet and physical activity. Consider HAV vaccination. The management of people with steatosis and CHB includes evaluation and monitoring liver fibrosis and antiviral therapy for CHB. Lifestyle modification could include weight reduction, regular exercise and avoiding alcohol, sugar-sweetened beverages and ultraprocessed foods and correct metabolic dysfunction (diabetes mellitus, obesity and dyslipidaemia).

In preparation for starting treatment, people with CHB should be counselled about indications for treatment, including likely benefits and side-effects, the need for and willingness to commit to long-term treatment and follow-up monitoring both on and off therapy, the importance of full adherence for treatment to be both effective and reduce the risk of drug resistance (and that abruptly ending treatment may cause acute liver failure) and cost implications.

Assessment of baseline risk for renal dysfunction[a] and measurement of baseline renal function[b] should be considered before initiating antiviral therapy and during monitoring, especially if a tenofovir-based regimen is used (see Chapter 16).

a Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, creatinine clearance (CrCl) <50 mL/min, older age, body mass index (BMI) <18.5 kg/m2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV and solid organ transplantation.

b Measurement of baseline renal function includes: serum creatinine levels and calculation of CrCl/estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi. For children, the Schwartz or similar formula can be used: http://nephron.com/bedsidepedsnic.cgi.

CG formula: eGFR = (140 – age) Í (weight in kg) Í 0.85 (if female)/(72 Í Cr in mg%)

MDRD formula: eGFR = 175 x serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if the person is Black) x 0.742 (if the person is female).

5.6 Research gaps

- Long-term studies to show the overall impact and effectiveness of expanding treatment eligibility on CHB liver-associated and all-cause morbidity and mortality, reduction in transmission, quality of life including impact on stigma (including self-stigma) and potential harm, including the economic burden of paying for treatment. Priority for studies in low- and middle-income countries, especially in sub-Saharan Africa but also in under-researched populations, such as children, young adults and pregnant women with CHB.
- RCTs of antiviral therapy to establish treatment impact among people with low-level viraemia and early fibrosis stages, especially in sub-Saharan Africa.
- Analysis of long-term prospective cohort studies to establish a minimum treatment duration and period of viral suppression needed to achieve some level of reduction of disease progression and development of HCC.
- Longitudinal studies to further evaluate cut-offs for abnormal ALT in a range of settings and populations and to determine the prognostic significance of persistently normal ALT levels despite high HBV DNA levels among people with CHB in sub-Saharan Africa and Asia.
- Assess the added value of repeat APRI or transient elastography (FibroScan®) to determine consistent non-invasive test threshold values above ≥F2 to meet treatment eligibility.

6. First-line antiviral therapies for CHB (adults, adolescents and children)

6.1 Recommendations

Existing and maintained recommendations *(1)*

Nucleos(t)ide analogues with a low genetic barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended.

(strong recommendation, moderate-certainty evidence)

Updated recommendation

For all adults, adolescents and children (two years or older) for whom antiviral therapy is indicated, the nucleos(t)ide analogues that have a high genetic barrier to drug resistance – tenofovir disoproxil fumarate (TDF) or entecavir (ETV) are recommended as preferred regimens.

TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) are recommended as alternative regimens (where TDF monotherapy is not available).

(strong recommendation, moderate-certainty evidence)

New recommendation

Entecavir (ETV) or tenofovir alafenamide fumarate (TAF)[a] (if available) are recommended for people with established osteoporosis and/or impaired kidney function, and for children (ETV for those aged two years or older) or adolescents (TAF for those aged 12 years or older as alternative regimen), for whom antiviral therapy is indicated.

(strong recommendation, moderate-certainty evidence).

a TAF is not recommended if eGFR is <15 mL/min.

Note: HIV and HBV coinfection

Dolutegravir (DTG) in combination with a nucleos(t)ide reverse-transcriptase inhibitor (NRTI) backbone is the preferred first-line drug regimen for adults, adolescents and children living with HIV initiating ART, including those with HIV and HBV coinfection. Efavirenz (EFV) at low dose (400 mg) is an alternative to DTG for adults and adolescents.

Knowing the HBsAg status of people living with HIV is important before initiating ART or switching regimens and before initiating PrEP. Current ART guidelines recommend using TDF (in combination with 3TC or FTC) as the preferred NRTI backbone option for most situations in HIV management, including HIV and HBV coinfection. TDF, TAF, 3TC and FTC are all active against both HIV and HBV. TAF could be an alternative to TDF in specific clinical situations for people coinfected with HIV and HBV, especially if renal or bone problems are a concern, and for adolescents. If neither TDF or TAF can be safely used, the alternative recommended hepatitis B therapy is ETV in addition to a fully suppressive ARV drug regimen. This nucleos(t)ide analogue combination should be retained if the ARV drug regimen is changed because of failure to suppress HIV viral loads. ARV drug regimens that do not include TDF, ETV or TAF are not appropriate for people coinfected with HIV and HBV.

Table 6.1 Summary of Preferred and alternative first-line antiviral regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults	TDF ETV	TDF + 3TC TDF + FTC (where TDF monotherapy is not available)	ETV TAF (for people with established osteoporosis and/or impaired kidney function)
Adolescents (12–17 years)	TDF ETV	TDF + 3TC TDF + FTC where TDF monotherapy is not available) TAF	
Children (2–11 years)	TDF* ETV		

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

*Low dose formulations of TDF may not be widely available

6.2 Background: treatment for CHB

The goal of antiviral therapy for CHB is to prevent, reduce or reverse necro-inflammatory change and hepatic fibrosis and thus reduce the risk of cirrhosis, decompensated cirrhosis and liver failure, HCC and death. Most of the initial evidence for treatment effectiveness had been based on surrogate measures of long-term treatment outcomes used in clinical trials. These include normalization of serum ALT levels (as a surrogate measure for the resolution of necroinflammation in the liver), a reduction in HBV DNA levels to undetectable levels, HBeAg loss or seroconversion

to anti-HBe or rarely, HBsAg loss or improvement and non-invasive measures of hepatic fibrosis. Data from clinical trials and systematic reviews now provide additional evidence of the effect of antiviral therapy on longer-term clinical outcomes, especially HCC risk *(2–8)*.

In 2015, the first WHO guidelines on hepatitis B treatment and care *(1)* recommended TDF or ETV – nucleos(t)ide analogues with a high genetic barrier to resistance – as the preferred first-line regimens for treatment of chronic hepatitis B. The previous widespread use of nucleos(t)ide analogues with a low genetic barrier to resistance, such as lamivudine, telbivudine and adefovir, had led to high rates of resistance. However, with the increasing use of nucleos(t)ide analogues with a high genetic barrier to resistance as first-line agents (tenofovir or entecavir), drug resistance has become an uncommon and manageable problem *(9)*. Since then, additional nucleos(t)ide analogue therapy options have also become available – including the dual therapy regimens of TDF + 3TC, TDF + FTC and TAF, a prodrug of tenofovir, with or without FTC. There are now also data on efficacy of antiviral regimens for certain subgroups that were lacking in the 2015 guidelines, including pregnant women, adolescents and children.

6.3 Summary of the evidence

6.3.1 Long-term follow-up studies

To inform the 2015 guidelines, an earlier systematic review and network meta-analysis evaluated the effectiveness of treating nucleos(t)ide analogue–naive HBeAg-positive and HBeAg-negative adults with CHB with TDF and ETV versus those with a lower barrier to resistance (lamivudine, telbivudine and adefovir) *(1)*. In recent longer-term follow-up studies, nucleos(t)ide analogues demonstrated antiviral and biochemical efficacy and histological improvement *(10)* with prolonged suppression of HBV DNA – more than 90% achieving HBV DNA <69 IU/mL and more than 75% achieving normal ALT levels. Regression of hepatic fibrosis was also documented *(1,4,10–14)*. Overall, HBeAg loss is uncommon (20–30% after one to two years) and HBsAg loss rare (0.22% per year and a 10-year cumulative incidence of about 2%) *(15)*, but HBsAg loss, if it occurs, improves outcomes *(16)*. More recent studies have indicated that nucleos(t)ide analogues lower the risk of HCC *(17–19)* and recurrent HCC after curative resection *(20,21)*. Several reports have suggested that TDF achieves a lower risk of de novo and recurrent HCC than ETV *(22,23)*, but the results are confounded by several methodological challenges *(24)*. In a large cohort study, TDF-treated people with CHB had a slightly higher risk of progression of chronic kidney disease. The five-year cumulative incidence of progression for TDF- versus ETV-treated groups and an untreated group was 48% (95% CI 45–51%) versus 43% (95% CI 40–46%) versus 43% (95% CI 39–47%), respectively. There was also a reduction in eGFR of >20% in the TDF-treated group compared with the ETV-treated and untreated groups (P = 0.02) *(25)*.

6.3.2 Meta-analysis of randomized trials comparing TAF with TDF in HBV monoinfection (Web annex C 6.1)

To inform current recommendations on the use of TAF for people with HBV monoinfection, a systematic review and meta-analysis was undertaken to assess the effectiveness of TAF versus

TDF among adults with CHB monoinfection (treatment naive or experienced). Five randomized trials with 2011 participants (TAF = 1222, TDF = 789) with CHB were included *(26-30)*. The duration of follow-up was 96 weeks and 48 weeks in three studies. In the complete analysis with results up to 96 weeks, those taking TAF were significantly more likely to show normalization of ALT (TAF versus TDF: 59% versus 55%, OR 1.45 (95% CI 1.19–1.77). TAF and TDF did not differ significantly for HBeAg loss (TAF versus TDF: 20% versus 15% OR 1.27, 95% CI 0.90–1.80) or HBsAg loss (TAF versus TDF: 0.7% versus 1.3%, OR 0.53 (95% CI 0.21–1.38) or the primary efficacy outcome of undetectable HBV DNA (TAF versus TDF: 77% versus 75%, OR 1.00 (95% CI 0.80–1.25). The mean percentage changes in hipbone and spine mineral density were significantly lower for TAF than TDF: hip bone mineral density OR 1.39 (95% CI 0.59–2.19) and spine bone mineral density OR 1.83 (95% CI 1.48–2.19), but the clinical significance of these changes is unknown, since no follow-up data on osteoporosis or bone fractures are available. TAF was associated with higher risks of grade 3 or 4 LDL elevation (TAF versus TDF: 5% versus 1% OR 4.52, 95% CI 1.17–17.43) but less worsening in renal biomarkers after 96 weeks. In two international double-blind randomized trials of 1733 participants, TDF resulted in significantly greater reduction in bone mineral density compared with TAF treatment *(31)*.

6.3.3 Meta-analysis of randomized trials comparing TDF + FTC with TDF alone in HBV monoinfection (Web annex C 6.1)

To inform recommendations on the use of TDF + 3TC or FTC for adults with CHB monoinfection, a systematic review and meta-analysis was undertaken comprising five randomized trials with 633 participants (TDF + FTC = 313, TDF = 320) to assess the effectiveness of dual therapy with TDF + FTC versus TDF *(32–36)*. TDF + FTC did not differ significantly from TDF for the primary outcomes of undetectable HBV DNA (TDF + FTC versus TDF: 80% versus 73%, OR 1.55, 95% CI 0.87–2.76), ALT normalization (TDF + FTC versus TDF: 72% versus 67%, OR 1.30, 95% CI 0.91–1.84), HBsAg loss (2.6% versus 2.0%, OR 1.28, 95% CI 0.24–6.74), HBeAg loss (TDF + FTC versus TDF: 11% versus 14%, OR 0.77, 95% CI 0.41–1.45) and HBeAg seroconversion (TDF + FTC versus TDF: 6.2% versus 9.8%, 0.64, 95% CI 0.26–1.58). The TDF + FTC and TDF groups also did not differ significantly for safety outcomes, including any adverse events (TDF + FTC versus TDF: 78% versus 81%, OR 0.84, 95% CI 0.38–1.82), grade 3 or 4 adverse events (TDF + FTC versus TDF: 16% versus 13%, OR 1.24, 95% CI 0.48–3.22) or serious adverse events (TDF + FTC versus TDF: 15% versus 11%, OR 1.36, 95% CI 0.48–3.83). In one double-blind trial with long-term follow-up, people with CHB were randomized to receive TDF or TDF + FTC for 168 weeks *(37)*, with an option of switching to open-label FTC + TDF if HBV DNA was >69 IU/mL at week 24. At week 168, long-term viral suppression was maintained for 84% of those receiving TDF + FTC and 82% receiving TDF. No resistance to TDF was observed through 168 weeks of treatment.

All studies included in this meta-analysis were evaluated for their quality based on the primary outcomes using the Cochrane Collaboration risk of bias assessment tool (RoB 2.0) *(30)* and GRADE. The meta-analysis of TAF versus TDF and the meta-analysis of TDF + FTC versus TDF were both rated as providing moderate-certainty evidence.

6.3.4 Efficacy and safety of TDF, TDF + FTC and TAF in specific populations with hepatitis B

HBV and HIV coinfection

A randomized trial of TAF versus TDF among 243 people with HIV and HBV coinfection *(37)* found no significant difference in log10 reduction in HBV DNA at any visit except for week 12, when the TAF arm had a higher rate of HBV DNA negativity. However, there was evidence of imbalanced randomization and differences in baseline characteristics between the arms.

Pregnant women with CHB

Pregnant women with hepatitis B infection have been treated with TDF, TDF + FTC or TAF in randomized trials and non-randomized studies *(38-44)*. A meta-analysis of nine studies involving 1046 pregnant mothers with high HBV DNA levels who received TDF during pregnancy found that TDF significantly reduced maternal HBV DNA levels and the infant immunoprophylaxis failure rate *(41)*. Observational studies also report 0% MTCT rates and favourable safety profiles *(44-46)*. There are no significant safety issues for using TDF or TAF during pregnancy. The Antiretroviral Pregnancy Registry report from December 2022 showed no significant increase in the risk of birth defects for infants born to mothers taking either TDF or TAF in any trimester of pregnancy *(45)*. TAF is not yet approved for hepatitis B treatment in pregnancy (Chapter 7).

For children and adolescents with CHB (see Chapter 8)

Both TDF (and assumed for TDF dual-therapy regimens TDF + 3TC or TDF + FTC) and ETV have been shown to be effective for children (see Chapter 8). There are limited data on TAF for children, but TAF may be a desirable option in the future because of concerns about the risk of bone toxicity with TDF. The European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) have approved TDF for children aged two years or older with CHB *(47-49)*. The FDA has approved TAF for children aged 12 years and older with compensated liver disease *(48)* and the EMA for children six years and older and weighing more than 25 kg *(49)*. As more adolescents start treatment, TDF-related bone loss may become an increasing consideration for children and adolescents, who still have developing bones.

For people with renal insufficiency or osteoporosis

Several studies have indicated the benefit of switching from TDF to TAF, with improvements in CrCl and hip and spine bone mineral density, although serum cholesterol may increase *(50-55)*.

6.3.5 Safety of TDF and TAF in ART regimens among people with HIV infection

Several randomized trials have compared TAF with TDF as part of combination treatment for HIV monoinfection – those with HBV coinfection were excluded. A systematic review with high certainty of evidence found that TAF versus TDF was associated with less negative impact on spine and hipbone mineral density and renal function markers *(56)*. Clinical renal and bone events were rare with both drugs, and there was no difference in the rate of HIV viral load suppression *(57)*. Moderate-certainty evidence indicated that those taking TAF experienced a greater rise in cholesterol levels and body weight gain *(58-61)*. To date, pharmacological studies have demonstrated acceptable TAF plasma concentrations in pregnancy, but more data are needed to establish safety in pregnancy *(62,63)*.

The evidence base for children and adolescents living with HIV using TAF is limited to safety and pharmacokinetic data using adult dosing in weight bands above 25 kg *(63,64)*. Limited data are available for children 14 to <25 kg and older than two years using a low dose of FTC + TAF 120/15 mg with a boosted third agent *(63)*. Bone and renal safety and suppression of viral loads were all favourable. The acceptability and tolerability of low-dose formulations containing TAF have also been demonstrated in this age group *(57)*.

6.4 Rationale for the recommendations

The 2015 WHO guidelines on hepatitis B care and treatment *(1)* recommended antiviral therapy using nucleos(t)ide analogues with a high genetic barrier to drug resistance (TDF or ETV). ETV was recommended for children aged 2–11 years. The evidence was assessed as moderate certainty, based on trials showing effectiveness of these regimens for achieving the intermediate outcomes of undetectable HBV DNA levels and normalization of ALT levels, with more limited evidence on effects on clinical outcomes.

For the 2024 updated guidelines, the Guidelines Development Group considered evidence for use of TAF and dual therapy as alternative antiviral regimens. The recommendation for using TDF or ETV as preferred first-line regimens was maintained, with the addition of dual therapy as an alternative regimen, where access to TDF monotherapy is lacking. The use of TAF was reserved for those with existing or risk of renal impairment or osteoporosis.

Key benefits of all recommended nucleos(t)ide analogues (TDF, ETC, TDF + 3TC or FTC, ETV and TAF)

- TDF, TDF + 3TC or TDF + FTC, ETV and TAF are all potent inhibitors of HBV replication, and, based on data from reported systematic reviews, are all highly effective in reducing disease progression. HBeAg seroconversion (among HBeAg-positive people) occurs in the minority (10–15% per year), and HBsAg loss is infrequent.
- All the drugs have a high genetic barrier to resistance and very low observed rates of drug resistance over long-term (five-year) follow-up. However, resistance to ETV occurs frequently among people with 3TC resistance, which can limit its use in settings where 3TC has been previously widely prescribed.
- The recommended first-line regimens (TDF, TDF + 3TC or TDF + FTC and ETV) can be used across all age groups – adults, adolescents and children down to two years (based on FDA and EMA regulatory approval).

6.4.1 Balance of benefits and harm for including dual therapies (TDF + 3TC or TDF + FTC) as alternative first-line regimens to TDV and ETV

The Guidelines Development Group recognized that many low- and middle-income countries continue to lack access to TDF monotherapy for CHB (and costs remain high), while there is access to the dual-therapy regimens of TDF + 3TC and TDF + FTC and at low cost as part of first-line ART regimens or for PrEP against HIV infection through existing Global Fund to Fight AIDS, Tuberculosis and Malaria and United States President's Emergency Plan for AIDS Relief (PEPFAR) ARV drug procurement.

It was noted that where there is reliable access to and availability of low-cost generic TDF monotherapy, there is no need to consider using dual therapy as an alternative regimen. However, in low- and middle-income countries that lack access to TDF monotherapy but have access to low-cost dual therapy, this should be considered an alternative first-line regimen. There is an additional potential benefit of protection from HIV infection if people with HBV monoinfection take TDF + 3TC or TDF + FTC as PrEP regimens in regions with a high burden of HIV infection.

A systematic review of five randomized trials among adults with CHB found moderate-certainty evidence that TDF + FTC did not differ significantly from TDF for HBV DNA negativity, ALT normalization, HBsAg loss, HBeAg loss and HBeAg seroconversion or adverse events. In one double-blind trial of TDF versus TDF + FTC with long-term follow-up to 168 weeks, long-term viral suppression was maintained for 84% of those receiving TDF + FTC and 82% receiving TDF.

6.4.2 Balance of benefits and harm for not including TAF as an alternative first-line regimen, but as an option in special circumstances

- A systematic review and meta-analysis of five randomized trials of TAF versus TDF in HBV monoinfection found moderate-certainty evidence that TAF and TDF had a very similar likelihood of achieving an undetectable HBV DNA level, but TAF was associated with an increased rate of ALT normalization.
- There were no statistically significant differences between TAF versus TDF in adverse events, although TAF was associated with less decline in bone mineral density and in renal function but increased likelihood of grade 3 or 4 abnormalities in LDL cholesterol level. The changes in bone mineral density and bone biomarkers observed after starting TDF are usually small (about 1–3%) and often stabilize if people remain on TDF for more than two years.
- The WHO consolidated HIV guidelines *(65)* do not make a formal recommendation for use of TAF as part of a preferred ARV drug regimen for adults and adolescents, but only in special circumstances in people with osteoporosis and/or impaired renal function.
- Another limitation with TAF is its interaction with rifampicin and other common anti-TB drugs, and the correct dose to administer during TB co-treatment has not yet been established.

- TDF remains widely available and affordable in low- and middle-income countries through access to reduced prices via a range of mechanisms. There is currently very limited access to TAF in limited-resource settings.
- There are still limited data on using TAF in pregnancy, but data from one RCT, several observational studies and the Antiretroviral Pregnancy Registry show favourable efficacy and safety profiles. Similarly, the evidence base for TAF for children and adolescents is also limited to safety and pharmacokinetic data using adult dosing in weight bands above 25 kg. The FDA has approved TAF for adolescents aged 12 years and older with compensated liver disease *(48)* and the EMA for children six years and older and weighing more than 25 kg *(49)*. Limited evidence for adolescents and children indicates that both TDF and TAF are effective at achieving intermediate outcomes and appeared safe.

6.4.3 Balance of benefits and harm for use of ETV or TAF only in those with renal impairment, osteoporosis or in children and adolescents (see chapter 9)

The use of TAF was recommended for treatment of CHB only in special circumstances when bone and renal problems are a particular concern (such as the presence of osteoporosis, renal impairment, or concomitant use of nephrotoxic drugs) when TDF should not be used, and in adolescents. This is consistent with the 2021 WHO consolidated HIV guidelines *(65)*, which also currently limit the use of TAF to those with renal impairment and osteoporosis, and in adolescents. Although the evidence base for TAF for children and adolescents is limited, bone and renal safety and viral suppression were favourable. The acceptability and palatability of low-dose formulations containing TAF have also been demonstrated in children.

6.4.4 Values, preferences, and acceptability (Web annex D)

The convenience of administration (once-daily oral), low rates of side-effects and minimal requirement for toxicity monitoring of TDF, TDF + 3TC or TDF + FTC and ETV (and TAF where indicated, available and affordable) favour their acceptability in low- and middle-income countries. The International Coalition to Eliminate Hepatitis B undertook a global survey in 2022 to identify priorities and barriers to hepatitis B care in low- and middle-income countries. There were 190 respondents. TDF remains the most frequently reported available treatment for hepatitis B for 85% followed by 3TC for 58%, ETV for 56% and TAF for 52%. The availability of TAF was lowest in sub-Saharan Africa (36%), followed by Europe (57%) and highest in North America (81%) and eastern Asia (80%). Key barriers to accessing hepatitis B care and treatment were the costs of treatment and additional testing (HBV DNA testing and serum aminotransferases) for clinical assessment. The convenience (once-daily oral administration) and minimal side-effects and requirement for toxicity monitoring of TDF, TAF and ETV favour their widespread acceptability for individuals and health-care workers in most countries. The requirement for prolonged (lifelong) treatment for most people is highlighted as a major challenge for long-term adherence and for ongoing monitoring by health-care providers.

6.4.5 Equity

The inclusion of the option of using dual therapy to treat chronic hepatitis B where there is current limited availability of TDF monotherapy may expand access to treatment in many low and middle-income countries, especially in sub-Saharan Africa.

6.4.6 Resource and access considerations (Web Annex C 6.2)

In general, generic TDF and ETV as well as dual therapy (TDF + 3TC or FTC) are widely available at low cost in many low- and middle-income countries through HIV treatment or PrEP programmes with access to reduced prices through licence agreements negotiated with the Medicines Patent Pool. TDF 300 mg is available for a ceiling price of US$ 2.40 per 30 tablets negotiated by the Clinton Health Access Initiative and The Hepatitis Fund with generic manufacturers. TDF + 3TC costs US$ 3.37 per month and TDF + FTC costs US$ 3.97. However, prices show huge variability across low- and middle-income countries when procured through the domestic or government budgets because of fragmented and low-order procurement. At present, those with HIV and HBV coinfection have preferential access to TDF treatment. The Global Fund is now permitting the inclusion of some viral hepatitis testing, treatment and prevention services in its latest funding round, which may improve access to treatment for some people with HBV monoinfection.

TAF has been approved for clinical use since 2015 (patent protected) but is still a branded, on-patent drug mainly used in high-income countries. TAF is currently much less available and more costly than either TDF or TDF + 3TC or FTC due in part to the overall lower demand. It is also not available under the Global Fund Pooled Procurement Mechanism or United States Agency for International Development. Procurement of TAF by programmes in low- and middle-income countries costs about 1.5 times more than TDF. However, only a few low- and middle-income countries, such as Botswana, Mexico and Zambia have included TAF in their hepatitis B guidelines, and others such as India and Viet Nam reserve TAF for those with reduced renal function or osteoporosis. Since the dose is much smaller for TAF (25 mg) versus TDF (300 mg), it is anticipated that TAF could achieve price parity as volumes increase with adoption by more country hepatitis B programmes.

6.5 Implementation considerations

- In regions with high HIV prevalence, especially sub-Saharan Africa, testing for HIV should be undertaken before commencing hepatitis B treatment to ensure an optimal ARV drug regimen for HIV and HBV coinfection for people testing positive. People coinfected with HIV and HBV would typically be treated with dual NRTI inhibitors, including TDF with 3TC or FTC together with an anchor drug (most commonly DTG). For those switching ARV drug regimens, the HBV component of the regimen (TDF) should always be maintained.

- TDF or TAF + 3TC (or FTC) is the preferred NRTI backbone for people with both HIV and hepatitis B and can also be used for people with TB and pregnant women. ETV is not an appropriate option for people with both HIV and hepatitis B. If access to TDF alone is challenging, dual treatment with TDF or TAF plus 3TC or FTC can be given to monoinfected people.
- Assessment of baseline risk for renal dysfunction and measurement of baseline renal function should be considered before initiating antiviral therapy to inform the choice of regimen (see section 16.2). Significant loss of renal function is uncommon with TDF although caution is required for older people or those with comorbidities.
- In countries where TDF monotherapy or ETV are not yet widely available for hepatitis B, access to treatment may be enhanced if TDF + FTC combination treatment available through ART programmes or existing procurement can be used for HBV monoinfection.
- Co-administration of rifampicin, phenytoin and carbamazepine with TAF are currently contraindicated.
- Discontinuation of agents with activity against HBV may cause serious hepatocellular damage resulting from reactivation of HBV replication; patients should be advised against stopping these medications before achieving specified criteria and only under supervision and careful monitoring (see Chapter 18).
- Use of IFN may be considered in very specific circumstances (such as an add-on strategy). Trials examining the effect of newer potentially curative strategies with RNA interference have incorporated IFN to improve efficacy.

6.6 Research gaps

- Assess the long-term outcomes of TAF versus TDF and TDF + XTC and TAF + XTC on bone mineral density, lipids, weight, hepatic steatosis and cardiovascular and other clinical outcomes (osteoporosis and fractures), especially in an ageing population and in low- and middle-income countries.
- Conduct cost-effectiveness and investment case studies on using other regimens (TAF, TDF + XTC and TAF + XTC) versus tenofovir or ETV among people with CHB, especially in sub-Saharan Africa, and also among children for whom antiviral therapy is indicated.
- Continue to develop and evaluate broadly curative antiviral strategies to achieve persistent clearance (cure) of HBV infection and enable discontinuation of nucleos(t)ide analogue therapy. This may include agents that directly target infected cells as well as novel immunotherapeutic strategies that boost HBV-specific adaptive immune responses or activate innate intrahepatic immunity.
- Evaluation of long-acting hepatitis B treatments, such as injectables and implants.

7. Preventing mother-to-child transmission of hepatitis B using antiviral prophylaxis

7.1 Recommendations

Antiviral prophylaxis among pregnant women and adolescent girls *(3)*

Updated recommendation

In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate (TDF) is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg[a] (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.

(strong recommendation, moderate-certainty evidence)

New recommendation

In settings where neither HBV DNA nor HBeAg testing[b] is available, prophylaxis with tenofovir disoproxil fumarate (TDF)[c] for all HBV-positive (HBsAg-positive) pregnant women may be considered (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent MTCT of HBV.

(conditional recommendation, low-certainty evidence)

All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose.

Note: It is advised that all pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health. However, this assessment should not delay the initiation of antiviral prophylaxis. For women and adolescent girls of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice (Table 7.1).

a The use of the HBeAg recommendation represents an additional option for determining eligibility, but HBeAg RDTs have poor diagnostic performance, which limits their routine use in low- and middle-income countries.

b The use of the HBeAg recommendation represents an additional option for determining eligibility, but HBeAg RDTs have poor diagnostic performance, which limits their routine use in low- and middle-income countries.

c TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy (see Chapter 6). TAF is not recommended if eGFR is <15 m l/min.

Existing and maintained recommendations

Immunization *(1)*

a. All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.

b. Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.

c. The birth dose should be followed by two or three additional doses to complete the primary immunization series.

HBsAg testing among pregnant women and adolescent girls *(2)*

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy.

(strong recommendation, low-certainty evidence)

Table 7.1 Who to treat among people with CHB (pregnant women and adolescent girls) and who to offer antiviral prophylaxis (pregnant women and adolescents with CHB) (from Chapter 5)

ELIGIBILITY FOR TREATMENT among pregnant and non-pregnant adults and adolescents aged 12 years or older

Note: It is advised that all pregnant women should be assessed first for eligibility for long-term treatment for their own health and then for antiviral prophylaxis to prevent mother-to-child transmission (if not eligible for treatment or pregnant mother declines). However, this assessment for long-term treatment should not delay initiation of prophylaxis.

Treat All (continuous treatment) with the following:

1. Evidence of significant fibrosis (≥F2) based on an APRI score of >0.5 or transient elastography value of >7 kPa[a] or evidence of cirrhosis (F4) (based on clinical criteria[b] or an APRI score of >1 or transient elastography value of >12.5 kPa[a]), regardless of HBV DNA or ALT levels.

OR

2. HBV DNA >2000 IU/mL and an ALT level above the ULN (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period.

OR

3. Presence of coinfections (such as HIV, HDV and HCV); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, cancer chemotherapy, solid organ or stem cell transplant); comorbidities (such as diabetes, metabolic dysfunction-associated steatotic liver disease; or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of APRI score or HBV DNA or ALT level.

OR

If no access to an HBV DNA assay:

4. Persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score.

ELIGIBILITY FOR ANTIVIRAL PROPHYLAXIS among pregnant women and adolescent girls who do not meet treatment eligibility criteria

Note: For women of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies or reproductive years, or for lifelong treatment.

TDF antiviral prophylaxis (from at least the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series)

- **If there is access to HBV DNA or HBeAg serology:** TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg
- **If there is no access to HBV DNA or HBeAg serology:** TDF prophylaxis for all HBsAg-positive pregnant women.

7.2 Background

Most of the global burden of CHB can be attributed to vertical MTCT of HBV peripartum at the time of or shortly after birth or through horizontal transmission in early childhood from infected children and adults. Such perinatal infections lead to a high rate of chronicity. The risk of developing CHB decreases from about 90% of those infected as neonates to 30% among children infected between one and four years old and less than 5% among those infected as adults *(4)*. The prevalence of HBsAg among children aged five years is a proxy for new hepatitis B infections from vertical and/or early horizontal transmission. WHO's global health sector strategy impact target for eliminating viral hepatitis includes a HBsAg prevalence target for children of ≤1% by 2020 and ≤0.1% by 2030 *(5)*. Considerable progress has been made towards eliminating the perinatal transmission of HBV and reducing new infections among children through universal infant HBV immunization, including a timely hepatitis B birth dose *(6)*.

WHO recommends universal infant immunization with at least three doses of the hepatitis B vaccine (HepB3), each separated by at least four weeks. The first dose of hepatitis B vaccine should be administered to all newborns as soon as possible after birth, preferably within 24 hours *(7)*. Completion of the infant hepatitis B vaccine series leads to immune protection and prevention of infection for >95% of children *(8)*. High coverage of the timely hepatitis B birth dose and completion of the infant hepatitis B vaccine series are the most important interventions for reducing MTCT of HBV as well as early childhood transmission and the foundation on which other interventions to reduce perinatal transmission can be built. There has been major expansion of routine hepatitis B vaccination (2022 HepB3 vaccine coverage 84%) *(9)*. However, hepatitis B birth-dose coverage remains variable: 2022 coverage: 45% globally, with lowest coverage (18%) in the WHO African Region *(9)*. In addition, since 2020, WHO has recommended universal HBsAg screening of pregnant women alongside HIV and syphilis testing and using antiviral prophylaxis to further prevent HBV MTCT among those with high HBV DNA (≥200 000 IU/mL) or positive HBeAg test *(3,10)*. However, significant challenges remain in accessing HBV DNA and/or HBeAg serology testing among HBsAg-positive pregnant women to determine eligibility for antiviral prophylaxis, especially in sub-Saharan Africa. As a result, there has been no effective uptake of this key recommendation to prevent MTCT of HBV. This is alongside the existing suboptimal coverage of universal infant immunization of HepB3, including a timely hepatitis B birth dose, in the most endemic regions and especially sub-Saharan Africa.

7.3 Summary of the evidence

7.3.1 Existing and maintained recommendation - efficacy and safety of maternal TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination)

For the 2020 WHO guidelines on antiviral prophylaxis in pregnancy *(3)*, a WHO-commissioned systematic review and meta-analysis evaluated the efficacy and safety of antiviral prophylaxis for HBV PMTCT among HBsAg-positive pregnant women *(11)*. The meta-analysis demonstrated a protective effect of antiviral therapy to prevent MTCT (TDF 300 mg: OR 0.16, 95% CI: 0.10–0.26; 3TC 100 mg: OR 0.17, 95% CI: 0.13–0.22; telbivudine 600 mg: OR 0.10, 95% CI: 0.08–0.13) *(3,11)*. No transmission was reported when the maternal HBV DNA was below 200 000 IU/mL. The evidence was rated moderate certainty. A recent study from the WHO African Region (Democratic Republic of the Congo) demonstrated high protective efficacy of TDF in addition to infant hepatitis B birth dose without hepatitis B immune globulin, with no cases of transmission observed among babies born to nine treated women *(12)*.

Timing of antiviral prophylaxis: Pooled estimates were similar for TDF prophylaxis starting at a median pregnancy duration of <28 weeks (OR 0.10, 95% CI 0.04–0.25), 28 weeks (OR 0.24, 95% CI 0.13–0.44) or >28 weeks (OR 0.09, 95% CI 0.02–0.32). However, starting prophylaxis during the second trimester has been shown to be more efficacious than starting during the third trimester *(11)*.

Safety: The safety of TDF has been widely documented with PMTCT of HIV *(13)* and for peripartum HBV PMTCT. Data on the safety of TAF during pregnancy are limited but also suggest an excellent safety profile *(14)*. However, TAF has not been approved yet for preventing MTCT of HBV.

Maternal safety: A meta-analysis of six studies estimated a risk of maternal HBV flare after TDF discontinuation of 8%, but statistically comparable to the 6% rate of flare observed among untreated women. There are limited data regarding restarting of antiviral therapy after postpartum flares *(11)*.

Infant safety: One RCT examined the effect of TDF prophylaxis against placebo on infant bone mineral density. There were no statistically significant differences in lumbar spine bone mineral density measured at one year of age *(11)*. Breastfeeding is not contraindicated among women taking TDF, since TDF has very low concentrations in breast-milk and no evidence of toxicity among infants exposed to TDF through breastfeeding *(15,16)*. The FDA classified TDF as a Pregnancy Category B drug (while ETV is classified as Category C), meaning there is no adequate evidence of risk in humans.

A recent systematic review and meta-analysis (131 studies from all WHO regions) found that the proportion of HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL was 21% (95% CI 17–25%) globally and ranged from 8% in the Eastern Mediterranean Region to 12% (95% CI 6–25%) in the African Region and 31% in the Western Pacific Region. The pooled global estimate of HBeAg-positive pregnant women was 24% (95% CI 21–27%) and ranged from 9% in the Eastern Mediterranean Region to 15% (95% CI 9–24%) in the African Region and 34% in the Western Pacific Region. A good correlation was also observed between HBV DNA level and HBeAg status: overall, 15% (0.75–20.1%) of HBsAg-positive pregnant women had HBV DNA level ≥200 000 IU/mL and positive HBeAg and 76% (95% CI 70–82%) had HBV DNA <200 000 IU/mL and were HBeAg negative. Only 2.6% (95% CI 1.8–3.8%) of women had high HBV DNA and negative HBeAg (Web annex C 7.1). Overall, the certainty of evidence was rated as moderate.

7.3.2 New recommendation - TDF prophylaxis for all HBsAg-positive pregnant women

Since 2020, WHO has recommended that HBsAg-positive pregnant women at high risk of transmitting HBV to their infants because of high HBV DNA (≥200 000 IU/mL) or positive HBeAg receive peripartum antiviral prophylaxis using TDF, preferably from the 28th week of pregnancy until at least delivery to prevent MTCT of HBV *(3)*. This recommendation is in addition to providing HepB3 for all infants (starting with a timely hepatitis B birth dose). However, significant challenges remain in accessing HBV DNA viral load or HBeAg serology testing among HBsAg-positive pregnant women to determine eligibility for antiviral prophylaxis, especially in sub-Saharan Africa.

To date, no studies have been undertaken to examine the clinical impact and feasibility of expanding antiviral prophylaxis access to all HBsAg-positive pregnant women. Therefore, WHO commissioned a modelling study of different scenarios of eligibility for antiviral prophylaxis.

Modelling study of TDF prophylaxis for all HBsAg-positive pregnant women (Web annex C 7.2)

Modelling suggests that scaling up HepB3 vaccination worldwide to 90% coverage including hepatitis B birth dose would prevent an additional 14 million new neonatal hepatitis B cases and 38 500 disability-adjusted life-years (DALYs) over the next 10 years *(17)*. Adding HBsAg testing and TDF prophylaxis for eligible pregnant women to the scenario of HepB3 vaccination and hepatitis B birth dose would prevent an additional 2.9–3.0 million neonatal infections over the same period. A recent modelling study of 110 countries across all WHO regions assessed the impact and cost-effectiveness of universal TDF prophylaxis among all HBsAg-positive pregnant women regardless of HBV DNA level in settings without access to HBV DNA testing *(18)*.

Impact on hepatitis B birth dose: The model found that the intervention of scaling up the hepatitis B birth-dose vaccination could avert approximately 6.0 million (95% CI 5.6 million–6.5 million) new neonatal HBV infections and 2969 DALYs (95% CI 2605–3371) from 2024 to 2030 *(18)*. The highest impact of scaling up the hepatitis B birth dose would be in the WHO African Region.

Impact on HBV DNA-driven prophylaxis: The model also found that the addition of antiviral prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL was estimated to avert an extra 1.1 million (95% CI 1.0 million–1.2 million) new neonatal infections by 2030 *(18)*. The highest impact of this strategy was expected in the African Region, with 1.9 million (95% CI 1.8 million–2.1 million) new neonatal infections averted by 2100 and 622 000 (95% CI 521 000–727 000) in the South-East Asia Region. Overall, this strategy should result in more than a 90% reduction of new HBV infections in all regions between 2015 and 2030.

Cost-effectiveness of hepatitis B prophylaxis guided by HBV DNA levels or HBeAg status: Based on consensus cost estimates, prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg strategy would probably be cost-effective in only 28 (26%) of 106 countries analysed, including China (incremental cost-effectiveness ratio US$ 8131, 95% CI US$ 3958–17 538), South Africa (US$ 1431, 95% CI US$ 943–2494), and Viet Nam (US$ 1374, 95% CI US$ 960–1832). However, lower diagnostic and monitoring costs would make the strategy cost-effective in 74 (70%) of 106 countries, including 24 in the African Region *(18)*.

Impact and cost-effectiveness of expanded treatment for all HBsAg-positive pregnant women: Universal antiviral prophylaxis, regardless of HBV DNA level or HBeAg serostatus, would have great impact on HBV PMTCT, with about 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted. At central cost estimates and compared with hepatitis B birth dose, the universal "prophylaxis for all" strategy would probably only be cost-effective in 42 (40%) of 106 countries. The relative cost-effectiveness of the universal and HBV DNA-driven strategies (each compared with sole hepatitis B birth-dose strategy) depended highly on the relative costs of treatment and diagnostic tests *(18)*.

7.4 Rationale for the recommendations

7.4.1 Existing 2020 recommendation – TDF prophylaxis for HBsAg-positive pregnant women with high HBV DNA level *(3)*

Where there is ready access to HBV DNA or HBeAg assays, there is now a strong recommendation based on moderate-certainty evidence for using TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA levels ≥200 000 IU/mL or a positive HBeAg. This is in addition to HepB3 infant vaccination, including hepatitis B birth dose to prevent HBV MTCT *(3)*. This intervention is now a universal standard where there is access to HBV DNA. Most clinical trials supporting this recommendation evaluated the efficacy of maternal TDF prophylaxis in addition to HepB3 infant immunization and hepatitis B immune globulin administration. Two recent studies showed the efficacy of immunoglobulin-free strategies based on maternal prophylaxis with TDF (given for at least four weeks before delivery alongside infant birth-dose vaccination) *(12,19)*. A recent systematic review found that all cases of MTCT occurred among women with high HBV DNA levels, and that a pregnant woman with HBV DNA (≥200 000 IU/mL) may transmit HBV to her infant even when the infant received the timely birth-dose vaccine and hepatitis B immune globulin and completed the hepatitis B vaccine series *(20)*.

7.4.2 New recommendation - TDF prophylaxis for all HBsAg-positive pregnant women (where there is no access to HBV DNA testing)

In many settings, HBV DNA or HBeAg testing is not available to enable targeted TDF prophylaxis for pregnant women with high HBV DNA levels at high risk of MTCT. In such settings, universal TDF prophylaxis could be a strategy to reduce the risk of MTCT of HBV infection, alongside HepB3 and birth-dose immunization. However, no study has compared directly the effectiveness among hBsAg positive pregnant women of universal TDF prophylaxis versus no or targeted prophylaxis. In addition, low- and middle-income countries with high prevalence of HBsAg positivity among pregnant women often overlap with those with low or no uptake of hepatitis B birth-dose vaccination.

The Guidelines Development Group recognized the lack of direct empirical evidence to directly support the effectiveness, cost-effectiveness and feasibility of a universal prophylaxis approach. In settings without access to HBV DNA assays, a conditional recommendation to expand TDF prophylaxis to all HBsAg-positive pregnant women was therefore based on an overall pragmatic approach. This includes addressing the challenge of ongoing MTCT in settings without access to HBV DNA assays, the overall significant balance towards benefits versus harms of this approach, as well as low-certainty evidence based on data from cost-effectiveness modelling. This modelling analysis across 110 countries representing all WHO regions suggested that prophylaxis for all HBsAg-positive pregnant women would have great impact on PMTCT of HBV, with about 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted. The relative cost-effectiveness of the universal and HBV DNA–driven strategies (each compared with a sole hepatitis B birth-dose strategy) was highly dependent on the relative costs of treatment and diagnostic tests *(18)*.

More recent data based on timing of antiviral prophylaxis from the previous systematic review *(11)* showed that antiviral therapy at least four weeks before delivery reduces HBV DNA levels at delivery *(19)* and may reduce the risk of MTCT among babies who do not receive a timely hepatitis B birth dose, hepatitis B immune globulin or complete HBV immunization, a common concern in endemic countries.

Other key considerations include the following.

1. HBV perinatal transmission continues to be the dominant mode of ongoing HBV transmission worldwide *(21)*, and especially in sub-Saharan Africa, which continues to have low uptake of hepatitis B birth-dose vaccination. Data also indicate a significant residual risk (>10%) of HBV MTCT among highly viraemic (≥200 000 IU/mL) pregnant women despite receiving a timely hepatitis B birth dose *(10,22)*.

2. Perinatal transmission is associated with a >90% risk of developing CHB and therefore also for liver complications of cirrhosis and HCC *(23)*. Hepatitis B immune globulin is not routinely available in most endemic countries, and its administration with hepatitis B birth dose does not fully prevent HBV MTCT among babies born to highly viraemic women.

3. Reliable alternatives to HBV DNA testing are lacking, such as an HBeAg RDT with good diagnostic performance.

7.4.3 Balance of benefits and harm of a TDF prophylaxis-for-all strategy for HBsAg-positive pregnant women (where there is no access to HBV DNA testing)

Benefits

1. TDF has become widely available at low cost globally, although dual therapy (TDF + 3TC or FTC) used in HIV ART programmes may be more accessible in some countries.

2. Prophylaxis based on a positive HBsAg test alone could be easier to integrate, implement and scale up in antenatal services in low- and middle-income countries with minimal access to HBV DNA assays. It could reduce the turnaround time from HBsAg testing to initiating antiviral prophylaxis. This approach therefore enhances equity in settings with limited diagnostic capacity.

3. It provides the option to continue TDF for mothers who meet the criteria for antiviral therapy for their own health (such as the presence of advanced fibrosis or cirrhosis, coinfections or with an HBV DNA level >2000 IU/mL – see Chapter 5) and among women of childbearing age planning additional pregnancies, to avoid multiple start-stop cycles and interrupted antiviral prophylaxis.

4. Universal prophylaxis may help to compensate for the suboptimal uptake and adherence to infant HBV vaccination and especially to the administration of timely birth dose of vaccine (with or without hepatitis B immune globulin) among neonates born in highly endemic regions and the residual risk of HBV MTCT with vaccination (and hepatitis B immune globulin) alone.

5. Birth-dose vaccination alone may not confer protection without antiviral prophylaxis because of incomplete cross-genotype protection conferred by recombinant A2 HBV vaccine in some regions.

6. Expanding the use of TDF will also reduce the horizontal transmission of HBV.

Potential challenges or harms and considerations of expanding antiviral prophylaxis to all HBsAg positive pregnant women

1. Globally, the proportion of HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL ranges from 12% in the WHO African Region to 31% in the Western Pacific Region. Most HBsAg-positive pregnant women therefore do not have an HBV DNA level above 200 000 IU/mL and are not at risk of transmitting HBV infection to their offspring. Adopting a universal prophylaxis approach would mean that most HBsAg-positive mothers would receive prophylaxis unnecessarily. Infants born to mothers with lower levels of HBV DNA are adequately protected by a timely hepatitis B birth dose. The risk of transmission is negligible when maternal HBV DNA levels are below 200 000 IU/mL. Universal prophylaxis only applies to settings with no access to HBV DNA testing. When this is available, antiviral prophylaxis should be used only for people with an established high HBV DNA level.

2. Expanded prophylaxis could lead to a misperception that peripartum TDF prophylaxis could replace the administration of the timely hepatitis B birth dose. Scaling up the hepatitis B birth dose remains the most cost-effective option that delivers the most health benefit for the lowest cost. Expanded prophylaxis is intended to augment and not replace the timely hepatitis B birth dose.

3. Mothers have a potential risk of exacerbation or postpartum flare after antiviral therapy ends *(24)*, and mothers therefore need to be monitored carefully postpartum after discontinuing TDF. The consequences of repeatedly interrupting antiviral therapy among young women are uncertain, but concerns included undocumented subclinical histological necroinflammatory liver injury and fibrosis progression and, rarely, hepatic decompensation.

4. Universal prophylaxis will substantially increase demand for antiviral therapy, and sufficient procurement and a sustained supply chain will be required. The increased administration of antiviral therapy and monitoring requirements could present significant challenges to antenatal services, especially in resource-limited settings.

5. There are insufficient data on the level of adherence to prophylaxis to achieve effective PMTCT. Studies have shown low serum levels of TDF among pregnant women despite good adherence, both self-reported and assessed by pill count *(12)*. The optimal timing of initiation of prophylaxis and duration postpartum is also uncertain.

7.4.4 Acceptability, feasibility and preferences (Web annex D)

Preferences of people living with hepatitis B: Four published *(25–28)* and one unpublished study from Burkina Faso assessed the preferences of pregnant women related to interventions for HBV PMTCT. These studies indicated that most women (range 66–97%) wanted to receive TDF prophylaxis during pregnancy when needed and for their infant to be given a timely hepatitis B birth dose *(25)*. A further recent survey of 130 HBsAg-positive pregnant women in The Gambia found that 97% were willing to take prophylaxis to prevent HBV MTCT. Of these, 71% would accept prophylaxis regardless of HBV DNA level or HBeAg status but 21% expressed a preference to take prophylaxis only when strongly indicated. Determinants of the choices for prophylaxis were mainly driven by cost, affordability, accessibility and safety considerations. In contrast, a study from Guangdong, China found that only 17% of 737 of women would accept taking antiviral prophylaxis when needed *(29)*.

Health-care worker preferences: A 2020 WHO global survey of 153 health-care workers, 56 programme managers and 81 civil society representatives found that one third of respondents expressed concerns about the costs of prophylaxis, especially in resource-limited settings where drug costs are paid out of pocket *(30)*. A 2022 International Coalition to Eliminate Hepatitis B global online survey of 178 health-care workers (37% from the WHO Africa Region) found that 79% supported expanded access to antiviral prophylaxis for HBV PMTCT but that only 59% of health-care workers currently offered antiviral prophylaxis to pregnant women in their setting. This was attributed to lack of policies (78%) or access to HBV DNA testing (73%), inadequate staff training (73%) and refusal among pregnant women (16%).

National hepatitis programme managers' perspectives: A 2023 WHO survey of 41 national hepatitis programme managers from 33 countries showed that 71% strongly supported expanding eligibility for antiviral prophylaxis to all HBsAg-positive pregnant women in settings without access to HBV DNA. Programme managers highlighted the limited availability and/or high out-of-pocket payment costs of TDF and limited availability of HBV testing in the early weeks of pregnancy as the main barriers to expanding the use of antiviral prophylaxis for PMTCT in their countries.

7.4.5 Equity

Implementation of the 2020 WHO recommendation to offer TDF prophylaxis to HBsAg-positive pregnant women with high HBV DNA levels or positive HBeAg to prevent MTCT in addition to hepatitis B birth dose has been limited by poor access to HBV DNA and HBeAg assays. Expanding TDF prophylaxis to all HBsAg-positive pregnant women in settings without access to HBV DNA would substantially improve equity in access, but implementation would require ready access to low-cost TDF.

7.4.6 Feasibility

For settings with ready access to HBV DNA or HBeAg assays, the existing 2020 recommendations for using TDF prophylaxis only for the HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL would apply. In settings and countries without ready access to HBV DNA or reliable HBeAg assays, especially those with low uptake of hepatitis B birth-dose vaccination, expanding prophylaxis to all HBsAg-positive women represents a clear and feasible pathway to address ongoing hepatitis B MTCT. However, it requires that the benefits and risks for the infant and mother be fully explained to and accepted by childbearing women.

Following the adoption of universal hepatitis B infant vaccination in 1992 in China, the SHIELD project was initiated first to scale up immunoprophylaxis of hepatitis B among infants (hepatitis B immune globulin and hepatitis B birth dose) born in 10 hospitals in China. This was followed by a nationwide hospital-based implementation study for HBV PMTCT (administering antiviral prophylaxis to highly viraemic pregnant women) and then further expanding PMTCT interventions at the community level such as electronic clinics with one-stop service. With a low rate of HBV MTCT (0.2%, 12 of 5290 infected babies born to HBsAg-positive women), this real-world programme shows that community integration and one-stop services for HBV PMTCT can further reduce HBV MTCT to <0.5% *(26)*.

7.4.7 Resource considerations

Costs of TDF and diagnostics

Generic TDF is available at low cost, although access to monotherapy remains difficult in some countries. TDF is also available as part of a fixed-dose combination (TDF + 3TC or TDF + FTC) used in ART regimens or for PrEP. The current market price for HBV DNA testing varies from US$ 15–50 in the Region of the Americas and to US$ 30–100 in the Western Pacific Region and the African Region. The best current market price for laboratory-based HBeAg testing is US$ 7.50. The price of HBsAg RDTs ranges between US$ 0.50 and US$ 1.30 (Web annex C).

Cost-effectiveness of TDF prophylaxis

A modelling study found that the global cost of scaling up hepatitis B birth dose to 90% is estimated to be US$ 1.6 billion for 2020–2030. The additional costs of antenatal testing of pregnant women for HBsAg and providing TDF prophylaxis for those at increased risk of MTCT guided by HBV DNA level would be an extra US$ 2.2 billion to US$ 2.7 billion over 10 years. The incremental cost-effectiveness ratios of this testing and prophylaxis strategy guided by HBV DNA, in addition to timely birth dose, range between US$ 890 and US$ 7355 per DALY averted, depending on the geographical region *(17)*. Compared with the status quo, scaling up the hepatitis B birth dose is the most cost-effective option that delivers the most health benefit for the lowest cost. However, in countries that have already scaled up the hepatitis B birth dose, adding antenatal testing of pregnant women and TDF prophylaxis for all HBsAg-positive women may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented *(18)*.

7.5 Implementation considerations

Several countries that used to be highly endemic for hepatitis B have achieved major progress in controlling hepatitis B through high coverage of infant hepatitis B vaccination, including a timely birth dose *(31)*. Because HBV MTCT continues to be the dominant mode of ongoing HBV transmission worldwide *(31,32)*, programmes for peripartum antiviral prophylaxis have been initiated in most regions *(33,34)*. However, in the WHO African Region, experience with peripartum prophylaxis remains limited.

Expanding antiviral therapy for HBV PMTCT will require the following.

- **Increased coverage of timely birth dose:** Where coverage of the timely birth dose remains low, increasing coverage should be the priority for two reasons. First, a timely birth dose followed by two or three additional doses is the intervention that leads to the greatest impact at the lowest cost. Second, studies demonstrating the efficacy of antiviral prophylaxis have been conducted only in the setting of routine use of infant vaccination (including a timely birth dose). In 2022, the global coverage of HepB3 was high (84%) *(9)*. However, some countries, especially in sub-Saharan Africa, still struggle to reach high coverage (>90%).

  Funding for introducing and scaling up hepatitis B birth-dose vaccination is available through Gavi for eligible countries. Details on accessing Gavi support are available online. Countries are encouraged to explore synergy with funding provided by other donors, including the Global Fund.

- **Universal testing for HBsAg, HIV and syphilis for pregnant women:** WHO recommends that all pregnant women be tested routinely for HIV, syphilis and HBsAg at least once and as early as possible during pregnancy as part of a triple mother-to-child transmission elimination strategy *(35)*. Excluding HIV infection is important before starting TDF or TDF + FTC to avoid adverse outcomes of treating HIV infection with TDF monotherapy.
- **Adequate sensitization and monitoring of pregnant women:** Informed choices must be offered to pregnant women. Increased public education and sensitization are needed to increase uptake of hepatitis B birth dose alongside HepB3 infant vaccination, HBsAg testing, adherence to antiviral therapy and retention in care following delivery. Childhood HBV acquisition, in contrast to HIV transmission, can be prevented for most mothers through effective HBV birth dose and infant vaccination and antiviral prophylaxis, especially for highly viraemic mothers.

- **Increased health-care worker capacity:** An increased number of trained health-care workers in antenatal clinic settings will be required to support expanded hepatitis B antiviral prophylaxis for all HBsAg-positive mothers who will require monitoring during and after treatment. Further assessment of a woman's need for treatment for her own health based on HBV DNA level will be more challenging if she is already receiving antiviral therapy with a suppressed viral load.
- **Expanding the use of antiviral prophylaxis requires a robust procurement and supply chain for TDF for antenatal services.** Good monitoring and evaluation systems are also required to ensure high-quality data for evaluating the impact of a prophylaxis-for-all strategy.
- Adopting universal antiviral prophylaxis for all HBsAg-positive women may be considered a time-limited intervention to address ongoing MTCT while access to HBV DNA assays is improved to enable more targeted use of antiviral prophylaxis. Where HBV DNA testing is available, antiviral prophylaxis should be used only for those with high HBV DNA level at risk of onward transmission. Baseline testing of HBV DNA for HBsAg-positive pregnant women enables a more complete assessment of treatment eligibility for women for their own health to inform decisions about starting lifelong treatment. Increasing access to lower-cost HBV DNA POC assays in antenatal clinic settings or reliable HBeAg assays would make universal prophylaxis for all HBsAg-positive mothers unnecessary.
- **Simplified, integrated and decentralized service delivery:** Integrated HIV, HBV and syphilis testing and treatment care pathways, ideally as part of antenatal services and in the context of triple elimination of MTCT of HIV, HBV and syphilis, will be key to support the implementation of universal hepatitis B prophylaxis alongside scale-up of hepatitis B birth dose and HepB3 coverage. In 2014, WHO launched criteria and processes for validating the elimination of MTCT of HIV and syphilis, known as dual elimination *(36)*. Triple elimination has been adopted in most WHO regions with more developed health-care systems, but implementation with integrated antenatal care pathways is still at an early stage, especially in low- and middle-income countries.
- **Accurate diagnostic strategies to identify pregnant women with advanced fibrosis, cirrhosis or HCC:** Although cirrhosis and HCC are uncommon during pregnancy, hepatitis B is a major cause, and both can have dramatic consequences for women and their babies *(37)*. Since 2017, the use of FibroScan® during pregnancy is no longer contraindicated, but there is a lack of validated cut-offs of non-invasive tests for diagnosis of liver fibrosis for pregnant women. Because of haemodilution related to pregnancy, biochemical markers such as APRI may not be accurate.

7.6 Research gaps

- Evaluation of the feasibility, effectiveness and cost-effectiveness of maternal peripartum antiviral prophylaxis (universal or high HBV DNA driven) for HBsAg-positive pregnant women, also in the absence of a timely birth dose, especially in settings such as home births, where access to birth-dose vaccination is limited.
- Studies of adherence to maternal peripartum antiviral prophylaxis (universal or high HBV DNA–driven prophylaxis), discontinuation rates, adverse outcomes and uptake of onward referral for assessing treatment eligibility among HBsAg-positive pregnant women.
- The optimal timing of TDF initiation and duration during pregnancy and postpartum continuation of treatment.
- Follow-up studies to examine comprehensively the benefits and potential harm of discontinuing versus continuing antiviral therapy postpartum. This may include evaluating fibrosis progression using non-invasive tests at intervals postpartum.
- Evaluation of the feasibility and effectiveness of different models of integrated and simplified service delivery of antenatal hepatitis B care and treatment and triple elimination of HIV, syphilis and hepatitis B.

8. Who to treat and what antiviral drugs to use for adolescents and children with CHB

8.1 Recommendations - Who to treat among adolescents (See Chapter 5)

New recommendations

Treatment is recommended for all adolescents (aged 12–17 years) with CHB[a] (including pregnant and non-pregnant adolescent girls of reproductive age) with:

1. Evidence of significant fibrosis (≥F2) based on clinical criteria[b] or an APRI score of >0.5 or transient elastography value of >7 kPa[c] or evidence of cirrhosis (F4) based on clinical criteria[c] (or an APRI score of >1 or transient elastography value of >12.5 kPa[d]), regardless of HBV DNA or ALT levels.

(adolescents: strong recommendation, low-certainty evidence)

OR

2. HBV DNA >2000 IU/mL and an ALT level above the ULN (30 U/L for boys and men and 19 U/L for girls and women). For adolescents, ALT>ULN at least twice in a 6- to 12-month period.[d]

(adolescents: conditional recommendation, low-certainty evidence)

OR

3. Presence of coinfections (such as HIV, HDV and HCV), family history of liver cancer or cirrhosis, immune suppression (such as long-term steroids, solid organ or stem cell transplant), comorbidities (such as diabetes, metabolic dysfunction–associated steatotic liver disease and iron overload secondary to treatment for disorders of the blood) or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of APRI score or HBV DNA or ALT level.

(adolescents: conditional recommendation, low-certainty evidence)

OR

4. Persistently abnormal ALT levels (in the absence of access to an HBV DNA assay), regardless of APRI score.[e]

(adolescents: conditional recommendation, very-low-certainty evidence)

a Defined as persistence of HBsAg for six months or more among adolescents and children.

b Clinical features of decompensated cirrhosis: ascites, variceal haemorrhage, hepatic encephalopathy, coagulopathy or jaundice. Other clinical features of advanced liver disease or cirrhosis may include hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

c The thresholds of non-invasive tests (APRI and transient elastography) for diagnosis of significant fibrosis or cirrhosis and treatment recommendation are based on extrapolating data from adults and have not yet been fully validated for children and adolescents.

d The ULNs for ALT for adolescents and children are based on the same criteria used for adults: 30 U/L for boys and men and 19 U/L for girls and women. Other guidelines have defined ULN for adolescents as <22 U/L for girls and <25 U/L for boys.

e Persistently abnormal ALT among adolescents is defined in these guidelines as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

No recommendation - who to treat among children aged 2-11 years old

Current evidence is insufficient to support extending the same treatment eligibility criteria used for adults and adolescents to include children with HBV 2–11 years old. However, treatment is generally offered on a case-by-case basis to selected children in this age range who are identified to have the following: cirrhosis or advancing liver fibrosis stage ≥F2, persistent hepatitis flare with HBV DNA >2000 IU/mL, comorbidities that increase the risk of progressive liver disease, or a need for immunosuppressive therapy.

8.1 Recommendations - What Antivirals to use in adolescents and children (see Chapter 6)

Existing and maintained recommendations (from WHO 2015 HBV guidelines)

Nucleos(t)ide analogues with a low barrier to resistance (lamivudine, adefovir or telbivudine) that can lead to drug resistance are not recommended.

(strong recommendation, moderate certainty of evidence)

Updated recommendation

For all adults, adolescents and children (two years or older) for whom antiviral therapy is indicated, the nucleos(t)ide analogues that have a high genetic barrier to drug resistance – tenofovir disoproxil fumarate (TDF) or entecavir (ETV) are recommended as preferred regimens. TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) are recommended as alternative regimens (where TDF monotherapy is not available).

(strong recommendation, moderate-certainty evidence)

New recommendation

Entecavir (ETV) or tenofovir alafenamide fumarate (TAF)a (if available) are recommended for people with established osteoporosis and/or impaired kidney function, and for children (ETC for those aged two years or older) or adolescents (TAF for those aged 12 years or older as alternative regimen), for whom antiviral therapy is indicated.

(strong recommendation, moderate-certainty evidence).

Table 8.1 Summary of Preferred and alternative first-line antiviral regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults	TDF ETV	TDF + 3TC TDF + FTC (where TDF monotherapy is not available)	ETV TAF (for people with established osteoporosis and/or impaired kidney function)
Adolescents (12–17 years)	TDF ETV	TDF + 3TC TDF + FTC where TDF monotherapy is not available) TAF	
Children (2–11 years)	TDF* ETV		

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

*Low dose formulations of TDF may not be widely available

Table 8.2 Dosing in children and adolescents

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

a ETV: approved for children aged two years or older.

b TDF: the EMA has approved TDF for children two years or older with CHB *(1)* and the FDA for children two years and older weighing at least 10 kg *(2)*.

c TAF: the EMA has approved TAF for children six years and older and weighing more than 25 kg *(3)* and the FDA for children 12 years and older with compensated liver disease *(4)*.

8.2 Background

In 2019, WHO estimated that the global prevalence of CHB among children younger than five years was 0.94% (95% CI 0.82–1.06%), with the highest prevalence in the African Region *(5)*. More than 80% of children younger than five years with CHB are in 16 countries, and four countries account for 57% of the global burden: – the Democratic Republic of the Congo, India, Indonesia and Nigeria *(6,7)*. In a recent systematic review of 27 studies from western Africa based on data up to 2019, the prevalence of hepatitis B among children and adolescents younger than 16 years was 5% *(8)*. Among children and adolescents living with HIV, the CHB prevalence was 6.8% (interquartile range 2.5–10.0%), with a higher prevalence in sub-Saharan Africa (especially western Africa (9%)) *(8,9)*. CHB is rare among children and adolescents in North America and western Europe, although the prevalence is increasing among those

who migrate from higher-prevalence countries. Global data on the prevalence of CHB among adolescents are lacking.

Vertical MTCT is the most common mode of transmission of HBV globally *(7,10–12)*. In 2019, vertical and horizontal transmission in early childhood caused about 1.8 million new HBV infections annually among children younger than five years *(6,7)*. Horizontal (child-to-child or household or intrafamilial) transmission is especially common in sub-Saharan Africa because of poor infection control and injection safety during health-care or traditional practices *(13–17)* and has been documented among unvaccinated migrant children in Europe. Data are lacking on acquisition of HBV infection among adolescents who inject drugs and adolescent boys who have sex with boys or men.

The 2015 WHO hepatitis B guidelines did not include specific treatment recommendations for either adolescents or children because of the few existing trials of nucleos(t)ide analogue treatment, generally low curative response rates necessitating long-term therapy and concerns about long-term safety and the risks of drug resistance. At that time, only one treatment option (ETV) was approved for children younger than 12 years. Overall, a conservative approach to treatment was advocated unless there were specific criteria for treatment, such as cirrhosis or evidence of severe ongoing necroinflammatory disease on liver biopsy. Additional studies have now provided data on antiviral drugs for adolescents and children. The 2024 updated guideline recommendations for expanded and simplified treatment eligibility provide an opportunity to apply the same treatment recommendations in adults to adolescents, as outlined in Chapter 5. Significant evidence gaps remain, and treatment for children younger than 12 years remains on a case-by-case basis only.

8.3 Summary of the evidence

8.3.1 Efficacy and safety of antiviral therapy for adolescents and children (Web annex C 5.2 and 5.3)

Who to treat

A systematic review identified 13 studies (12 RCTs and one retrospective cohort) of children and adolescents. All but one study focused on children and adolescents with very high baseline viral load levels above 2 million IU/mL, and none reported outcomes for baseline viral load levels below 20 000 IU/mL. This reflects both the high prevalence of high HBV DNA levels among children with hepatitis B and the selection criteria of the trials. There was a statistically significant interaction between higher baseline viral load levels and the treatment outcome of ALT normalization, but not between baseline viral load or ALT levels and other outcomes (HBsAg seroconversion, HBsAg loss, HBeAg seroconversion, HBeAg loss or HBV DNA suppression). There were no studies on clinical outcomes such as HCC or cirrhosis, and only one study reported histological outcomes. The certainty of the evidence was rated as very low to high for viral load 2 million–20 million IU/mL (five different outcomes), very low to moderate for viral load 20 million–200 million IU/mL (six different outcomes) and moderate for >200 million IU/mL (one outcome).

Three of the RCTs *(18–20)* studied relevant nucleos(t)ide analogues – ETV (n = 180 *(18)*, TDF (n = 106) *(18)* and adefovir (n = 173) *(20)* versus placebo among HBeAg-positive children and adolescents 2–17 years old with persistently elevated ALT levels and treated for a relatively short duration (24–96 weeks). The meta-analysis showed that antiviral therapy produced an increased likelihood of ALT normalization (RR = 2.22, 95% CI 1.51–3.56), HBeAg seroconversion (RR = 2.33, 95% CI 1.37–4.03) and undetectable HBV DNA (RR = 6.18, 95% CI 3.39–15.5).

What antiviral drugs to use

In a double-blind trial, children and adolescents aged 2–17 years with CHB were randomized to receive ETV 0.015 mg/kg (up to a maximum of 0.5 mg) or placebo once daily for 48 weeks, after which participants with HBeAg seroconversion continued blinded therapy and others switched to open-label ETV *(18)*. The primary endpoint of HBeAg seroconversion with HBV DNA <50 IU/mL was reached by 24% of the treatment group and 3% of the placebo group. At week 48, ALT normalized in 67% vs. 23% and viral suppression to HBV DNA <50 IU/mL in 49% vs. 3%. Adverse events requiring cessation of treatment only occurred in the placebo group. Overall, there was no excess of adverse events in the ETV group. Viral resistance was observed in 0.6% of children after one year of ETV treatment and 2.6% after two years. After ETV treatment ended, eight (7%) showed ALT flares (two required retreatment, three self-resolved and three were unresolved when study follow-up ended).

In a double-blind trial, adolescents aged 12–17 years with CHB were randomized to receive TDF 300 mg or placebo once daily for 72 weeks *(21)*. The TDF group had a higher proportion than the placebo group with HBV DNA suppressed to <400 copies/mL (89% versus 0%) and ALT normalization (74% versus 31%). No resistance to TDF developed through the 72 weeks of treatment. No participants in either group met the safety endpoint of a 6% decrease in spine bone mineral density, although the mean change in total body bone mineral density z-score was –0.15 in the TDF group and +0.06 in controls. None had a creatinine increase greater than 0.5 mg/dL (44 µmol/L). No post-treatment flares were reported with TDF, but there was no off-treatment follow-up *(19)*.

The systematic review of TDF, TAF and TDF + FTC across all age groups (Chapter 5) included preliminary results from an ongoing placebo-controlled RCT of TAF among children and adolescents with CHB *(22)*. Eighty-eight participants (5–17 years) with CHB were randomized to receive either TAF 25 mg or placebo once daily *(22)*. Following 24 weeks of treatment, the TAF group had a significantly higher proportion with HBV DNA <20 IU/mL (19% versus 0%) and ALT normalization (45% versus 0%) than in the placebo group *(22)*. After 24 weeks, all participants received 25 mg of open-label TAF once daily *(22)*, and after 48 weeks of treatment, 37% of the TAF group versus 21% of the placebo-to-TAF switch group had HBV DNA <20 IU/mL, and HBeAg loss was 17% versus 7%, respectively. The percentage change in bone mineral density was similar in both groups. No studies were identified on the efficacy of TDF + FTC for HBV monoinfection for children and adolescents, but the meta-analysis for adults showed similar outcomes for safety and treatment efficacy (DNA normalization, ALT normalization, HBeAg loss or seroconversion and HBsAg loss or seroconversion) (Web annex C).

TAF for children and adolescents living with HIV

The evidence base for TAF for children and adolescents is limited to safety and pharmacokinetic data using adult dosing in weight bands above 25 kg *(22,23)*. Limited data are available for children 14 to <25 kg and older than two years using a low dose of TAF + FTC 15/120 mg with a boosted third agent *(21)*. Bone and renal safety and suppression of viral loads were all favourable. The acceptability and palatability of low-dose formulations containing TAF have also been demonstrated in this age group *(22)*.

The EMA has approved TDF for children two years or older with CHB *(1)* and the FDA for children two years and older weighing at least 10 kg *(2)*. The EMA has approved TAF for children six years and older and weighing more than 25 kg *(3)* and the FDA for children 12 years and older with compensated liver disease *(4)*.

8.3.2 Non-invasive tests of liver fibrosis in adolescents and children

Evaluation and validation of transient elastography and APRI thresholds for fibrosis or cirrhosis has been limited among children and adolescents with CHB. In a systematic review of non-invasive tests (see Chapter 4), five studies had evaluated non-invasive tests of liver fibrosis or cirrhosis for children and adolescents with CHB (Table 8.1). One study evaluated APRI at a cut-off value of 0.5 *(25)* and another transient elastography at a cut-off of 8.4 kPa *(26)*. Other studies used various cut-off values for ≥F2 or F4 that differed from those recommended for adults. Of note, all five studies evaluated the performance of non-invasive tests in a highly selected subgroup of children and adolescents with CHB who had undergone liver biopsy and were therefore likely to have a higher prevalence of liver fibrosis. The thresholds used for diagnosing significant fibrosis or cirrhosis (F4) in the treatment recommendations are therefore based on extrapolating the data from adults to adolescents.

Table 8.3 Studies of non-invasive tests of liver fibrosis for children and adolescents with CHB

Study	*n*	Mean age in years (range)	Transient elastography for ≥F2		Transient elastography for ≥F3		APRI for ≥F2	
			Cut-off (kPa)	Sensitivity/ specificity (%)	Cut-off (kPa)	Sensitivity/ specificity (%)	Cut-off	Sensitivity/ specificity (%)
Luo et al. *(25)*	148	3.96	8.4	82/78			0.76	61/73
Pavlovic et al. *(26)*	68	10.46	6	65/67				
Xu et al. *(27)*	157	3	5.6	76/67	6.9	91/81	0.71	64/78
Zhang et al. *(28)*	116	6					0.26 0.9	86/23 35/87
Zhijian et al. *(24)*	88	8.9 (1–18)					0.5 1.5	91/31 28/89

8.4 Rationale for the recommendations for adolescents

Who to treat among adolescents

In the updated guidelines, of the four recommended treatment eligibility criteria for adults (Chapter 4), all recommendations are conditional for adolescents (12–17 years old) with CHB based on low- or very-low-certainty evidence, except the first criterion – those with significant fibrosis and cirrhosis – for which there was also a strong recommendation for treating adolescents.

Antiviral therapy will continue to be indicated on a case-by-case basis for only a very few children younger than 12 years, and for this reason no formal recommendations were made.

What antiviral drugs to use

The preferred treatment of adolescents with CHB are TFV or ETV, and for children aged two years or older, ETV. TAF can be considered for use as an alternative regimen in adolescents (aged 12 years and older and weighing more than 35 kg).

The key evidence to support expanding treatment was based on the following.

Summary of evidence review for adults: The recommendations for adults and also adolescents were based on two WHO-commissioned systematic reviews: one focused on factors associated with clinical progression (development of liver-related morbidity, progression of liver disease or mortality) and the other on the factors associated with benefits from antiviral therapy. The first review found evidence of a dose–response relationship between higher HBV DNA level and risk of HCC, cirrhosis and liver-related mortality for adults. Evidence for adolescents and children was limited, without a clear association between viral load at baseline and long-term clinical outcomes. The second systematic review among adults found evidence indicating beneficial effects of antiviral therapy among adults with HBV DNA above 20 000 IU/mL or 20 000–200 000 IU/mL, consistent with the benefits observed for people with higher (>200 000 IU/mL) viral loads, but very limited evidence for those with HBV DNA 2000–20 000 IU/mL.

Summary of evidence review in adolescents: In an additional systematic review that specifically examined treatment effectiveness for children and adolescents, 13 studies were identified, 12 of which were RCTs. The studies were generally short in duration and only examined the impact on intermediate outcomes such as ALT normalization and HBeAg seroconversion. All but one study focused on children and adolescents with very high baseline viral load levels above 2 million IU/mL. There was no significant interaction between treatment efficacy and baseline viral load or ALT levels for HBsAg seroconversion, HBsAg loss, HBeAg seroconversion, HBeAg loss and HBV DNA suppression. There were also no studies on clinical outcomes such as HCC or cirrhosis in adolescents, and only one study reported histological outcomes. Three randomized trials of HBeAg-positive children and adolescents with persistently elevated ALT levels found that antiviral therapy was associated with increased likelihood of ALT normalization (RR 2.22, 95% CI 1.51–3.56), HBeAg seroconversion (RR 2.33, 95% CI 1.37–4.03) and undetectable HBV DNA level (RR 6.18, 95% CI 3.39–15.5).

8.4.1 Balance of benefits and harm for treating adolescents

The balance of benefits and harm for expanding treatment to include adolescents (12–17 years) with CHB was considered in the context of a limited number of generally short-duration clinical trials involving adolescents and children and the fact that significant evidence gaps remain.

The key rationale for the strong recommendation for treating ALL adults (moderate-certainty evidence) and adolescents (low-certainty evidence) with significant fibrosis and cirrhosis, and the conditional recommendations for other treatment eligibility criteria among adolescents is based on the following.

1. Similar to adults, adolescents with evidence of significant fibrosis stage ≥F2 (in addition to those with cirrhosis) have a higher risk of progressing to advanced liver disease. In addition, treatment has the greatest effect on morbidity and mortality in this group, based mainly on evidence from studies of reversal of fibrosis among adults. Despite the limited direct evidence of treatment effectiveness from studies of adolescents and lower risk of cirrhosis and HCC among adolescents and therefore low-certainty evidence, the Guidelines Development Group considered that the indirect evidence supported substantially greater benefits that outweigh the harm and therefore made a strong recommendation.

2. Liver fibrosis is common among adolescents with CHB undergoing liver biopsy for clinical indications. In one recent study, only 18% of 134 liver biopsies among children and adolescents showed no fibrosis *(29)*.

Two other recommendations for treatment were strong for adults but conditional for adolescents, reflecting the weaker direct evidence base for adolescents and therefore narrower balance of benefits to harm for adolescents. These include the recommendations for treatment based on HBV DNA >2000 IU/mL and an ALT level above the ULN and also based on the presence of coinfections (such as HIV and HDV), family history of liver cancer or cirrhosis, immune suppression, comorbidities (such as diabetes) or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of fibrosis stage or HBV DNA or ALT level. The rationale is based on the following.

1. Most of the evidence for treatment effectiveness is based on studies of adults, showing that antiviral therapy for those with high viral load improves intermediate outcomes (HBV DNA and ALT levels) but also reduces the progression of fibrosis to cirrhosis and incidence of HCC.

2. Direct evidence for treatment efficacy among adolescents (TDF and ETV and assumed for the TDF dual-therapy regimens (TDF + 3TC or TDF + FTC)) shows that antiviral therapy for adolescents with CHB and elevated ALT twice over a 6- to 12-month period and HBV DNA >2000 IU/mL had positive intermediate outcomes and effectively reduces HBV DNA levels, normalizes ALT and achieves HBeAg seroconversion, which are intermediate outcomes associated with reduced risk of progression to cirrhosis and HCC.

3. The lack of significant relevant physiological differences between adolescents and adults and therefore little basis to expect a difference in efficacy outcomes was considered a further reason why the adult evidence could be reasonably applied to adolescents.

4. Treating adolescents with TDF, ETV or TAF is sufficiently safe, such that the benefits of treatment generally outweigh the risks, regardless of age, ALT or HBV DNA levels. This is especially the case in the presence of fibrosis or cirrhosis and the basis of the strong recommendation for treatment across all age groups (adults, adolescents and children).

Other potential benefits of expanding treatment to adolescents include the following.

- Expansion of treatment to include adolescents is most relevant to sub-Saharan Africa, where much of the population is younger than 20 years, and currently a significant proportion of those HBsAg positive are younger than 20 years (25% versus 5% or less in other regions), in part because of lack of HBV birth-dose vaccination. This is a key factor in explaining (alongside aflatoxin exposure) the occurrence of potentially preventable HCC cases at a young age in sub-Saharan Africa. In other regions, adolescents and children have a low prevalence of HBsAg.

- Expanded criteria may provide the opportunity to identify and offer treatment to adolescents with a strong family history who are at risk of progressing to cirrhosis and HCC in early adulthood. This potential advantage may be especially important in sub-Saharan Africa, where HCC occurs at an earlier age *(30)*.
- Expanded treatment for adolescent girls of reproductive age may reduce vertical and early horizontal transmission to infants, which remains the most important route of transmission globally and accounts for most of the global burden of CHB.
- Expanded treatment among adolescents with CHB represents an opportunity to reduce viral DNA integration events for those with high levels of HBV replication but minimal necroinflammatory change and treatment before the onset of severe T- and B-cell dysfunction that is common in older individuals *(31)*. Direct evidence to support this is currently lacking.
- Treatment may improve mental health and reduce self-stigma for adolescents living with hepatitis B by providing greater confidence that the risk of transmitting infection to others may be reduced and infection may be better controlled.

Potential harm

1. Data on the long-term safety of antiviral therapy for adolescents are still limited. In one study, TDF for children and adolescents was associated with some reduction in bone density and increased creatinine over 72 weeks of treatment *(19)*. Longer-term studies of bone and kidney health among children are currently not available to determine whether these effects continue to accumulate over time and may result in reduced peak bone mineral density achieved during adolescence or are time-limited in magnitude, as observed for adults *(32)*. Long-term TAF treatment may be associated with weight gain and hyperlipidaemia for adults living with HIV *(33)*. The extent to which this may increase the risk of diabetes and cardiovascular disease has not yet been determined, and safety data for children using TAF have not yet been reported in full *(21,34)*.

2. Children and adolescents may experience significant hepatitis flares after stopping nucleos(t)ide analogue treatment, which sometimes requires retreatment *(18)*. There are particular concerns about such flares occurring with unplanned and therefore generally unmonitored discontinuation of treatment during adolescence. Although this concern alone should not be a reason to avoid treatment, programmes need to plan how to mitigate the risks associated with non-adherence with careful monitoring during treatment *(21,34)*.

8.4.2 Treatment for children 2-11 years old

Current evidence is insufficient to support including children younger than 12 years of age in the above recommendations for adults and adolescents. Hepatitis B very rarely causes significant clinical events for children younger than 12 years, and the evidence base for the benefits and risks of treatment is even less clear than for adolescents (this age group was not included in the paediatric TDF hepatitis B treatment trial). Treatment is generally offered on a case-by-case basis to the few selected children in this age range who develop significant, persistent hepatitis flares, with HBV DNA >2000 IU/mL, cirrhosis or HCC or have comorbidities that increase the risk of progressive liver disease (such as coinfection with HIV, HCV or HDV, iron overload secondary to treatment for disorders of the blood and blood-forming organs or those who need immunosuppressive therapy).

8.4.3 Values and preferences

In a global survey of 150 health-care workers from 41 countries evaluating values and preferences for hepatitis B treatment for children and adolescents, respondents gave priority for treatment to the adolescents with elevated ALT or those who are immune suppressed (Web annex D); 50% of respondents supported treatment criteria for adolescents being the same as for adults, and 69% considered that the treatment criteria for children 0–11 years old should differ from those for adults. The reasons for considering children younger than 12 years differently included the possibility of “immune tolerance” for a period after neonatal and childhood acquisition, absence of fibrosis or cirrhosis, lower risk of HCC and concerns around long-term treatment in the absence of dosing recommendations for children and concerns about long-term drug safety.

Even in high-income countries, uptake of treatment recommendations for children provided by professional society guidelines is low, and only a minority of eligible children and adolescents are receiving treatment *(35)*. The reasons include lack of knowledge and pre-existing beliefs among health-care practitioners, people with hepatitis B and their family members and limited access to health care, diagnostic testing and medications.

8.5 Implementation considerations

- Implementing expanded treatment for adolescents will require appropriate resources at each level of the care pathway from diagnosis to treatment initiation and long-term monitoring. Systems must be developed and capacity enhanced to deliver widespread testing and treatment, especially in areas with high prevalence. The existence of well-established adolescent-friendly services for offering HIV prevention, testing and treatment services for HIV clients presents an opportunity for integrating similar hepatitis B services.
- A person- and family-centred approach should be adopted, ensuring that the uncertainties around benefits and harm and the financial implications of long-term treatment are fully explained and understood, so that caregivers and adolescents, alongside their health-care provider, can make an informed choice about starting treatment or not.
- All countries need to incorporate testing for adolescents and children and treatment for adolescents in their national policies and guidelines. This includes focused testing of children and adolescents from populations most severely affected by HBV infection (such as those with mothers or other household members with CHB, adolescent boys and men who have sex with boys or men, people who inject drugs and those living with HIV) and also when viral hepatitis is clinically suspected.
- Simplified treatment eligibility criteria that apply to both adolescents and adults should be easier to implement in low- and middle-income countries, in which non-specialist physicians who routinely treat both adults and adolescents will likely be the main health-care workers treating people with HBV infection.
- The age of consent for testing varies across countries and can pose barriers to adolescents' access to services. Engaging adolescents in testing and treatment should be based on adolescent-friendly services. Locally sensitive education for health-care practitioners and target populations is needed to improve HBV testing uptake among adolescents.
- These guidelines base the ALT ULN for children and adolescents on the same criteria used for adults: 30 U/L for boys and men and 19 U/L for girls and women. Other guidelines have defined ULN for adolescents as <22 U/L for girls and <25 U/L for boys. These guidelines also define persistently abnormal ALT among adolescents as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period. This is because treatment trials only included children and adolescents with persistent ALT elevation. Brief, spontaneous elevations of ALT are very common for children and adolescents with hepatitis B *(40)*, and no studies show any benefit of treatment for those with only transient elevations. In addition, elevation of ALT in this age group may herald spontaneous HBeAg seroconversion to a sustained state of low viral load and normal ALT, which should be allowed to occur without the need for initiating treatment *(40)*.
- Treatment of children is dependent on the availability of appropriate drug formulations to administer correct dose. Country programmes should review what formulations are available for procurement. There is ongoing work to ensure paediatric medicines are more widely available.

8.6 Research gaps

- Comparative trials and long-term follow-up studies are needed to determine how treatment during childhood or early adolescence in different regions affects the development of liver fibrosis, cirrhosis or HCC during adolescence or adulthood but also HBV transmission and health-related quality of life.
- Long-term prospective studies to understand the potential adverse effects of long-term nucleos(t)ide analogue treatment on kidney and bone health, including any effect on peak bone mass achieved during teenage years and lifetime fracture risk.
- Long-term follow-up studies to examine the rate of discontinuation of nucleos(t)ide analogue treatment and the optimal strategies to promote and maintain adherence among adolescents and children and minimize the risks of clinically silent hepatitis flares.
- Data on the burden and routes of transmission of HBV among children and adolescents in different regions and rates of transmission among higher-risk groups, including adolescents who inject drugs and adolescent boys and men who have sex with boys or men.
- Determining the population-based prevalence of liver fibrosis caused by hepatitis B and the progression of fibrosis during childhood and further validating non-invasive tests of liver fibrosis for children and adolescents.

9. Second-line antiviral therapies for managing treatment failure

9.1 Recommendations

Existing and maintained recommendation

Among people with evidence of treatment failure due to confirmed or suspected antiviral resistance[a,b,c] (based on history of previous exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen, if available.

(strong recommendation, low-certainty evidence)

a Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.
b Some countries and health-care providers may consider switching people to TDF (or TAF, if available) from existing antiviral regimens with a low barrier to resistance before evidence of treatment failure, but these guidelines make no formal recommendations.
c To date, there are only isolated case reports of TDF or TAF resistance when used for hepatitis B treatment. If there is primary non-response, then treatment adherence should be reinforced and monitored. At present, there is therefore no indication to switch to an alternative drug regimen.

Box 9.1 Diagnosing treatment failure

Objective monitoring of adherence to antiviral therapy is essential for effective long-term management of CHB. Each clinic visit is an opportunity for assessing and supporting treatment adherence and may require a combination of approaches depending on the local context. Treatment adherence should be reinforced for everyone with confirmed or suspected antiviral resistance. See also Box 6.2.disease.

Definition of treatment failure

In settings where HBV DNA testing is available:
Primary antiviral therapy failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by >1 Í log10 IU/mL within three months. Secondary antiviral therapy failure may be defined as a rebound of HBV DNA levels of >1 Í log10 IU/mL from the nadir among people with an initial antiviral therapy effect (>1 Í log10 IU/mL decrease in serum HBV DNA).

In settings where HBV DNA testing is not available:
Treatment failure and drug resistance may be suspected based on the following features: receiving antiviral drugs with a low genetic barrier to resistance, documented or suspected poor adherence and laboratory measures such as an increase in serum aminotransferases and/or evidence of progression of liver disease.

Note: ALT level tends to be elevated late and is a relatively poor predictive marker of resistance. Antiviral drug failure can be confirmed by sequencing the HBV DNA polymerase and identifying specific genetic markers of antiviral drug resistance.

9.2 Background

An initial concern with long-term nucleos(t)ide analogue therapy was the potential for selection of drug-resistance mutations among people treated with nucleos(t)ide analogues with a low barrier to resistance. HBV has a high rate of replication, with up to 10^{10} to 10^{12} mutations generated every day. Several drug-resistance mutations in the HBV polymerase reduce efficacy to more than one nucleos(t)ide analogue, resulting in cross-resistance to more than one agent, which could lead to multidrug resistance and limit future options for treatment (Table 9.1). Higher rates of resistance were observed among people with high baseline HBV DNA levels, longer duration of treatment and a slower treatment-related decline in HBV DNA levels *(1,2)*. This is a particular risk among people previously treated sequentially with nucleos(t)ide analogues with a low barrier to resistance (3TC, adefovir and telbivudine) as monotherapy *(3-5)*. The previous widespread use of these drugs for people with CHB led to a high rate of 3TC-resistant hepatitis B, especially in Asia and the Pacific, where the prevalence of hepatitis B is high, and 3TC and adefovir were widely used without access to appropriate second-line regimens *(6,7)*. With the adoption of first-line drugs with a high genetic barrier to resistance (TDF, ETV and TAF), resistance is now much less of an issue and is generally manageable. ETV has very low rates of resistance (except among people previously exposed to 3TC and adefovir), and currently there is little definitive evidence of resistance among people with HBV monoinfection treated with TDF or TAF *(8)*.

The emergence of antiviral resistance usually leads to an increase in HBV DNA levels or viral rebound after initial response during therapy, which is likely to be followed by biochemical breakthrough with a rise in the ALT levels and, in some cases, hepatitis flares and progression to hepatic decompensation. HBV DNA monitoring generally identifies the presence of treatment failure and likelihood of underlying resistance. Identification of resistance mutations should lead to the appropriate second-line therapy based on the most effective antiviral drug that does not share cross-resistance.

Table 9.1 Cross-resistance data for the most frequent HBV variants *(9)*

HBV variant	LAM	ETV	ADV	TDF/ TAF*
Wild-type	S	S	S	S
M204V	R	I	I	S
M204I	R	I	I	S
L180M + M204V	R	I	I	S
A181T/V	I	S	R	I
N236T	S	S	R	I
L180M + M204V/ ±1169T±V173L±M250V	R	R	S	S
L180M + M204V/±T184G± S202I/G	R	R	D	S

The amino-acid substitution profiles are shown in the left column and the level of susceptibility is given for each group: S (sensitive), I (intermediate/reduced susceptibility), R (resistant)

ADV, adefovir; EFV, entecavir; LAM, lamivudine; TDF, tenofovir; TAF, tenofovir alafenamide

9.3 Summary of the evidence

A previous evidence review was undertaken to inform the 2015 guidelines and assess the most effective treatment regimen for managing treatment failure from resistance among people previously treated with single agents with a low barrier to resistance (3TC, telbivudine or adefovir). The interventions analysed include switching to treatment with agents with a high genetic barrier to resistance (TDF or ETV) versus adding in a second agent (combination therapy) or continuing regimens with a low barrier to resistance (3TC, telbivudine or adefovir). This systematic review was based on data from one existing systematic review *(10)* comprising five RCTs and three non-randomized studies in China and the Republic of Korea, together with several randomized trials among people with 3TC resistance or a partial response to 3TC *(10–16)*.

A network meta-analysis was also undertaken and found that TDF followed by ETV plus adefovir combination therapy had the highest probability of achieving undetectable HBV DNA and HBeAg seroconversion at the end of one year of treatment among all the evaluated treatments. After one year of TDF treatment, 89% (95% CI: 52–98%) of 3TC-resistant people would be expected to achieve undetectable HBV DNA and 18% (95% CI: 1–75%) HBeAg seroconversion. The certainty of the direct evidence (pairwise comparisons) was rated as moderate to very low. The evidence from the previous review has been further complemented by more recent data on using TDF, TAF and the combination of TDF with ETV as second-line therapy in several clinical studies *(9)* that have confirmed the effectiveness of this approach *(17–19)*, including monotherapy with TDF *(20,21)*.

9.4 Rationale for the recommendations

9.4.1 Balance of benefits and harm

For people who had previously received a nucleos(t)ide analogue with a low barrier to resistance (3TC, adefovir and telbivudine), and especially among people with confirmed or suspected 3TC or ETV resistance, based on detectable HBV DNA level, it is recommended to change to an effective antiviral drug that does not share cross-resistance (TDF, ETV or TAF (if available)). The key reasons for this approach are as follows.

1. The most common reason for viral breakthrough is poor adherence, and regular counselling should therefore be offered on the importance of treatment adherence, especially among people with evidence of viral breakthrough.

2. Continuing treatment with an ineffective antiviral drug leads to an increased risk of ongoing HBV replication and disease progression.

3. TDF is associated with the highest probability at one year of achieving low or undetectable HBV DNA levels among people with 3TC-resistant HBV *(22)*.

4. The use of TDF (or TAF, if available), which does not share cross-resistance, would avoid the selection of further compensatory mutations and development of drug resistance with reservoirs of resistant HBV mutants. Clinical and molecular evidence indicates that resistance to 3TC (L180M + M204V/I) confers cross-resistance to telbivudine and ETV but not TDF or TAF. In addition, although 3TC-naive people treated with ETV rarely experience treatment failure or develop resistance, resistance to ETV is more common among people with 3TC resistance. ETV should therefore not be used as salvage therapy among people with known or suspected 3TC resistance.

5. Currently, TDF + 3TC + DTG are recommended as a first-line ART regimen for managing HBV + HIV coinfection. Treating HIV in HBV + HIV coinfection with antiretroviral drugs and 3TC alone without TDF or TAF could lead to higher prevalence of HBV 3TC resistance mutations *(23)*.

9.4.2 Resource and access considerations

Drug costs: see Chapter 6.

In general, generic TDF and ETV as well as dual therapy (TDF + 3TC or FTC) are widely available at low cost in many low- and middle-income countries through HIV treatment or PrEP programmes and access to reduced prices such as licence agreements negotiated with the Medicines Patent Pool. TDF 300 mg is available for a ceiling price of US$ 2.40 per 30 tablets negotiated by the Clinton Health Access Initiative and The Hepatitis Fund with generic manufacturers. TDF + 3TC costs US$ 3.37 per month and TDF + FTC costs US$ 3.97. TAF has been approved for clinical use since 2015 (patent protected) but is still a branded, on-patent drug mainly used in high-income countries. TAF is currently much less available and more costly (about 1.5 times) than either TDF or TDF + 3TC or FTC, partly because of the overall lower demand.

9.5 Implementation considerations

- Diagnosis of treatment failure: measuring HBV DNA levels and testing for drug resistance are fundamental to confirming treatment failure and genotypic HBV resistance, but low- and middle-income countries have extremely limited access to these. In these settings, ascertaining the development of resistance is largely based on clinical suspicion and, in some instances, by an increase in serum aminotransferases. However, elevation in ALT tends to occur later after the rise in HBV DNA and has been shown to be a relatively poor predictive marker of resistance *(24)*. In countries where resistance testing is not available, a change to TDF would not incur added costs.
- People with hepatitis B undergoing antiviral therapy require regular testing for HBV DNA every 12 months. If insufficient viral suppression or viral breakthrough (>1 log increase in HBV DNA above the nadir) is detected, strict adherence to therapy needs to be ensured.
- If antiviral resistance is confirmed through molecular testing, appropriate strategies are switching to an antiviral drug that does not share cross resistance. 3TC-, telbivudine- and ETV-resistant HBV can be treated with TDF monotherapy, adefovir resistance with ETV or TDF and insufficient responses to TDF may require ETV either as monotherapy or combination therapy. Some professional society guidelines focused on high-income countries include more detailed guidance *(9,25)*. For people with multidrug resistance, genotypic resistance testing should be performed by a reference laboratory.

9.6 Research gaps

- Assess the prevalence of resistance to TDF or TAF monotherapy or as part of ART with different genotypes of hepatitis B and in different regions and also in among children and adolescents initiating treatment.
- Evaluate further the utility and predictive value of monitoring ALT levels and other markers to identify the development of genotypic or phenotypic resistance.
- Evaluate how treatment with nucleos(t)ide analogues with a high genetic barrier to resistance affects people with treatment failure and other important outcomes, such as histological improvement, development of further drug resistance and adverse events.
- Examine the potential for vertical and horizontal transmission of resistance.

HBV and HDV diagnostics

Chapter 10: Measuring HBV DNA to guide treatment eligibility and monitor the response

Chapter 11: HBV DNA reflex testing

Chapter 6: Who to test for hepatitis Delta virus (HDV) infection

Chapter 7: How to test for HDV infection: testing strategy and choice of serological and NAT assays

Chapter 8: How to test for HDV infection: Laboratory-based reflex testing

10. Measuring HBV DNA to guide treatment eligibility and monitor the response

10.1 Recommendations

Existing and maintained recommendation

Laboratory-based HBV DNA assays[a] *(1,2)*: Directly following a positive HBsAg serological test result, the use of HBV DNA nucleic acid testing (NAT) (quantitative or qualitative) is recommended as the preferred strategy to assess viral load level for treatment eligibility and to monitor treatment response.

(strong recommendation, moderate-certainty evidence)

New recommendation

Point-of-care (POC) HBV DNA assays: POC HBV DNA nucleic acid testing (NAT) assays may be used as an alternative approach to laboratory-based HBV DNA testing to assess HBV DNA level for treatment eligibility and to monitor treatment response.

(conditional recommendation, low-certainty evidence)

a Assays should meet minimum quality, safety and performance standards.

10.2 Background

The primary diagnosis of CHB is based on a positive HBsAg test. However, quantifying HBV DNA is critical for determining eligibility for both treatment and antiviral prophylaxis for PMTCT and monitoring treatment response among those receiving antiviral therapy *(1)*. The 2015 hepatitis B guidelines *(1)* recommended initial assessment and annual monitoring of HBV DNA levels for those receiving treatment to ensure the suppression of HBV DNA replication to low or undetectable levels and also for those not yet receiving antiviral therapy to assess disease progression. WHO guidelines *(1–3)* also recommended laboratory-based nucleic acid amplification as the gold standard to quantify HBV DNA. However, in many low- and middle-income countries, especially in sub-Saharan Africa, access to HBV DNA assays is limited *(4)* because of high costs and requirements for specialized laboratory infrastructure, trained personnel and a sample transport system. This has been a major barrier to more widespread uptake and initiation of hepatitis B treatment. There is now high-certainty evidence demonstrating the clinical impact of POC assays for HIV viral load monitoring *(5)*, early infant diagnosis of HIV *(6)*, diagnosis of TB *(7)* and diagnosis of chronic viraemic HCV infection and as a test of cure *(8)*. Data on using POC HBV DNA assays to promote access to quantifying HBV DNA to determine treatment eligibility and promote treatment uptake have been more limited. The increased availability of these POC platforms for HIV and TB care and during the COVID-19 pandemic *(9,10)* represents an opportunity for access to HBV DNA assays.

Laboratory-based HBV DNA NAT assays (Table 10.1)

Both quantitative and qualitative methods are available for detecting HBV DNA. Quantitative HBV DNA NAT has been widely used for measuring HBV DNA and identifying those who need treatment and in assessing treatment response or monitoring disease progression *(1,2)*. Qualitative NAT enables rapid and sensitive detection of the virus and evidence of a decline in HBV DNA level below a defined threshold. The 2015 hepatitis B guidelines *(1)* strongly recommended using laboratory-based HBV DNA NAT (quantitative or qualitative) as the key assays to guide decisions about who to treat or not treat. Several manufacturers offer HBV DNA assays with stringent regulatory authority approvals as defined by WHO *(11)*. However, most of these products are intended for use on high-throughput platforms at centralized laboratories (Table 10.1). Six laboratory-based quantitative HBV DNA assays are currently commercially available, with others in the pipeline as summarized in a 2022 HBV diagnostics landscape report *(4)*. Although these NAT assays are very sensitive and specific for detecting HBV DNA, they require sophisticated laboratory equipment and skilled personnel. Assays to detect HBV DNA that may be used at or near the point of care have now become commercially available.

Table 10.1 Summary of quality-assured HBV DNA laboratory-based technologies

Product	Manu-facturer	Specimen type	Analyser platform	Regulatory status	Price (US$)	Incoterm
Alinity m HBV	Abbott	serum, plasma	Alinity m System	CE-Mark	not available	not available
Real*Time* HBV Viral Load Assay		serum, plasma	m2000 RealTime System	CE-Mark	9.60–15.55[a]	FCA
Artus HBV RG RT-PCR Kit / Artus HBV QS-RGQ Kit	Qiagen	plasma	Rotor-Gene Q or Rotor-Gene Instrument	CE-Mark	not available[b]	not available
AccuPower HBV Quantitative PCR Kit	Bioneer	serum, plasma	ExiStation Universal Molecular Diagnostic System	CE-Mark	not available	not available
Cobas HBV Test	Roche	serum, plasma	CAP/CTM, Cobas 4800/5800/ 6800/8800 systems	CE-Mark and US FDA	8.90[a]	CPT
Aptima HBV Quant Assay	Hologic	serum, plasma	Panther System	CE-Mark, US FDA	11.28[c] (all-inclusive)	DAP

Note: Bolded products above from Abbott, Qiagen, Bioneer, Roche and Cepheid are available for procurement through the Global Fund (see the list of HIV diagnostic test kits classified according to the Global Fund Quality Assurance Policy) *(12)*.

a Prices are global access prices from the ASLM diagnostic pricing database (https://aslm.org/diagnostic-pricing-database) *(13)*.

b Prices for HBV DNA assays for other diseases range from US$ 8.78 to 11.17 free carrier.

c Prices provided by the manufacturer.

POC HBV DNA assays (Table 10.2)

Laboratory-based quantitative HBV DNA NAT assays have generally been the standard-of-care assays for diagnosing and monitoring HBV DNA. However, the high cost of these assays and laboratory requirements means that they are not widely available in resource-limited settings. The market for quality-assured POC HBV DNA products is smaller, and only two manufacturers offer HBV DNA for use on near-POC platforms: the Xpert HBV Viral Load (Cepheid, United States of America) and the Truenat HBV (Molbio, India). At present, these products do not have WHO prequalification approval for this use. Existing platforms may expand test menus to include HBV, and future platforms and platform-free products may launch with HBV DNA assays.

Table 10.2 Summary of POC HBV DNA assays

		
Product	**Xpert HBV DNA**	**Truenat HBV**
Manufacturer	Cepheid	Molbio
Analyser	Cepheid GeneXpert Instruments (GeneX-pert-II, GeneXpert-IV, GeneXpert-XVI Instruments)	Truelab Real Time micro PCR platform (UNO/DUO/QUATTRO / QUATTRO 4x4)
Cost	US$ 14.90 ex works per assay,[a] about US$ 17 000–70 000 per machine	US$ 12 ex works per assay[a]
Assay	Specimen type: plasma, serum Limit of detection 6 IU/mL	Specimen type: plasma, serum, whole blood Limit of detection 56 IU/mL
Regulatory approval	CE-Mark	No stringent regulatory authority approval
Availability	Global footprint in at least 142 countries for TB and increasing use for other diseases (HIV, COVID-19, HCV, HPV etc.)	Platform available across 35 countries, primarily in the Asia, Africa and Europe regions
Requirements	• Needs dedicated space with controlled conditions (temperature, humidity) to minimize dust and humidity, and no direct sunlight • GeneXpert device requires stable continuous electricity supply, and a laboratory environment at 15–30°C and 20–80% humidity • Xpert cartridges have a shelf life of 12 months from manufacture, require storage at 2–28°C and must be stored upright	• Needs dedicated space with controlled conditions (temperature and humidity) • Molbio device requires ambient room temperatures at 15–40°C and relative humidity should be 10–80% • Separate extraction and amplification steps with interim manual transfer

a Prices are global access prices from ASLM diagnostic pricing database (https://aslm.org/diagnostic-pricing-database).

10.3 Summary of the evidence - POC HBV DNA assays

10.3.1 Clinical impact (Web annex C 10.1)

A systematic review and meta-analysis was undertaken to evaluate the impact of using quantitative POC HBV DNA assays versus laboratory-based standard-of-care assays on the uptake of HBV DNA testing and treatment and turnaround times to treatment initiation among HBsAg-positive people. Seven studies were included (six prospective cohorts and one retrospective cohort). Five studies were based in sub-Saharan Africa (four in the general population), one in the Middle East and one in Europe among west African migrants. Six arms had POC assays on site and two used mobile POC assays. The certainty of evidence was rated as very low because of imprecision and risk of bias.

Outcomes – turnaround time

Five studies (seven arms) had turnaround times for at least one step of the hepatitis B cascade, including uptake of HBV DNA testing, treatment or both. Of these, two studies (three arms) reported a turnaround time between screened HBsAg positive and HBV DNA test of less than one day, and the other two reported a turnaround time between seven and 11 days. Three studies reported time to HBV DNA test result of less than one day, and three studies reported the turnaround time from receipt of DNA testing results to treatment initiation ranging from one to eight days. Two studies reported the overall turnaround time between a positive HBsAg test and treatment initiation (less than one day in one study and 27 days in another study). Comparator turnaround time from HBV DNA test to available results for the one study using non-POC laboratory-based testing was between two weeks and two months, and 26 days from the receipt of DNA testing results to treatment initiation.

Outcomes – HBV DNA testing uptake and treatment uptake

The percentage of those HBsAg positive (n = 3101) who had a POC HBV DNA test was 89% (95% CI: 55–100%) in five studies (six arms). The pooled percentage of people with a detectable HBV DNA viral load among the 594 who had HBV DNA testing was 86% (95% CI: 62–100%) in five studies (seven arms), and the distribution was 384 (69%) <2000 IU/mL; 80 (14%) 2000–20 000 IU/mL; and 59 (11%) >20 000 IU/mL. The pooled proportion for the people deemed eligible for treatment among those with detectable HBV DNA was 23% (95% CI: 7–44%) in four studies (six arms), and the percentage of people who initiated treatment among those assessed as eligible for treatment was 88% (95% CI: 66–100%) in five studies (seven arms).

10.3.2 Diagnostic accuracy (Web annex C 10.2)

A complementary systematic review and meta-analysis was undertaken to determine the diagnostic accuracy (sensitivity and specificity) of POC HBV DNA assays compared with laboratory-based NAT. Fifteen studies were included, comprising data from 8791 people, of which six studies evaluated Xpert HBV DNA assay and nine other laboratory-based POC assays (HBV-LAMP Assay, Duplex real-time RAA, HBV-MCDA-LFB Assay and Cas12a-DETECTR Assay). Six studies used only plasma, seven used serum or plasma and two used whole blood. Four used fresh samples, and eight used frozen samples. Compared with a laboratory-based

reference standard, the pooled sensitivity and specificity of Xpert were 96% (95% CI: 94–98%) and 98% (95% CI: 90–100%), respectively. The pooled sensitivity and specificity for other POC assays also demonstrated high sensitivity and specificity: 98% (95% CI: 94–99%) and 99% (95% CI: 93–100%), respectively. The certainty of the evidence was rated as moderate to high.

10.3.3 Additional supporting evidence from HIV, HCV and other diseases

WHO recommends using POC molecular assays for the rapid first-step identification of rifampicin-resistant and multidrug-resistant TB and for routine diagnosis of TB *(7)*. In 2021, WHO also recommended using POC RNA assays for early infant diagnosis of HIV and routine viral load monitoring for people living with HIV receiving ART *(9)*. This was based on high-certainty data from RCTs and large well-characterized cohorts showing that POC early infant diagnosis testing was associated with more rapid result delivery time and more rapid ART initiation among infants living with HIV *(4)*. Infants who received POC testing were eight times more likely to start treatment within 60 days of initial sample collection. Similarly, POC HIV RNA testing for viral load monitoring resulted in more rapid return of results to patients and clinicians and time to clinical action for elevated viral load than standard-of-care comparators *(15)*. A recent systematic review of 45 studies of HCV care found that POC testing for HCV RNA was associated with reduced turnaround time from antibody test to treatment initiation and increased uptake of RNA testing and treatment versus laboratory-based RNA testing, especially among marginalized populations with high rates of loss to follow-up, such as people who inject drugs, based on moderate-certainty evidence *(8)*. Despite differences in the care models, this data can be regarded as indirect evidence to support the use of POC viral load platforms for reducing delays between testing and clinical decision-making for treatment initiation.

10.4 Rationale for the recommendations

The Guidelines Development Group recognized the limited access to laboratory-based HBV DNA NAT assays in resource-limited settings because of the high cost and laboratory requirements of these assays and the fact that this represents an important barrier to treatment uptake. The increased availability of these POC platforms for use in HIV and TB care and during the COVID-19 pandemic represents an opportunity for greater access to HBV DNA assays.

The Guidelines Development Group conditionally recommended the use of POC NAT assays as an alternative to laboratory-based NAT assays to measure HBV DNA based on moderate to high certainty of evidence for high diagnostic accuracy (sensitivity (96–98%) and specificity (98–99%)) from a systematic review of 15 studies of POC versus conventional laboratory-based HBV viral load assays

A further systematic review of seven studies found that POC DNA testing was associated with high uptake of viral load (89% (95% CI 55–100%) and of treatment, with 88% (95% CI 66–100%) of those eligible for treatment initiating treatment. The time from testing to return of results to the clinician and to treatment initiation ranged from one to eight days, with fewer health-care facility visits. This was based on very-low-certainty evidence because of serious risk of bias and very serious indirectness (only one study included a non-POC comparison group).

10.4.1 Balance of benefits and harm

Other key benefits of using POC HBV DNA assays include the following.

1. HBV DNA and HCV RNA POC platforms can be decentralized to lower levels of health-care facilities given their relative ease of use and the ability to run single tests.

2. POC NAT assays can potentially be used to expand access both for HBV assessment of eligibility for treatment or for antiviral prophylaxis among pregnant women with high viral load at risk of transmitting hepatitis B to their offspring and for monitoring response to treatment. This may be especially helpful in hard-to-reach settings and communities with poor access to laboratory-based services and NATs or where sample transport systems are lacking.

3. POC NAT molecular platforms are already in use for several other infectious diseases and are recommended by WHO for HIV monitoring and early infant diagnosis *(1-3)* and diagnosis of TB, including drug-resistant TB, and access to HBV DNA and HCV RNA testing can therefore be expanded through existing POC platforms.

4. POC testing may reduce some operational needs (such as phlebotomy, sample transport and central result return systems).

POC HBV testing has no notable harm but presents several challenges.

1. POC platforms have more limited test throughput than laboratory-based platforms. Therefore, depending on daily volumes, health-care facilities may need to set priorities for who should receive POC testing. This is particularly a challenge when POC platforms are used for multiple diseases.

2. There are still few manufacturers of POC HBV NAT assays and therefore limited competition to drive down costs and options for country selection.

3. There are specific requirements of high-temperature incineration for safe waste disposal of guanidinium thiocyanate, which is contained in some assays, including those for Xpert assays.

10.4.2 Acceptability, feasibility and preferences (Web annex D1)

A multicountry online survey of more than 400 people with hepatitis B across 78 countries addressed questions about preferences of where to get tested for hepatitis B and the most important considerations regarding the delivery of hepatitis B testing and treatment at a health-care facility. The main priorities were confidentiality of test results (68%, n = 273), access to knowledgeable staff (56%, n = 223), appropriate counselling (49%, n = 198) and non-stigmatizing approaches (40%, n = 162), minimizing costs associated with the visit (45%, n = 182) and a convenient location for testing and treatment. A total of 50% (n = 199) preferred to start treatment whenever their doctor recommends or on the same day (29%, n = 115). Respondents frequently highlighted the challenges of accessing HBV DNA testing because of cost and availability and the importance of POC NAT assays as an option in open-ended responses.

10.4.3 Equity

POC HBV DNA assays would help to promote equity if used in settings and populations at high risk of loss to follow-up that would benefit from the convenience of POC testing and a rapid decision on treatment or antiviral prophylaxis for HBsAg-positive pregnant mothers, such as in antenatal care settings, in prisons and among people who inject drugs at harm-reduction sites. The introduction of multi-disease testing devices (polyvalent testing platforms) brings additional opportunities for integration that may further expand access and equity and achieve significant system efficiency and cost savings. Countries with existing multi-disease platforms for HIV viral load or TB or those that are planning to introduce them can consider collaboration and integration of HBV DNA testing.

10.4.4 Resource considerations (Web annex C10.3)

A 2022 market landscape report provides a summary of costs and access issues of commercially available hepatitis B diagnostics including HBV DNA assays *(4)* (Web annex D). Countries report varying costs paid in the public sector for an HBV DNA test (both for centralized laboratory based and POC testing), ranging from US$ 9.30 (Rwanda) to US$ 62.00 (Indonesia) (Fig. 10.2). Additional costs that may add a further 30% include freight, customs and distributor fees, procurement and supply chain costs and machine leasing, servicing and maintenance costs *(16)*. The introduction of global access programme pricing ensures that HBV DNA assays are available at a standard base price to select low- and middle-income countries *(4)*. Country programmes with higher volumes and pooled procurement (including with other disease assays) may achieve lower pricing. In the future, increased competition for HBV DNA assays may further decrease prices.

10.4.5 Feasibility (Web annex D4)

A 2023 survey of national hepatitis programme managers based on 41 responses from 33 countries across six WHO regions reported limited access to laboratory-based HBV DNA assays. Access to POC HBV DNA assays was especially limited in sub-Saharan Africa, and about 50% of respondents reported no access to these assays. The main reported barriers to accessing HBV DNA testing services and POC testing were high cost, lack of available POC instruments or only in large urban-based hospitals and lack of HBV DNA cartridges even when POC instruments were available.

There are only two commercially available assays for HBV DNA. POC testing programmes using similar platforms have been successfully deployed in multiple countries for other infections such as HIV early infant diagnosis testing, HIV viral load monitoring, TB diagnosis and HCV diagnosis and test of cure. Therefore, there is potential to consider collaboration and integration of HBV DNA testing using both high-throughput laboratory-based and POC instruments for HIV, HCV, TB and SARS-CoV-2. Existing platforms may expand test menus to include HBV, and future platforms and platform-free products may launch with HBV DNA assays.

10.5 Implementation considerations

- **Use of laboratory-based versus POC NAT testing platforms:** The choice of whether to use POC NAT versus laboratory assays depends on a variety of factors, including cost and ease of use and the characteristics of the testing site, such as storage facilities, infrastructure, level of staff skills and cost. Although POC assays may promote the uptake of viral load testing and turnaround time, there are also many excellent examples of a centralized laboratory-based system being highly effective when supported by efficient sample transport and rapid electronic delivery of results *(1)*.
- **Reflex NAT after a positive serological result:** WHO now recommends reflex HBV DNA testing for people with positive HBsAg as an additional strategy to promote uptake and reduce time to HBV DNA testing and treatment. This can be achieved either through laboratory-based reflex NAT using a sample already held in the laboratory or clinic-based reflex testing in a health facility with immediate sample collection for HBV DNA testing following a positive HBsAg RDT.
- **Multi-disease testing platform and diagnostic integration across programmes:** The introduction of multi-disease testing platforms, using either high-throughput laboratory-based or POC devices, brings additional opportunity for integration that may further expand access and achieve significant system efficiency and cost savings. Countries with existing multi-disease platforms for HIV, TB, HCV and SARS-CoV-2 or those that are planning to introduce them can consider collaboration and optimization of diagnostic networks across programmes *(9)* and integrating platforms across disease areas (HIV, TB, COVID-19 and HCV) can improve the rational utilization of existing capacity and save costs.
- **WHO prequalification:** WHO recently extended the prequalification process to include quantitative HBV DNA, inviting manufacturers to submit applications (see the list of WHO prequalified hepatitis B assays). As suppliers receive WHO prequalification status, this will facilitate expansion of these tests into countries with a high burden of hepatitis B.
- **HBV DNA units:** Serum HBV DNA levels should be expressed in IU/mL to ensure comparability. Values given as copies/mL can be converted to IU/mL by dividing by a factor of 5 to approximate the conversion used in the most commonly used assays (10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL).

POC HBV DNA assay platforms

- Priority settings for placing HBV POC platforms are likely to be more remote locations that lack laboratory infrastructure or sample transport, where testing volumes are low or settings such as antenatal care clinics, especially if a population of pregnant women with a high prevalence of hepatitis B need access to HBV DNA to assess eligibility for antiviral prophylaxis or treatment *(2)*. With low volumes (less than 20 samples a day), a 4-, 8- or 16-cartridge machine with two or three runs per day may be adequate to meet demand.
- The optimal placement of a POC instrument is where testing and treatment are at the same site: Using POC platforms may not achieve expected outcomes if other aspects of the care pathway require travel to another clinic for treatment, with associated transport and other costs. For HCV care, POC assays achieved the best results when they were placed at sites where HCV testing and treatment were available at the same site as a one-stop shop, integrated into existing care, especially for people who inject drugs at harm-reduction sites, among people living with HIV in ART clinics, among prisoners and in primary care. This may be less applicable to hepatitis B care, since many people may meet treatment eligibility without need for an HBV DNA assay.

Operational considerations for using and maintaining POC assays

- POC testing requires strong decentralized systems (such as quality control, platform maintenance, supply chain, trained personnel, adequate maintenance and waste disposal) and should consider patient flow and how to optimize sample collection, sample processing and results return.
- Basic laboratory infrastructure includes a centrifuge, a POC device and laptop, an air-conditioner for temperature control, a room with a door to minimize dust, clinical waste disposal bins and access to a sink with running water for basic laboratory cleaning and managing accidents. If electricity is unstable and interrupted, an online uninterruptible power supply and voltage stabilizer are required.
- Regular internal quality control and quality assurance checks can ensure appropriate use of the POC device and identify errors.
- Personnel training could include laboratory experience or specific skill training required for preparing plasma samples for a POC instrument: centrifuging and pipetting an exact sample amount.
- Annual calibration checks are required for the validity of the device warranty, and he service contract and warranty should include maintenance or replacements.

- Storage and transport: some POC analysers require storage at 2–28°C, stable continuous electricity supply, no direct sunlight and an environment controlled to minimize dust and humidity.
- Transport and disposal: cartridges should be transported similar to storage conditions and disposed of using clinical waste disposal, ensuring that chemicals are not released into the environment (requiring high-temperature incineration if they contain guanidinium thiocyanate).

10.6 Research gaps

- More rigorous studies (ideally comparative RCTs) to assess the use POC platforms for hepatitis B treatment decisions and monitoring. Future studies should fully describe the diagnostic platform and service delivery model, and evaluation should capture effectiveness across the entire continuum of care (beyond treatment-related outcomes). Including costs would enable comparative cost–effectiveness analysis.
- The utility of POC platforms for treatment evaluation and monitoring among adolescents and children should be assessed.
- Evaluation in various settings of multiple-platform technologies for HBV DNA testing alongside other diseases such as TB, HCV and HIV.

11. HBV DNA reflex testing

11.1 Recommendations

New recommendation

Where available, Reflex HBV DNA testing for those testing positive for HBsAg may be used as an additional strategy to promote linkage to care and treatment.

This can be achieved through either laboratory-based reflex HBV DNA testing using a sample already held in the laboratory or clinic-based reflex testing in a health-care facility through immediate sample collection following a positive HBsAg rapid diagnostic test (RDT).

(conditional recommendation, low-certainty evidence)

11.2 Background

A key barrier to hepatitis B treatment following a positive HBsAg test remains lack of access to HBV DNA testing as one of the criteria for treatment eligibility and the need to attend additional visits for collecting blood samples and receiving results *(1-3)*. As a result, many people are not linked to subsequent hepatitis B care and treatment *(4)*. One potential way to promote and accelerate access to HBV DNA testing is by implementing reflex testing. HBV DNA reflex testing is defined as an HBV DNA test that is triggered among all people who have a positive initial HBsAg screening test. Reflex HBV DNA testing may be implemented in two ways: either laboratory-based reflex testing or clinic-based reflex testing.

- **Laboratory-based HBV DNA reflex testing refers to a testing** algorithm with only a single clinical encounter and one blood draw or specimen for an initial laboratory-based HBsAg test that is then sent to the laboratory. If the sample for HBsAg test in the laboratory is positive, then the same existing or a duplicate sample is automatically used for a prompt reflex laboratory-based HBV DNA test. The result returned to the person with hepatitis B and health-care worker is therefore for both the HBsAg test result, and if positive, the HBV DNA result. No further visit or sample collection is required.

- **Clinic-based reflex testing** refers to a testing algorithm with only a single clinical encounter for an initial HBsAg RDT. A finger-stick sample is first taken and tested using a HBsAg RDT that, if positive (usually after a 15-minute wait), is then immediately followed by a reflex second blood sample collection (either venous blood sample or finger-stick) for HBV DNA testing. The second blood sample for HBV DNA testing may either be sent to a laboratory or an on-site POC HBV DNA assay may be used.

Six assays are commercially available: Artus HBV RG RT-PCR Kit/Artus HBV QS-RGQ Kit (Qiagen), Alinity m HBV and RealTime HBV Viral Load Assay (Abbott), AccuPower HBV Quantitative PCR Kit (Bioneer), Cobas HBV Test (Roche) and Aptima HBV Quant Assay (Hologic). Two manufacturers offer HBV DNA for use on near-POC platforms – the Xpert (Cepheid, United States of America) and Truenat HBV (Molbio, India).

11.3 Summary of the evidence (Web annex C 11.1)

A systematic review and meta-analysis evaluated the impact of laboratory or clinic-based reflex DNA testing versus non-reflex approaches on HBV DNA testing uptake, linkage to care, treatment initiation and turnaround times. Eight studies (seven prospective and one retrospective) were included, of which five used laboratory-based reflex and three clinic-based reflex DNA testing. Only one of the five laboratory-based reflex studies and none of the clinic-based reflex studies had a non-reflex comparator group. Five studies were in high-income countries and three were in low- or middle-income countries. Three studies focused on migrants, two on pregnant women, one on the general population and one on hospital outpatients.

Only one study had a direct within-study comparator arm for laboratory-based reflex and non-reflex testing. Sites with reflex HBV laboratory testing had higher rates (100%) of timely HBV DNA testing within 14 days of an initial HBsAg-positive result than sites without reflex HBV laboratory testing (50–55%). Of the five studies using laboratory-based reflex testing, 100% of those with HBsAg-positive test results had HBV DNA testing, and 17% (95% CI: 12–21%) were referred to HBV specialists versus only 55% (95% CI: 40–69%) and 32% (95% CI: 19–46%) in the two studies using laboratory-based non-reflex testing.

The median time from the HBsAg test to reflex sample collection was 0 days, since reflex testing was an immediate one-step testing strategy and a median 105 minutes from HBV DNA testing to results and 40 minutes from results to treatment initiation. The overall turnaround time from being screened HBsAg positive to treatment initiation was three hours and 25 minutes.

All included studies were either cross-sectional or cohort studies, and most were assessed as having a high or moderate risk of bias. The overall certainty of the evidence was rated as low.

11.4 Rationale for the recommendations

The Guidelines Development Group conditionally recommended adopting HBV DNA reflex testing (either laboratory-based or clinic-based) as an additional strategy to promote the uptake of NAT following a positive HBsAg test to promote linkage to care and treatment initiation. This was based on a WHO-commissioned systematic review of eight studies on the impact of reflex HBV viral load testing versus standard non-reflex approaches on DNA level testing rates, initiation of treatment and turnaround times. The proportion of patients who underwent HBV viral load testing was 100% for laboratory-based reflex testing and 96% (95% CI 68–100%) for clinic-based reflex testing. The proportion initiating antiviral therapy was 100% (95% CI 90–100%) for laboratory-based reflex testing and 100% (95% CI 95–100%) for clinic-based reflex testing. In the only study that evaluated non-reflex approaches as a comparison, the proportion undergoing viral load testing was 55% (95% CI 40–69%). The turnaround time between a positive HBsAg test and treatment initiation ranged from 25 minutes to 3 hours. The certainty of evidence was rated as very low because of serious risk of bias and very serious indirectness (only one study included a non-reflex testing comparison group).

11.4.1 Balance of benefits and harm

A systematic review provided low-certainty evidence that HBV DNA reflex testing increased uptake of HBV DNA testing and, to a lesser extent, reduced overall turnaround time to treatment initiation compared with non-reflex testing strategies across diverse settings and populations.

Both laboratory-based and clinic-based reflex testing are also cost saving and feasible to implement and have the potential to be widely adopted, even in resource-limited settings, to promote HBV testing and treatment uptake. Laboratory-based reflex testing also avoids the need for additional venepuncture and blood draws, which is especially relevant for people who inject drugs, who are more likely to have compromised veins *(4)*. No harm was reported for reflex testing.

11.4.2 Values, preferences and acceptability (Web annex D1)

In a multicountry online survey of more than 400 people living with hepatitis B from 78 countries, participants highlighted limited access to HBV DNA testing and routine monitoring of liver enzymes as a key barrier to care and treatment. Both people with hepatitis B and health-care workers requested greater simplicity in care pathways to reduce cost, with reduced clinical or laboratory visits as in reflex viral load testing.

Survey of key public and private laboratories on laboratory-based reflex NAT

Key laboratory networks and referrals, public and private laboratories and national programmes were invited to respond to a web-based survey on their experiences in implementing laboratory-based reflex NAT. Twenty-two laboratories responded to the survey, of which six reported

implementing HBV DNA reflex NAT. The main motivations given for implementing reflex NAT were: improving care and management for people living with hepatitis B; strengthening laboratory capacity; improving the assessment of the burden of hepatitis B among those who have it; and improving the cascade of hepatitis B care. The main challenges with implementation were securing buy-in from administrators and training of clinicians and laboratory staff. The findings of the survey informed the implementation considerations reported in section 11.5 (Web annex D).

11.4.3 Resource considerations

There have been few formal cost comparisons. In a previous survey of key laboratory networks about hepatitis C reflex testing, all respondents reported that reflex testing was cost saving compared with traditional two-step testing as the result of a reduced number of clinic visits and clinician time *(4,5)*. Reflex testing does not require capital investment or increase costs.

11.4.5 Feasibility

There are many examples of implementation of routine laboratory-based reflex viral load testing from high-income countries and especially for hepatitis C. Six laboratories (in Spain, the United Kingdom, Canada and the United States of America) reported specific experience in HBV DNA reflex testing. No capital investment was required to establish reflex testing. The main initial requirements were in developing laboratory standard operating procedures and initial training for laboratory personnel and clinicians. The feasibility of implementing HBV clinic-based reflex testing is largely based on the experience with hepatitis C. The reflex testing or sample collection considerably simplified the care pathway and reduced the need for additional clinic visits and time to NAT and linkage to care. Programmatic experience with hepatitis B clinic-based reflex testing remains limited, but the principles of laboratory reflex testing are not disease specific and require only embedding automatic viral load testing into laboratory protocols or automatic sample collection in clinic settings with a positive HBsAg test result.

11.5 Implementation considerations

11.5.1 Adapting reflex NAT recommendations for various country contexts

Programmatic experience with hepatitis B clinic-based reflex testing is currently limited. Countries in different regions should consider incorporating routine reflex hepatitis C RNA and hepatitis B DNA NAT into their national testing guidelines and infrastructure. The adoption of laboratory-based reflex testing versus clinic-based reflex testing with POC NAT will depend on the current national testing infrastructure, reliance on centralized high-throughput laboratories, the available sample transport network and the location of testing and treatment services.

Although a laboratory-based reflex testing strategy is more appropriate in settings with large testing volumes supported by extensive sample transport networks, clinic-based reflex sample collection for NAT may be a preferred testing algorithm for populations such as pregnant women in antenatal clinics, key populations (people who inject drugs and men who have sex with men) and migrants and refugees who receive health care in community-based settings or in

primary care settings that may have limited access to full-range phlebotomy as well as laboratory services. Instead, clinic-based reflex testing with initial HBsAg RDT followed by reflex sample collection for HBV DNA testing for those antibody positive and then using clinic-based POC NAT testing devices may yield the greatest linkage to care for such populations. A mix of clinic-based and laboratory-based reflex testing strategies may be required to meet the needs of different populations or regions in a country.

11.5.2 Key steps to initiate laboratory-based reflex NAT testing

- Train outpatient clinic phlebotomy and laboratory personnel on new procedures for collecting specimens and processing HBV DNA tests. If the local laboratory reflex testing protocol requires two specimens (to minimize the risk of contamination) and phlebotomists are used to only collecting one specimen for HBV testing, appropriate training and quality assurance systems are needed to sensitize phlebotomists to collecting and labelling two sample tubes.
- Update electronic laboratory order forms for HBsAg and HBV DNA testing to list reflex-only testing options and develop laboratory guidance for HBV DNA reflex testing. Electronic ordering systems are not necessary for reflex testing but can help to streamline the transition to a new clinical process.
- The laboratory process should be designed to preserve specimen integrity and limit risk of cross-contamination. Laboratory managers should assess the risk of cross-contamination for available testing platforms and develop procedures to minimize this risk. Using two tubes to minimize the risk of cross-contamination will require additional commodity, transport and storage costs.
- Planning for additional costs as needed: additional tubes, transport and storage if two tubes are collected for HBsAg and HBV DNA testing.
- Laboratory-based reflex HBV DNA virological testing can be integrated with other strategies, such as clinic-based reflex testing, to meet the needs of different populations.
- Evaluating HBV laboratory-based reflex testing programmes: providing feedback to providers and laboratory managers for quality improvement.

11.6 Research gaps

- Implementation research on optimizing clinical and laboratory workflows for HBV reflex testing and providing fuller descriptions of diagnostic and service delivery models.
- Comparing laboratory-based and clinic-based reflex testing to understand which approaches work best across various populations and settings.

12. Hepatitis D virus (HDV) testing: who to test for HDV infection

12.1 Recommendations

New recommendations

For people with CHB, serological testing for anti-HDV antibodies may be performed for all individuals who are HBsAg positive, as the preferred approach to scale up access to HDV diagnosis and linkage to care.

(conditional recommendation, very-low-certainty evidence)

In settings in which a universal anti-HDV antibody testing approach is not feasible because laboratory capacity or other resources are limited, testing for anti-HDV may be given priority in specific populations of HBsAg-positive individuals, including the following:

- people born in HDV-endemic countries, regions and areas;
- people with advanced liver disease, those receiving hepatitis B treatment and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and
- people considered to have increased risk of HDV infection, including haemodialysis recipients, people living with HCV or HIV infection, people who inject drugs, sex workers and men who have sex with men.

(conditional recommendation, very-low-certainty evidence)

Note: The 2024 recommendations focus on testing and case-finding for HDV infection. WHO recognizes that the HDV treatment landscape is rapidly evolving. Until recently, PEG-IFNα had been the only treatment option for CHD but had poor treatment outcomes, a significant side-effect profile and many contraindications. WHO continues to monitor the outcomes of ongoing HDV treatment trials and will consider formal recommendations on treatment when further evidence becomes available.

12.2 Background

12.2.1 General background

Virology

HDV is a small defective RNA virus that requires HBV for virion packaging, secretion and entry into cells. As a result, HDV can only infect people who are also infected with HBV *(1)*. HDV has eight genotypes and several subgenotypes, with genotype 1 being the most prevalent globally *(2,3)*. Other genotypes are more prevalent in certain regions: for example, genotype 2 in Asia, genotype 3 in South America, genotype 4 in eastern Asia, genotype 5 in western Africa and genotypes 6 to 8 in central Africa *(4)*.

Natural history

There are two main types of HDV infection. Coinfection occurs when a person is infected simultaneously with HBV and HDV and has increased risk of a severe type of acute hepatitis and acute liver failure *(2,5)*. Recovery from this type of HDV infection is usually complete and chronic infection rare. Superinfection occurs among people with established CHB and frequently leads to CHD with an increased risk of rapid progression to cirrhosis and development of HCC *(2,5)*.

CHD is considered to be the most aggressive form of viral hepatitis because of its accelerated progression to liver cirrhosis or liver cancer compared with CHB monoinfection *(2,6)*. Overall, HDV infection is estimated to contribute to one in six cases of cirrhosis and one in five cases of liver cancer among people with CHB globally *(7)*. A large nationwide study of 1112 people with HDV from France found that after three years of follow-up, the prevalence of cirrhosis was 49%, liver decompensation was 24% and HCC 9% and 5% had died; liver-related mortality accounted for 71% of the deaths *(4)*. Another smaller cohort from Europe followed over 6.6 years also reported a high risk of cirrhosis, HCC, hepatic decompensation and mortality *(8)*. Although natural history studies evaluating the predictors of long-term disease outcomes of CHD are very limited, several longitudinal studies have suggested factors associated with disease progression, including male sex, older age, concomitant HIV infection or HCV infection, persistent HDV viraemia, HBV replication, diabetes and obesity *(4,8-11)*.

Infection with HDV is parenterally transmitted. Transmission of HDV can occur by inapparent intrafamilial household transmission, facilitated by poor hygiene and the sharing of hygiene items, such as razors or toothbrushes. Transmission can occur as well in high-risk populations, such as people who inject drugs and people exposed to blood or blood products. Sexual transmission and perinatal transmission of HDV are rare *(12,13,14)*

Global epidemiology

A meta-analysis estimated the global prevalence of total antibodies against HDV (anti-HDV) among people who are HBsAg positive in the general population to be 4.5%, equivalent to about 12 million people (95% CI: 8.7 million–18.7 million) and ranged from 3.0% in Europe to 6.0% in Africa *(7)*. The prevalence among people attending a hepatology clinic was 16% and higher among those with cirrhosis or liver cancer than among asymptomatic HBsAg-positive people *(7)*. The prevalence of anti-HDV is significantly higher among populations at increased risk of bloodborne virus infections, including people who inject drugs, sex workers, men who have sex with men, haemodialysis recipients and people who are hepatitis C or HIV antibody positive versus the general population or asymptomatic HBsAg-positive people, suggesting shared risk factors *(7)*.

The geographical distribution of HDV infection among HBsAg-positive people globally is very heterogeneous, with endemic pockets and high prevalence reported in Mongolia, the Republic of Moldova and countries in western and central Africa, central Asia, eastern Europe, some Pacific Islands and the Amazon Basin (Fig. 12.1) *(7)*, driven by key factors including migration, socioeconomic conditions, timing and coverage of HBV vaccination and differences between HDV genotypes *(10)*. There are limited data on anti-HDV prevalence among adolescents and children. The estimated proportion with detectable HDV RNA among anti-HDV-positive individuals is estimated at 58% *(7)* but higher in hepatology clinic populations and other cohorts with a high anti-HDV prevalence *(2,7)*.

Testing and diagnosis

Diagnosing CHD requires serology to demonstrate exposure (past or current infection) and molecular methods to demonstrate active infection *(2)*. Serological markers for HDV infection include hepatitis D antigen as well as IgM, IgG and total anti-HDV *(2)*. The most commonly used and relevant serological marker to screen for CHD is anti-HDV antibodies (total or IgG) *(2)*. Standard diagnostic serological methods can be used for detecting these markers, including enzyme-linked immunosorbent assays (ELISA) and chemiluminescent immunoassays *(2)*. Detecting the presence of viraemia for diagnosing active HDV infection requires detecting HDV RNA with nucleic acid amplification tests, commonly PCR *(15)*. Quantitative reverse-transcription PCR may be used to quantify viral load to monitor viral response to treatment *(16)*.

Key challenges in diagnosing HDV infection include universally low rates of HDV antibody testing, even in high-income settings *(17–22)*, such that most people living with hepatitis D are unaware of their status. In addition, the clinical performance of HDV RNA assays is suboptimal, especially in detecting African genotypes 5 to 8 *(23)*, which may be addressed by using validated pangenotypic assays. Overall, testing approaches, algorithms and strategies and diagnostics for HDV infection lack standardization *(24)*.

Treatment

Until recently, PEG-IFNα had been used off licence as the only treatment option for CHD *(10)*. However, its use has been limited by poor treatment outcomes, side-effects and contraindications *(2,25)*. Only about 30% of those treated with PEG-IFNα achieve undetectable HDV RNA 24 weeks after treatment ends, and relapse is frequent *(26)*. Nucleos(t)ide analogues used for hepatitis B treatment have shown no benefit in controlling HDV although they are generally used for managing the HBV infection *(2)*. The HDV treatment landscape is now rapidly evolving, with novel agents showing favourable results in Phase 2 and 3 clinical trials *(2)*. Of note, with HDV infection, viral response rates after treatment ends do not strongly predict clinical outcomes or sustained suppression of viral load over time, in contrast to the experience with HBV and HCV treatment *(2)*.

In 2023, bulevirtide received EMA approval for CHD among adults testing positive for HDV RNA with compensated liver disease *(27,28)*. In Phase 2 and 3 trials, bulevirtide was evaluated at different doses (2 mg/day versus 10 mg/day) for 24 or 48 weeks, either in monotherapy or in combination with PEG-IFNα *(2,25,29)*. In a real-world evaluation of treatment outcomes for 2 mg of bulevirtide without additional IFN, HDV RNA declined at least 2 log10 or HDV RNA was undetectable in 76% of cases, with a mean time to viral load response of 23 weeks *(30)*. Treatment was well tolerated, and there were no reports of serious drug-related adverse events *(25,30)*.

12.2.2 Background – who to test?

Understanding the natural history, global epidemiology routes of transmission, risk factors, diagnosis and treatment landscape of HDV infection among people with CHB is critical to inform the development of WHO testing recommendations for HDV infection.

The 2015 CHB guidelines *(31)* highlighted HDV testing as part of the routine initial assessment of HBsAg-positive people before therapy but had no specific recommendations on who to test and what tests to use for HDV infection. Until recently, professional society organizations had provided limited guidance on testing, diagnosis and treatment for HDV *(10,32–34)*. These updated WHO guidelines promote two main approaches: universal HDV antibody testing and focused HDV antibody testing among high-risk groups *(10,32–34)*.

1. **Universal HDV antibody testing:** This approach performs routine HDV antibody testing of everyone with CHB (HBsAg positive), regardless of place of birth, risk behaviour or clinical characteristics. All HBsAg-positive individuals are systematically offered HDV testing services.

2. **Focused (risk-based) HDV antibody testing:** This approach tests specific populations of HBsAg-positive individuals considered at increased risk of HDV infection based on current knowledge of epidemiology, risk factors and clinical characteristics of CHD. These include people born in regions with reported high HDV endemicity, people who inject drugs, men who have sex with men, sex workers, people living with HCV or HIV, haemodialysis recipients, people reporting high-risk sexual behaviour and people with advanced liver disease (cirrhosis or HCC).

12.3. Summary of the evidence

Evidence for the impact and cost-effectiveness of different approaches on who to test for HDV infection is very limited. A narrative review was conducted (Web annex C). No studies were identified that directly evaluated the impact, cost and cost effectiveness of testing approaches for the serological detection of HDV among people with CHB. The overall certainty of evidence was therefore rated as very low.

Very low rates of serological testing for HDV have been reported by several studies in high-income settings *(17–22)*, suggesting that many people living with CHD likely remain undiagnosed through risk-based screening and even in countries in which universal screening of all HBsAg-positive individuals is recommended. A retrospective cohort of CHB participants attending tertiary hospitals in the US between 2016 and 2021 found that only 13% had been screened for HDV *(20)*, and the anti-HDV prevalence was 6%. This demonstrates the poor adoption of a focused (risk-based) approach, since this requires that health-care providers know about factors associated with HDV infection, including high-risk behaviour, and being born in high HDV prevalence countries, to prompt the offer of HDV testing to at-risk individuals *(20,21,35)*.

Two studies demonstrated marked increase in anti-HDV antibody testing uptake and case detection following adoption of laboratory-based universal reflex HDV antibody testing among people positive for HBsAg *(17,36)*. In a before and after study in Spain *(17)*, there was a 13-fold increase in uptake of anti HDV antibody testing (93% (691 of 744) of HBsAg-positive cases were HDV antibody tested versus 7% (114 of 1492) before reflex testing. The absolute number of anti-HDV-positive people diagnosed increased five-fold, but the anti-HDV prevalence was similar before and after reflex testing (10% and 8%, respectively) *(17)*. Similarly, a tertiary hospital in France demonstrated a steady increase in HDV testing rates over time following the implementation of laboratory-based reflex HDV antibody testing (from 85–87% in 2012–2015 to 95–98% in 2019–2022), while the annual frequency of HDV antibody positivity among HBsAg-positive samples tested remained relatively stable (range: 4.4–7.7%) *(36)*.

12.4 Rationale for the recommendations

The Guidelines Development Group made an overall conditional recommendation for a universal HDV antibody testing approach among people living with CHB based on very-low-quality evidence. But also given that implementing this approach may not be feasible because of limited laboratory capacity or other resources, the Guidelines Development Group made a complementary conditional recommendation for testing for anti-HDV to be prioritised in specific HBsAg-positive populations or settings with well-established higher prevalence of HDV infection based on context-specific epidemiological data. This includes 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.

WHO undertook a systematic review on the testing approaches for serological detection of HDV among people with CHB. However, there was a limited evidence base, and no study identified that directly evaluated the outcomes of universal or focused HDV antibody testing approaches. A narrative review of the literature found some evidence that suggested laboratory-based universal reflex HDV antibody testing increased the proportion of patients with CHB who are tested as well as the proportion of patients identified with HDV infection.

The Guidelines Development Group recognized the critical need to expand HDV testing from the current very low uptake, in which most people with CHD remain undiagnosed *(17–22,37)*.

1. CHD is associated with accelerated progression to cirrhosis and increased incidence of HCC *(2,6)* and accounts for much of the morbidity among people with CHB globally (one in six cases of cirrhosis and one in five cases of liver cancer) *(7)*.

2. There is evidence from several countries of poor uptake of testing based on the risk-based approach for case finding and a marked increase in case finding with the adoption of a universal testing approach in which everyone positive for HBsAg is tested for HDV antibody regardless of risk factors. This approach is currently being implemented through a laboratory-based reflex testing strategy, which can be considered a proxy for universal screening of HBsAg-positive individuals in a specific setting or country – defined as an anti-HDV antibody test that is triggered among everyone with a positive initial HBsAg screening test. Reflex testing for HCV RNA for those HCV antibody positive *(38,39)* or HBV DNA for those HBsAg positive (Chapter 13) is a widely adopted strategy to promote the uptake of viral load testing and treatment. The limitation of reflex anti-HDV testing approach is that this can only be applied to laboratory-based testing for HBsAg detection, since the only available anti-HDV antibody tests are laboratory-based.

3. Until recently, treatment options for CHD were limited to PEG-IFNα, with low efficacy and high toxicity, but new treatment options are rapidly evolving and offer the potential for significantly better treatment outcomes *(2)*.

4. In addition to treatment, identifying individuals with HDV infection is crucial for implementing other preventive interventions to prevent onward transmission (including HBV vaccination for sexual partners and household members), linkage to counselling and treatment and enhanced monitoring for early detection of liver cancer.

5. Expanded testing would also improve the availability of high-quality and accurate epidemiological data to improve understanding of the national epidemiology of HDV infection.

12.4.1 Balance of benefits and harm

The Guidelines Development Group acknowledged the absence of direct evidence comparing universal versus focused (risk-based) testing but noted the consistent findings from observational data in several countries highlighting the poor uptake of HDV testing with a risk-based testing approach, and the marked increase in case finding with the adoption of a universal testing approach using laboratory-based reflex testing of anti-HDV antibody for all HBsAg-positive people. Overall, it was considered that the anticipated benefits of a universal HDV testing recommendation (and the poor implementation of a risk-based approach) although uncertain, most likely outweighs the potential harm.

Key benefits of a universal HDV antibody testing approach

1. Universal HDV antibody testing among those HBsAg positive will likely increase testing uptake, case finding and early diagnosis and individuals' knowledge of their HDV status and prognosis, and so facilitate linkage to measures to prevent onward transmission, monitoring for HCC and in the future, treatment options.

2. Novel treatment options are showing promising results in clinical trials and one drug has EMA approval. Identifying people with HDV infection provides an opportunity to establish facility-based patient registries that can be used to promptly link people to optimal care and monitoring, as well as clinical trials or approved effective treatments as they become available.

3. A universal HDV antibody testing approach will help to improve the availability and quality of HDV epidemiological data and surveillance, which will inform national testing strategies and public health responses.

4. A universal HDV antibody testing approach may drive demand for higher-quality diagnostics and competition. New diagnostics may include the development of HDV antibody RDT to facilitate decentralized care and a standardized commercial HDV RNA assay.

Challenges of universal HDV antibody testing

1. A universal HDV antibody testing approach will inevitably cost more initially than a focused (risk-based) testing approach, since many samples will be automatically screened – especially in countries with high hepatitis B prevalence.

2. The implementation of a universal reflex HDV antibody testing approach will be challenging in low- and middle-income country settings where most HBsAg testing is done using RDTs in clinics or in the community, and there is limited laboratory capacity to undertake anti-HDV antibody testing. An alternative approach would be to take an additional sample on receipt of a positive HBsAg rapid diagnostic test result and send to a central laboratory with capacity to perform anti-HDV antibody testing.

3. Implementation of a universal HDV antibody testing approach will require a substantial increase in diagnostics laboratory capacity and resources. This may be challenging in low- and middle-income countries for the near future.

4. Individuals tested for HDV antibody and found to be anti-HDV positive will still require additional HDV RNA testing to assess for active (viraemic) infection and then linkage to care and potentially treatment.

5. The currently limited options for effective and affordable treatment options for HDV infection means that many people identified as positive with both anti-HDV antibody and HDV RNA may not initially receive treatment. This presents an important ethical challenge, and individuals being tested will require thorough pre- and post-test counselling. However, those with a diagnosis of HDV infection will be prioritised for more frequent monitoring including HCC screening.

Risk-based HDV testing approach

The current patchy implementation of a risk-based HDV testing approach has been a key contributor to the overall current low HDV testing and diagnosis rates. This is because for this approach to be effective, health-care providers need to have knowledge of the national and local prevalence of HDV and which groups are at higher risk for HDV infection to guide who should be offered HDV testing *(19,21,35)*. At present, health-care provider knowledge and awareness of HDV epidemiology and which individuals to screen are limited and contribute to the failure to offer screening *(21,35,37)*. This is further compounded by the incomplete data on the global epidemiology and disease burden of HDV infection. Other barriers to HDV testing include lack of awareness and unwillingness of people to report stigmatizing high-risk behaviours (such as injecting drug use and high-risk sexual behaviour), limited access to HDV testing, variable HDV assay diagnostic performance and lack of highly effective and well tolerated HDV treatment options *(2,24,35)*.

12.4.2 Values, preferences and acceptability

No surveys of acceptability, values or preferences specifically on HDV testing among people living with hepatitis D or health-care workers were identified. However, the Guidelines Development Group acknowledged that universal HDV antibody testing does not require specific knowledge of risk factors, and simple and broad education and awareness initiatives among health-care providers and people living with hepatitis B are needed. In addition, individuals living with hepatitis B benefit from knowing their HDV status and being linked to appropriate care and monitoring. Individuals may also value receiving testing without having to disclose high-risk behaviour. Difficulties in accessing services and experiences of stigma and discrimination among populations because of high-risk behaviour such as injecting drug use have been well documented in the HCV and HIV literature *(40,41)*.

In an online WHO commissioned survey of 190 health-care workers, 20% of respondents reported routine anti-HDV testing among HBsAg-positive people in their practice but only 5% in sub-Saharan Africa. The main priorities were confidentiality of test results (68%), access to knowledgeable personnel (56%), appropriate counselling (49%) and non-stigmatizing approaches (40%), minimizing costs associated with the visit (45%) and convenient location for testing and treatment (50%). Concerns regarding confidentiality and potential discrimination highlight the challenges in using a risk-based approach to identify those to give priority for HDV testing, which requires self-disclosure of high-risk behaviour, which many people may be reluctant to do.

12.4.3 Equity

Universal anti-HDV antibody testing of all HBsAg-positive people should promote equity in access to testing across populations and facilities without requiring information about risk group or high-risk behaviour. However, this is contingent on widespread access to HBsAg testing as the basis for universal HDV antibody testing. Those in high-risk groups, especially in low- and middle-income countries, may be less likely to access HBV testing services and therefore also HDV testing.

12.4.4 Cost and cost-effectiveness and access considerations

Although, no formal cost–effectiveness analyses have compared universal versus risk-based screening, universal HDV antibody testing will inevitably require increased resources to test all HBsAg-positive samples for anti-HDV antibody. Existing studies have shown a substantial increase in cases identified *(17,36)*. There remains uncertainty regarding the costs associated with tests and additional service delivery for a universal HDV antibody testing approach, which will vary widely according to the epidemiology, setting and country. There are currently only a few commercially available HDV serology and molecular tests, and competition is low (see section 15.4). The indicative cost from manufacturers for a laboratory-based HDV antibody test is US$ 1.16, and US$ 19.50 to US$ 44.80 for an HDV RNA test. The costs for treatment that will apply to cases identified using either risk-based or universal testing approaches will likely change as new treatment options become available and their associated monitoring requirements.

12.4.5 Feasibility

Several professional society guidelines now recommend a universal HDV testing approach *(10,32)*. In addition, they recommend retesting HBsAg-positive individuals for anti-HDV antibodies whenever clinically indicated, such as in case of aminotransferase flares or acute decompensation of chronic liver disease *(10)*. Laboratory-based reflex anti-HDV testing among people positive for HBsAg has been implemented in multiple hospitals across Europe and elsewhere. These have demonstrated marked increase in anti-HDV antibody testing uptake and case detection *(17,36)* (section 12.3).

13. How to test for HDV infection: testing strategy and choice of serological and NAT assays

13.1 Recommendations

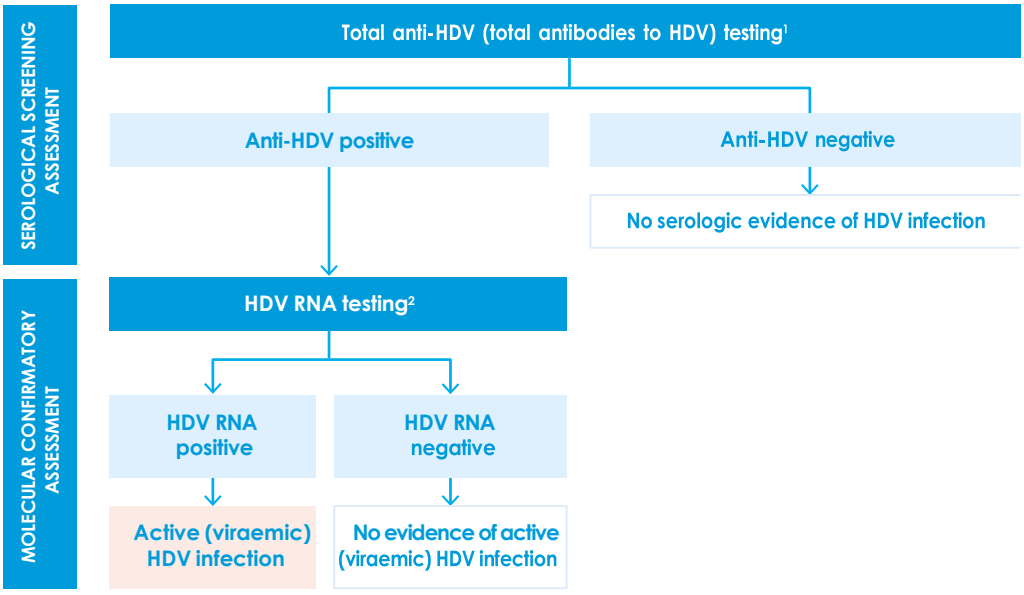
New recommendation

People with CHB (HBsAg positive) may be diagnosed with hepatitis D by using a serological assay to detect total anti-HDV followed by an NAT to detect HDV RNA and active (viraemic) infection among those who are anti-HDV positive. Assays should meet minimum quality, safety and performance standards.[a]

(conditional recommendation, low-certainty evidence)

a The NAT for detecting HDV RNA should be harmonized with the WHO HDV RNA standard and the results reported in IU/mL. The assays should have a limit of detection of 100 IU/mL or better. Primers used in in-house assays should target the ribozyme region, which is the most conserved region of the HDV genome, for genotype inclusivity. HDV genotypes 5–8 and African genotype 1 are suboptimally detected in sub-Saharan Africa.

Figure 13.1 Testing strategy for diagnosing HDV infection among individuals who are HBsAg positive



Abbreviations: HDV: hepatitis D virus; RNA: ribonucleic acid

1 Reflex testing for anti-HDV may be considered for specimens testing hepatitis B surface antigen positive, where feasible.

2 Reflex testing for HDV RNA may be considered for specimens identified as positive anti-HDV, where feasible.

13.2 Background

CHD is diagnosed based on serological assays for anti-HDV antibodies to screen for exposure *(1–3)* and NAT for detecting and quantifying HDV RNA to confirm active (viraemic) infection *(1,3)*. The use of serology for children younger than two years is limited by the transfer of maternally derived placentally transferred antibodies up to this age, resulting in false-positive anti-HDV serology. About 60% of people with anti-HDV antibodies have HDV RNA in serum *(4)*, but this is higher in hepatology clinics and other high-risk populations *(1,4)* that are at high risk of transmitting HDV infection to others.

13.3 Summary of the evidence

13.3.1 Diagnostic accuracy of available HDV diagnostic products (Web annex C 13.1)

Several commercial anti-HDV and molecular PCR assays have received regulatory approval and have demonstrated good diagnostic accuracy. Since recognized reference gold standard assays are lacking and there have been few independent evaluations or details provided on comparator assays, only a narrative summary of the diagnostic performance of the individual commercially available HDV serological and molecular assays is reported. The review identified several serological anti-HDV ELISA and chemiluminescent immunoassays with stringent regulatory authority approval (one ELISA and one chemiluminescence immunoassay with CE marking) (Table 13.1) and molecular HDV RNA assays (five commercial assays identified with CE marking) (Table 13.2). Information on research-use-only anti-HDV and HDV RNA assays was also included. All assays were laboratory based and therefore not currently available for use at decentralized sites or for POC testing.

13.3.2 Diagnostic performance of available serological assays for anti-HDV antibodies

ELISA kits

Several commercially available ELISA kits have shown good reproducibility of results across laboratories *(5)*. A 2012 quality control survey of 24 laboratories, mainly in France, using commercial ELISA kits showed 100% concordance on results against a panel of positive and negative samples from a reference standard *(5)*. Similarly, another commercial ELISA kit showed high diagnostic performance versus two existing commercial assays in a study in Taiwan *(6)*. There was 100% sensitivity in both serum (95% CI: 96.3–100.0%) and plasma; (95% CI: 88.7–100.0%), with specificity of 99.3% (95% CI: 98.4–99.7%) in serum.

Chemiluminescent immunoassays kits

A fully automated and now commercially available chemiluminescent assay had 97.5% concordance with a reference assay among 124 HBsAg-positive serum samples in a study from Italy *(7)*. This offers potential efficiency of using automated, high-throughput chemiluminescent assays for screening for HDV.

RDT (investigational)

Although laboratory-based immunoassay techniques for anti-HDV testing are currently the main screening assay, an investigational in-house, simple lateral flow anti-HDV RDT has demonstrated promising results, with 94.6% (95% CI: 91.6–96.5%) sensitivity and 100% (95% CI: 97.4–100.0%) specificity versus two commercial enzyme immunoassays *(8)*. The assay is not yet commercially available and is being further evaluated.

13.3.3 Diagnostic performance of available nucleic acid assays for HDV RNA (Web annex C 13.1)

Several HDV RNA assays are commercially available, but only five have stringent regulatory authority approval for clinical use (Table 13.2). Most of these are based on assays whose reagents and/or protocols are developed in-house for use in one particular laboratory. There are currently no POC assays for HDV RNA. Diagnostic performance was generally high, but most were not based on independent evaluations (Table 13.2). An evaluation of the performance of an HDV RNA quantification kit against a French National Reference Laboratory in-house assay demonstrated 97.7% sensitivity and 100% specificity *(9)*.

Although HDV RNA assays have been able to consistently quantify HDV genotype 1 in plasma, they underestimate or sometimes fail to detect genotype strains native to the WHO African Region (HDV genotype 1 African strain and African genotypes 5 to 8) *(10)*, as demonstrated in the first international external quality control assessment conducted in 2016 using the WHO international standard for HDV RNA genotype 1 *(11)*. Most of the laboratories that performed well at detecting samples used primers and probes for the well-conserved ribozyme region.

13.4 Rationale for the recommendations

WHO commissioned a review on the diagnostic accuracy of assays for detecting total anti-HDV and HDV RNA. It found that the evaluated anti-HDV assays as well as PCR assays appeared to correlate well with one another. However, interpreting findings was a challenge because of the lack of a fully recognized or standardized gold standard. The certainty of evidence was assessed as being low.

Standardized testing strategies are essential for ensuring high-quality care and optimal use of resources. The Guidelines Development Group recognized that the available evidence suggested that the available commercial anti-HDV and molecular PCR assays have generally demonstrated good diagnostic accuracy and correlate well with one another. The most important limitation remains the lack of well-established gold standard assays validated for accurate diagnosis across various populations and genotypes and the lack of an RDT for anti-HDV antibody.

The overall certainty of evidence was low based on imprecision and the low quality of studies and, for HDV RNA, lack of external and independent validation against a reference standard, except for one developed for HDV genotype 1

13.4.1 Balance of benefits and harm

Serological testing followed by PCR RNA assessment are standard methods for diagnosing HDV infection. Although the data were limited, the reported diagnostic accuracy for anti-HDV and HDV RNA assays was satisfactory. The underlying HDV prevalence for the HBsAg-positive populations tested will also influence the rate of false-positive and false-negative test results among people tested for HDV. All anti-HDV-positive results should be followed by HDV RNA measurement to confirm viraemic infection, which will minimize the implications of false-positive HDV serology. Adequate counselling and education on interpreting test results and linkage to care are important.

13.4.2 Feasibility

A WHO review identified several commercially available options for anti-HDV assays and HDV RNA assays (and additional in-house non-commercial assays). At present, all options are laboratory based, requiring relevant equipment and serum or plasma specimen collection and handling, which means that testing at decentralized sites or in smaller laboratories is not available. ELISA is the most commonly used assay, but chemiluminescence immunoassays offer a faster but more costly process and require using proprietary platforms, which may not be widely available in low- and middle-income countries. HDV RNA commercial manual test kits used with open PCR systems (systems compatible with reagents from different suppliers) are widely available at central laboratories but require appropriate training. Increased test demand is anticipated to expedite assay development on closed PCR systems in the future to expand access.

13.4.3 Resource and cost considerations

The indicative costs reported by manufacturers were US$ 1.13 for anti-HDV ELISA assays and US$ 5.45 for HDV RNA assays, but costs vary widely depending on the setting and country. With only a few tests for HDV serology and HDV RNA currently on the market, competition is low and therefore costs higher.

Table 13.1 Summary of commercially available anti-HDV assays (non-exhaustive list) and reported performance characteristics

Company	Test name	Assay type	Required analyser	Manufacturer-reported sensitivity	Manufacturer-reported specificity	Regulatory approval	Estimated price per test (US$)	Sample types
Dia.Pro Diag-nostic Bi-oprobes (Italy)	HDV Ab ELISA (IFU)	ELISA	ELISA microwell reader with 450-nm (reading), if possible 620–630 nm (blanking) filters	>98%[a]	>98%[a]	CE mark[a]	1.16[a]	Serum, plasma
Diasorin (Italy)	LIAISON XL murex Anti-HDV	chemilumi-nescence immunoassay	LIAISON or LIASON XL	100%[b]	99.35%[b]	CE mark[a]	not available	Serum, plasma
General Biological Corporation (Taiwan, China)	GB HDV Ab (IFU)	ELISA	ELISA microwell reader: dual wavelength 450 nm with 620–690 nm as reference	100%[b]	97.84% (serum); 97.03% (plasma)[b]	TFDA (Taiwan, China), CE mark pending[b]	not available	Serum, plasma

a *Source*: product information based on email communication with the company.

b *Source*: product information based on existing informational materials or instructions for use.

Table 13.2 Summary of commercially available HDV RNA molecular assays (non-exhaustive list) and reported performance characteristics

Company	Test name	Recommended analysers	Genomic target	Reported sensitivity	Reported lower limit of detection	Reported specificity	Regulatory approval	Estimated price per test (US$)	Sample types
RoboGene (Germany)	RoboGene HDV RNA Quantification Kit 2.0 (IFU)	LightCycler 480 (Roche), 7500 Fast (Applied Biosys-tems), or Rotor-Gene 3000/6000/Q (Corbett Re-search/Qiagen)	HDV antigen[a]	95%[a]	6–14 IU/mL[a]	100%[a]	CE mark[a]	not available	Serum, plasma

Table 13.2 Summary of commercially available HDV RNA molecular assays (non-exhaustive list) and reported performance characteristics

Company	Test name	Recommended analysers	Genomic target	Reported sensitivity	Reported lower limit of detection	Reported specificity	Regulatory approval	Estimated price per test (US$)	Sample types
Dia.Pro (Italy)	HDV ONESTEP Quantitation (QT)	7500 Real Time (Applied Biosys-tems), CFX96 RTS (Bio Rad)	HDV antigen[a]	100%[b]	67-86 IU/mL[a]	>99.5%[b]	CE mark[b]	19.52[b]	Serum
Eurobio (France)[a]	EuroBioPlex HDV	m2000sp Abbott Automated extrac-tion System, Nucle-oSpin Dx Virus Kit (MACHEREY-NAGEL), or In-visorb Spin virus RNA mini virus kit (STRATEC Molec-ular)	HDV antigen	97.7%[a]	100 IU/mL[a]	93.4%[a]	CE mark[a]	44.81[c]	Serum, plasma
IONTEK (Austria)[a]	Fluorine HDV QNP 1.0 Real-Time PCR Kit	Fluorion i12, i24/i12 Nucleic Acid Extraction Kit (Iontek) and Fluorion Detection System (Iontek)	HDV antigen[a]	not available	400 IU/mL[a]	100%[b]	CE mark[b]	not available	Serum
Anatolia Geneworks (Türkiye)	Bosphore HDV Quantification / Detection Kit v1 (IFU)	Multiple extraction and amplification devices	HDV antigen[a]	100% (33/33) TBC	45 cp/mL[a]	100%[b]	CE mark[b]	5.00[b]	Serum, plasma

a *Source*: product information based on existing informational materials and product insert.
b *Source*: product information based on email communication with the company.
c *Source*: initial WHO scoping around HDV assays.

14. How to test for HDV: laboratory-based reflex testing

14.1 Recommendations

New recommendation

Reflex testing 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 results, may be used as an additional strategy to promote diagnosis.

(conditional recommendation, low-certainty evidence)

BOX 4.1 Laboratory-based reflex HDV testing

Laboratory-based reflex HDV testing refers to a testing algorithm in which individuals have only a single clinical encounter and one blood draw or specimen for an initial laboratory-based HDV antibody test. If the individual's sample for HBsAg screening in the laboratory is positive, then the same or a duplicate specimen is automatically used for a prompt reflex laboratory-based anti-HDV test. The results returned to the individual and health-care worker are therefore for both the HBsAg result and, if positive, the anti-HDV result. Further reflex testing for the presence of HDV RNA may also be performed at the laboratory level for individuals testing positive for anti-HDV. Currently, reflex testing for anti-HDV can only be implemented through a laboratory-based testing strategy since HDV RDTs are not commercially available to enable clinic-based reflex testing.

14.2 Background

Globally, very few of the people who are HBsAg positive are tested for HDV infection (anti-HDV antibody) and then, if positive, promptly tested for HDV RNA to diagnose viraemic HDV infection *(1–7)*. Similar to HCV and HBV, one potential way to promote the uptake of HDV serological testing and confirmation of HDV RNA viraemic infection is by implementing reflex testing. Some of the potential advantages of HDV reflex serological testing and then NAT are improved outcomes across the cascade of care, with increased uptake and reduced turnaround time to hepatitis D diagnosis, and increased linkage to further clinical assessment and care (Box 14.1).

14.3 Summary of the evidence (Web annex C 14.1)

A WHO-commissioned systematic review and meta-analysis evaluated the effectiveness of laboratory-based reflex anti-HDV testing on uptake of anti-HDV serological testing and then HDV RNA testing for those anti-HDV antibody positive and linkage to care among people who are HBsAg positive. The analysis included 11 studies, three of which had comparator non-reflex arms and two were from low- and middle-income countries (Web annex C 14.1). In 11 studies, the pooled estimate of the proportion of HBsAg-positive individuals undergoing reflex anti-HDV testing was very high at 97% (95% CI: 92–100%) and the anti-HDV prevalence was 6% (95% CI: 4–9%). In eight studies assessing reflex anti-HDV testing and reporting on HDV RNA testing uptake, 98% (95% CI: 77–100%) of those anti-HDV positive had testing for HDV RNA and 32% (95% CI: 17–49%) were diagnosed as HDV RNA positive. 100% (95% CI: 99–100%) of the HDV RNA–positive individuals were linked to care. In the three comparative studies that compared the outcomes of laboratory-based reflex testing versus non-reflex testing (standard of care) arm, the pooled estimate of HBsAg-positive individuals tested for anti-HDV was 45% (95% CI: 0.3–98%) in the non-reflex testing arm, and 8% (95% CI: 4–13%) were positive for anti-HDV antibodies. In one study assessing non-reflex anti-HDV testing and reporting on HDV RNA testing uptake, 100% (95% CI: 40–100%) of those HDV antibody positive were tested for HDV RNA, and 50% (95% CI: 7–93%) were HDV RNA positive.

Using the ROBINS-I tool *(8)*, the risk of bias was assessed as being serious for all outcomes across the cascade of care, and the certainty of evidence was assessed as being low. The lack of a comparator group, selection bias of the samples and lack of adjustment for potential confounders were the most common problems with the included studies.

14.4 Rationale for the recommendations

The Guidelines Development Group conditionally recommended adopting reflex anti-HDV testing (either laboratory-based or clinic-based should an RDT become available) for those HBsAg positive and HDV RNA for those anti-HDV antibody positive. This recommendation was based on low-certainty evidence from a systematic review showing that reflex testing for anti-HDV antibody substantially increased the uptake of HDV serology testing and case finding for people with positive HBsAg test results and the uptake of HDV RNA testing and detection for those anti-HDV antibody positive with linkage to care versus non-reflex testing approaches (Web annex C). Clinic- or laboratory-based HCV RNA and HBV DNA reflex testing for those with positive serology (HCV antibody positive or HBsAg positive) has been demonstrated to markedly increase the uptake of NAT and detection of viraemia and treatment and reduce time to treatment initiation and is now recommended by WHO *(9–11)*.

Reflex anti-HDV antibody testing among people with the presence of HBsAg has been shown to increase uptake of HDV testing and case detection *(1,12)*. Some of the potential advantages of reflex HDV testing are improved outcomes across the cascade of care, with increased uptake and reduced turnaround time to HDV diagnosis and increased linkage to further clinical assessment and care. The practice of reflex testing is becoming increasingly commonly adopted as part of laboratory and clinic protocols for HBV, HDV and HCV testing, especially in high-income countries.

14.4.1 Balance of benefits and harm

Key benefits of reflex anti-HDV and HDV RNA testing

1. Reflex testing for HDV can increase the uptake of anti-HDV antibody and also HDV RNA testing, case finding of cases with viraemic infection and linkage to care compared with non-reflex testing approaches and thus reduce loss to follow-up over the care cascade.

2. Laboratory-based reflex testing for HDV can be cost saving by reducing the number of clinic visits for blood sample collection and follow-up, which will also be more convenient and acceptable for patients and reduce their transport costs.

3. Laboratory-based reflex testing also avoids the need for additional venepuncture and blood draws, which is especially important for people who inject drugs, who are more likely to have compromised veins.

4. The adoption of laboratory-based reflex anti-HDV testing is an essential component of implementing a universal anti-HDV testing approach among all those with a positive HBsAg test result.

Reflex testing had no reported harm or drawbacks.

14.4.2 Values, preferences and acceptability (Web annex D)

A survey assessing HDV testing practices (subcontracting, reflex testing and virological techniques, especially reverse-transcription PCR) across laboratories in France *(13)* showed that 45% of 131 laboratories responding to the survey were using reflex testing for HDV antibody but only 14% for HDV RNA. In addition, 13% and 8% of respondents agreed that the formalization of reflex testing would lead them to become autonomous in conducting anti-HDV and HDV RNA assays, respectively.

In a 2023 WHO-commissioned web-based survey of 26 laboratories experiences implementing laboratory-based HBV and HDV reflex testing, 31% (8 of 26) laboratories performed HDV serology, 12% (n = 3) had implemented reflex HDV serology testing in HBsAg-positive samples, 15% (n = 4) HDV RNA testing and 12% (n = 3) reflex HDV RNA testing in HDV serology–positive samples. Only four of the eight laboratories performing HDV serology also performed HDV RNA testing. Among laboratories conducting HDV RNA testing, most are implementing reflex testing of positive HDV serology samples. The main reasons given for implementing reflex testing were: improving the care and management of people living with HBV and HDV through better retention over the cascade of care; strengthening laboratory capacity; and improving assessment of the burden of HDV among people with CHB. The main challenges with implementation were securing buy-in from administrators, training clinicians and laboratory staff, supplying quality-assured HDV tests and the costs associated with testing.

Individuals may prefer the reduced number of clinic and laboratory visits required to diagnose HDV infection by using a single specimen held in the laboratory, reducing turnaround time to diagnosis and loss to follow-up. Individuals may also prefer having the initial serological screening test and reflex HDV RNA testing at the same place for convenience. A further consideration in favour of reflex HDV testing is that people who inject drugs may prefer a testing strategy that requires only one standard venepuncture.

14.4.3 Equity

Simplifying the diagnostic pathway through HDV reflex testing will increase testing uptake across diverse settings and populations and contribute to increased health equity. This is especially the case if the cost of testing may be paid out of pocket and if used in settings and populations at high risk of loss to follow-up, which benefit from the convenience of a single sample collection approach, such as people who inject drugs.

14.4.4 Feasibility

Reflex HBV DNA and reflex HDV testing is already being implemented in diverse settings globally, both in high-income and low- and middle-income countries. Reflex HDV testing can be incorporated into standard laboratory protocols to increase access to HDV antibody and RNA testing and care, especially in settings with low HBV and high HDV prevalence. Some of the key challenges reported that may limit the feasibility of HDV reflex testing are the need for training laboratory personnel for both reflex and total anti-HDV and reflex HDV RNA testing and access to supply of approved HDV tests. In addition, full-range phlebotomy services may not be

available at community-based organizations or other facilities and will depend on centralized and specialized laboratories.

14.4.5 Resource and cost considerations

Evidence on the costs and resources required for reflex testing is still limited, although one study found that the additional cost per anti-HDV-positive case detected with reflex testing among all HBsAg-positive individuals in Spain would be €124 *(14)*. For reflex testing, there would be potential savings resulting from reduced number of clinic visits and additional specimen collection. Section 14.5 outlines the access and implementation considerations for HDV serological and molecular testing.

14.5 Implementation considerations for HDV testing (who to test and how to test, including reflex testing)

The successful implementation of a universal or risk-based HDV antibody testing approach and testing strategy is underpinned by the following considerations.

1. **Development of HDV testing policy and guidelines.** Countries should develop national testing policy and guidelines that incorporate their selected HDV testing approach and routine reflex HDV antibody testing. These can be integrated into HBV testing guidelines and/or in a stand-alone HDV clinical management guideline.

2. **Procurement and supply of quality-assured assays.** Access to low-cost and well-performing quality-assured HDV serological and molecular assays is critical in ensuring the reliability of HDV diagnosis and the success of HDV testing strategies. Assays should meet minimum quality, safety and performance standards.

3. **Enabling testing environment and enhanced laboratory capacity.** Implementing a universal HDV antibody testing approach, including routine reflex testing, requires expanded laboratory capacity, which may be challenging in resource-limited settings. Testing environments should operate in accordance with quality management systems and have access to qualified, proficient laboratory personnel trained specifically in performing the various assays with adequate and supervisory support. Updating electronic laboratory order forms for HBsAg and HDV serology to list reflex-only testing options should be considered, and laboratory guidance for HDV antibody (and, if possible, HDV RNA) reflex testing should be developed. Planning for additional costs should be considered as needed, such as additional tubes, transport and storage.

4. **Education and training of health-care providers and laboratory personnel.** Implementation of HDV testing will require training clinic phlebotomy and laboratory personnel on new procedures for collecting and processing specimens for anti-HDV serology and HDV RNA. Health-care workers should be able to counsel individuals who are screened and advise appropriate action on the results, both positive and negative.

5. **Assuring accurate diagnosis.** The variability in diagnostic performance of various HDV RNA assays must be considered when performing HDV testing and in clinical practice.

    a. Commercial assays must be performed in accordance with the manufacturer's instructions, and any modification of the original protocols – including in-house protocols – must be further validated against the reference standard.

    b. Potential non-detection or underestimation of HDV RNA levels among populations or individuals with certain genotypes – especially African subgenotype 1 and African genotypes 5 to 8 – must be considered in clinical practice and individuals adequately counselled on their test result and linked to care.

    c. Standardized real-time NATs for HDV RNA are recommended to assure accurate diagnosis of active (viraemic) HDV infection and to monitor antiviral therapy. HDV RNA should be quantified by a reference laboratory using well-standardized validated assays, and the results should be given in IU/mL to improve precision and comparability across laboratory test systems *(15)*.

6. **Counselling and linkage to care.** Individuals must be provided with adequate pre- and post-test counselling and linkage to care, and clinical pathways should be established for individuals diagnosed with HDV infection for linkage to care and treatment and monitoring for liver-disease complications. Additionally, individuals should be counselled on preventing transmission to household members, sexual partners and in the case of people who inject drugs, injecting partners, by promoting preventive interventions, such as HBV vaccination and harm reduction.

7. **Retesting for anti-HDV antibodies for HBsAg-positive individuals.** This should be considered where clinically indicated, such as in cases of aminotransferase flares or acute decompensation of chronic liver disease and for those remaining at risk of infection *(15)*. Evidence also suggests that HDV RNA levels for individuals with HDV infection may fluctuate over time, and this therefore needs to be considered in clinical practice and retesting considered to confirm ongoing active infection or possible clearance of HDV RNA *(16,17)*.

8. **Monitoring and evaluation systems.** Monitoring and evaluating HDV testing approaches (universal and risk-based) and testing strategies (including laboratory-based HDV reflex testing) and providing reports to providers and laboratory managers are essential for improving quality. A database of people with HDV can be established based on simple individual clinical or laboratory records and integrated into HBV national reporting systems to monitor testing, diagnosis and treatment indicators.

14.6 Research gaps for HDV testing (who to test and how to test, including reflex testing)

- The availability of high-quality data is crucial to inform future HDV testing approaches and recommendations. High-quality, well-defined and representative (in terms of population, clinical setting, geographical area and selection method) HDV epidemiological studies need to be undertaken using quality-assured diagnostics. Data are lacking on HDV infection among children, adolescents and pregnant women.
- Cost–effectiveness modelling and feasibility studies of a universal HDV testing approach in low- and middle-income countries with different epidemiological scenarios are needed, especially in countries with both high HBV prevalence and low HDV prevalence or low HBV prevalence and low HDV prevalence.
- The diagnostic performance of HDV serological assays and NATs need to be validated. This should include developing an international reference standard for key genotypes to evaluate HDV assay performance across different genotypes and populations.
- Give priority to developing anti-HDV RDTs to facilitate the decentralization of testing and care, especially in low- and middle-income countries.
- Developing a target product profile for anti-HDV and HDV RNA assays to better align recommended clinical performance thresholds and operational characteristics of assays.
- Developing fully automated NATs that enable more accurate and reliable quantitative HDV RNA detection of all HDV genotypes.
- Impact, cost-effectiveness and feasibility of anti-HDV reflex testing on uptake and linkage to care in different settings and countries with low and high HBV and HDV prevalence.

HBV service delivery and monitoring

15. Approaches to promote delivery of high-quality health services for CHB

15.1 Background

The 2022 integrated global health sector strategies for HIV, viral hepatitis B and C and sexually transmitted infections *(1)* state a goal of eliminating viral hepatitis as a public health problem by 2030. In 2022, WHO estimated that only 13% of the estimated 296 million people with CHB globally had been diagnosed and only 3% treated *(2)*. The coverage rates are even lower in sub-Saharan Africa – one of the regions with the highest burden, where only 4% have been diagnosed and 0.2% treated. Addressing these major testing and treatment gaps and reaching the 90% testing and 80% treatment coverage targets to achieve the elimination goals will require substantially scaling up testing and case-finding and simplifying and decentralizing service delivery to promote uptake of and adherence to long-term antiviral therapy. Until recently, delivery of viral hepatitis B and C testing and treatment in many countries relied on models of specialist-led care in hospital settings. Even when testing was undertaken at the community level, there was often significant attrition because of the requirement for referral to hospital-based specialist care for further assessment and initiation and monitoring long-term antiviral therapy.

Decentralizing HIV treatment services beyond hospital sites to peripheral health facilities and community-based venues was a key factor in successful global scale-up of ART, improving uptake of both testing and treatment and reducing loss to follow-up *(3,4)*. The opportunities for decentralizing HCV care to lower-level facilities have been even greater with the availability of short-course, curative, pangenotypic direct-acting antiviral drug regimens requiring minimal expertise and monitoring. In the 2018 update to the WHO HCV guidelines *(5)*, WHO described eight key good practice principles to simplify service delivery across the continuum of care and support implementation of the "treat all" recommendations. By 2022, the evidence base to support simplified service delivery had increased substantially, and a systematic review of 149 studies *(4)* was undertaken to inform new recommendations in the 2022 updated guidelines on three key interrelated components of HCV simplified service delivery – decentralization of services from specialized centres, integration of hepatitis testing, care and treatment with existing services and task sharing to non-specialist health-care workers *(6)*.

Hepatitis B still has a very limited and inadequate direct evidence base to guide formal recommendations on service delivery. This chapter provides key approaches for delivery of high-quality health services for hepatitis B care applied from similar principles in HCV care *(5,6)* approved in the 2018 and 2022 guidelines. In addition, in recognition of the many similarities between treatment and care for HIV and CHB (for example, lifelong treatment using tenofovir antiviral therapy, importance of high-level adherence to maintain viral load suppression and strategies to trace those lost to follow-up and re-engage in care), this chapter also summarizes

the relevant literature and evidence base and recommendations from HIV for approaches used to promote long-term adherence to ART and retention in HIV care. The collective evidence base was used to inform key approaches for delivering high-quality health services for hepatitis B care (Box 15.1). It is anticipated that these will transition to recommendations as formal comparative studies are undertaken and an evidence base specific to hepatitis B care is established.

Box 15.1 Eight Approaches to promote access and delivery of high-quality health services for CHB

1. **Strategies to promote uptake of testing and strengthen linkage to care, treatment and prevention:** This includes adopting existing recommendations from the 2017 WHO hepatitis testing guidelines *(7)* for using dried blood spots for serological and virological testing; peer and lay health worker support in community-based settings; electronic reminders and clinician prompts for facility-based testing; and providing testing as part of integrated services.

2. **Strategies to promote and sustain adherence to long-term antiviral therapy.** This includes adopting and adapting existing recommended strategies from the 2021 WHO consolidated HIV guidelines *(8)* for using peer counsellors, mobile text reminders, cognitive behavioural therapy, behavioural skills training and medication adherence training.

3. **Strategies to promote retention in care and track and re-engage those disengaged from care.** This includes adopting and adapting existing recommended strategies from 2021 WHO consolidated HIV guidelines *(8)* for using lay adherence counsellors, peer and family support and adherence clubs.

4. **Integrating hepatitis testing, care and treatment with other services** (such as HIV services and primary care) to increase the efficiency and reach of hepatitis services. This includes adopting and adapting existing recommended strategies for integration from the updated 2022 WHO HCV guidelines *(6)*.

5. **Decentralized testing and treatment services at primary health facilities or HIV and ART clinics to promote access to care.** This is facilitated by task-sharing and a differentiated care approach. This includes adopting and adapting existing recommended strategies for decentralization from the updated 2022 WHO HCV guidelines *(6)*.

6. **Task-sharing.** This is supported by training and mentoring health-care workers and peer workers and includes adopting and adapting existing recommended strategies for task-sharing from the updated 2022 WHO HCV guidelines *(6)*.

7. **Differentiated care strategy.** Various care needs need to be assessed with referral to specialists as appropriate for those with complex problems. This includes adopting and adapting existing recommended strategies for differentiated care from the updated 2022 WHO HCV guidelines *(6)*.

8. **Community engagement and peer support.** These promote access to services and linkage to care, which includes addressing stigma and discrimination.

Sources: Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics *(6)* and Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection *(5)*.

15.2 Summary of available evidence

15.2.1 Summary of literature on service delivery models for decentralization and integrated care for hepatitis B (Web annex C15.1)

A systematic review and meta-analysis of models of care for hepatitis B service delivery and care cascade outcomes was undertaken that included 92 studies from 48 countries (59% were from high-income countries) and 482 686 people living with CHB. Most were observational studies (66%), and 18% were non-randomized single-arm interventional studies. The most common service delivery models were hospital-based with specialist-led care (42%), primary or co-managed care (19%) and community screening with linkage to specialist clinics (9%). There were no randomized studies comparing hospital-based care models with decentralized primary care models. Fewer than 5% of the studies evaluated outcomes across the entire cascade of care, and few captured the later steps of the care cascade, especially retention in care and suppression of viral load. The outcome proportions were highly heterogeneous across studies.

Linkage to care

Pooled estimates of linkage to care (assessment of eligibility for treatment following a diagnosis of hepatitis B) were 72% (95% CI 63–80%) for specialist care, 57% (95% CI 47–67%) for primary or co-managed care and 80% (95% CI 54–93%) for community-based testing.

Treatment initiation

Among people eligible for antiviral therapy, the proportion initiating treatment was 77% (95% CI 66–86%) among hospital-based models and highest at large tertiary centres in high-income countries and for research cohorts with dedicated research staff and lower in primary care or co-managed care (60%, 95% CI 50–70%).

Retention in care

For hospital- or specialist-delivered care, pooled retention in care among people receiving antiviral therapy was 84% (95% CI 75–91%) after a median interval of 15 months. Increasing time on antiviral therapy was associated with greater loss to follow-up, and retention in care declined to 66% (40–85%) after 48 months. In a single study of co-managed care (primary and secondary care), retention rates were lower (57%, 95% CI 56–58%). In five studies from specialist centres of people who had not started antiviral therapy, the pooled proportion of retention in care was 42% (95% CI 27–58%) after a median 24 months. Overall, the pooled relative risk for retention in care was 0.58 (95% CI 0.44–0.78) among those not yet receiving antiviral therapy versus those initiating within the same clinic.

Suppression of viral loads

Pooled estimates of suppression of HBV DNA viral loads in 10 studies from specialist centres ranged from 49% to 86% with a pooled estimate of 72% (95% CI 64–79%) after a mean two years of treatment.

Overall, the data were insufficient to robustly compare models of decentralized or integrated care or formally evaluate specific interventions, such as task-sharing. There were also no intervention studies for promoting adherence or retention in care for CHB care. The evidence was not formally graded.

15.2.2 Evidence from HIV literature for decentralization and integrated care, adherence support and retention in care

Decentralization and integrated care

Findings from the HIV literature on decentralized models of care show that ART provides high suppression of viral loads and full decentralization increases uptake of testing and treatment (for example, community-based HIV testing and treatment at lower-level health facilities) versus hospital-delivered care *(3,9–12)*. WHO recommends decentralizing HIV services, integrating HIV testing and ART for people who inject drugs, including opioid substitution therapy programmes *(13–15)*, and integrating HIV care with many other clinical services, such as services for TB, maternal and child health and sexual and reproductive health *(15)*.

ART adherence support

A systematic review and network meta-analysis of 85 randomized trials *(16)* evaluated various interventions to improve adherence to inform the 2016 WHO consolidated HIV guidelines. The review found moderate-certainty evidence that peer counselling improves adherence and HIV viral load suppression. Other interventions found to significantly improve adherence include text messaging and cognitive behavioural therapy. Financial support can also reduce the risk of non-adherence and improve viral suppression *(17–19)*.

Measuring ART adherence

A systematic review of 50 studies *(20)* compared the diagnostic accuracy of different measures of adherence to inform the 2021 WHO consolidated HIV guidelines *(8)*. Overall, the review found that all adherence measures had low sensitivity for identifying people who are non-adherent and had unsuppressed viral loads. For self-reported adherence, asking five or more specific questions as part of the assessment provided higher sensitivity in diagnosing viral non-suppression. Composite adherence measures, such as combining self-reported adherence with pharmacy refill or tablet count, appeared to provide higher sensitivity.

Retention in care

A systematic review of seven studies (one individual randomized controlled trial, one cluster-randomized controlled trial and five cohort studies) *(21)* evaluated community-level interventions to strengthen retention in HIV care. It strongly recommended adopting a package of community-based interventions, adherence support clubs and providing extra care for people at higher risk

(21), despite low-certainty evidence, because of the high degree of acceptability to people living with HIV and the positive outcomes of implementing the interventions for people living with HIV and programmes.

Tracing and re-engagement in care

A systematic review of 37 studies (eight of which included children and adolescents) assessed activities to trace individuals who have disengaged in care and to identify interventions to support re-engagement in care *(22)*. Approaches to tracing included remote communication (phone, text messages, mail and email), in-person tracing or a combination of both approaches. Overall, among those who were still alive, 58% (95% CI 51–65%) re-engaged in care. Tracing and re-engagement action appeared to be more successful when people were traced soon after a missed visit compared with a longer period of disengagement.

15.3 Eight approaches to promote access to and delivery of high-quality health services for people with CHB

The Guidelines Development Group recognized both that the established 2018 approaches for simplified service delivery for HIV and also hepatitis C are applicable to CHB. This section reinforces these same principles and summarizes eight approaches for delivery of high-quality health services for people with CHB. These are intended to support implementation of the main recommendations for expanded hepatitis B treatment eligibility and improve access to effective testing, treatment and care *(5,6)*. There is particular emphasis on strategies to promote long-term adherence and retention in care, since most people with CHB will need lifelong antiviral therapy. These approaches are expected to transition to formal recommendations as comparative studies are undertaken and an evidence base specific to hepatitis B is established.

1. Strategies to promote uptake of testing and strengthen linkage to care, treatment and prevention *(7)*

Multiple factors may hinder the successful uptake of testing and linkage to care, treatment and prevention. These include factors related to the people with CHB (such as mental health problems, substance abuse, misinformation, depression, lack of social or family support and fear of disclosure) and structural or economic factors (such as stigma and discrimination, high cost of care, distance from care sites, transport costs and long waiting times at the facility) *(23)*. Optimizing the impact of effective treatment and prevention will require interventions to both expand the uptake of testing and improve linkage to confirmatory viral load testing and uptake of treatment. This includes adopting existing recommendations from the 2017 WHO guidelines on hepatitis testing *(7)* for using dried blood spots for serological and virological testing; peer and lay health worker support in community-based settings; electronic reminders and clinician prompts for facility-based testing; and providing testing as part of integrated services. Interventions that affect multiple steps along the care continuum will generally be more resource efficient.

Box 15.2 **Key existing recommendations on strategies to enhance uptake of hepatitis testing and linkage to care (from 2017 WHO Guidelines on hepatitis B and C testing *(1)***

The 2017 WHO Guidelines on hepatitis B and C testing recommended that all facility- and community-based hepatitis testing services adopt and implement strategies to enhance uptake of testing and linkage to care *(strong recommendation, moderate quality of evidence) (1)*.

In particular, the following evidence-based interventions should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation *(All conditional recommendations)*:

- trained peer and lay health worker support in community-based settings *(moderate quality of evidence)*;
- clinician reminders to prompt provider-initiated, facility-based hepatitis B serological testing in settings that have electronic records or analogous reminder systems *(very low quality of evidence)*; provision of hepatitis testing as part of integrated services within a single facility, especially mental health/substance use *(very low quality of evidence)*;
- dried blood spot (DBS) specimens for NAT ± serology in some settings *(low/moderate quality of evidence)*.

Other approaches that may be considered to promote linkage include *(1)*

- on-site single rapid diagnostic test (RDT) with same-day results;
- reflex laboratory-based virological NAT of positive serology samples;
- providing assistance with transport if the treatment centre is far from the testing site.

2. Strategies to promote and sustain adherence to long-term antiviral therapy

Suboptimal adherence to antiviral therapy is a major challenge to achieving sustained HBV DNA viral load suppression and the intended impact on disease progression, development of HCC and death. Diverse individual, community and structural factors are associated with poor adherence to ART *(24-26)*, including forgetfulness, a change to daily routine, depression, alcohol and substance misuse and stigma.

An evidence base is lacking for specific adherence support strategies with long-term CHB care. However, the general principles of interventions that have been effective for long-term ART adherence support are also applicable to long-term antiviral support for hepatitis B care and treatment. However, in contrast to HIV, some people with CHB receiving antiviral therapy have long-term low level viraemia despite good adherence, although most will eventually achieve HBV DNA viral load suppression.

Box 15.3 Summary of recommended interventions from HIV care to improve ART adherence and suppression of HIV viral load (from 2021 WHO Guidelines consolidated HIV guidelines *(8)*

The 2021 WHO consolidated HIV guidelines *(8)* recommend the following interventions with demonstrated effectiveness be provided to people receiving ART (strong recommendation, moderate-certainty evidence) to improve adherence and suppression of HIV viral load *(20)* (see subsection 15.2.2):

- peer counsellors (moderate-certainty evidence)
- mobile phone text messages (moderate-certainty evidence)
- reminder devices (moderate-certainty evidence)
- cognitive behavioural therapy (moderate-certainty evidence)
- behavioural skills training and medication adherence training (moderate-certainty evidence)
- fixed-dose combinations and once-daily regimens (moderate-certainty evidence)

3. Strategies to promote retention in care and track and re-engage those disengaged from care

Discontinuation of treatment and loss to follow-up from care is a major challenge for people with CHB in all settings and across populations and undermines programme and patient outcomes. Multiple factors may play a role in disengagement from care, including male sex, lower educational status, poor adherence, nondisclosure, distance from a clinic and lack of understanding of the need for lifelong care. Retention in care after four years on antiviral therapy was 66% (40–85%) for hospital- or specialist-delivered care and 42% (95% CI 27–58%) after two years for those not yet receiving antiviral therapy (Web annex C 15.1).

Although an evidence base for specific strategies to promote retention in long-term CHB care is lacking, the general principles of interventions that have been effective for long-term ART retention support may also be applicable to CHB care and treatment.

Box 15.4 Summary of relevant recommended interventions from HIV care to trace people who have disengaged from HIV care, and interventions to promote retention (from 2021 WHO Guidelines consolidated HIV guidelines *(8)*

For HIV, the 2021 WHO consolidated HIV guidelines *(8)* recommend that programmes implement interventions to trace people who have disengaged from HIV care and provide support for re-engagement *(strong recommendation, low-certainty evidence)*. Tracing activities can successfully re-engage people in care and achieve suppression of viral loads. Tracing and re-engagement actions were generally more successful when people were traced soon after a missed visit compared with a longer period of disengagement.

Approaches to tracing include (see subsection 15.2.2):

- remote communication (phone, text messages, mail and email); and
- in-person tracing and a combination of both approaches.

Approaches to promote retention

The following community-based interventions have demonstrated benefit in improving retention in care and are recommended in the 2021 WHO consolidated HIV guidelines *(8) (strong recommendation based on either very-low-certainty or moderate-certainty evidence)* (see subsection 15.2.2):

- package of community-based interventions (patient advocates, treatment and peer-support interventions providing treatment and psychosocial support in the community) (children: low certaintyevidence; adults: very-low certainty evidence)
- adherence clubs (peer support, distribution of ARV drugs and assessment by non-clinical or lay health-care providers) (moderate certainty evidence).

4. Integrating hepatitis B testing, care and treatment with existing services

The primary purpose of programme collaboration is to create integrated delivery systems that can facilitate access to hepatitis testing and treatment alongside other health services.

There are three main types of potential service integration:

- providing testing for CHB in various settings, such as antenatal clinics, ART clinics, TB clinics and sexually transmitted infection clinics);
- integrating the diagnosis of CHB with existing diagnostic platforms (RDT kits and molecular diagnostic platforms) and laboratory services used for other infections; and
- integrated service delivery of care, prevention and treatment (hepatitis B care at HIV clinics or primary care sites).

Providing testing for CHB in various settings

The primary purpose of integration and programme collaboration is to make HBV, HCV and HIV testing more convenient for people coming to health facilities and thereby expand the reach and uptake of viral hepatitis testing. Integrating hepatitis testing into other health services may facilitate addressing other health needs at the same time, thereby saving time and money. For the health system, integration may reduce duplication of services and improve coordination (such as in managing stocks of diagnostic assays and linking reporting systems).

WHO already recommends integrating HIV testing *(8)* and HCV testing *(6)* into a range of other clinical services, such as services for TB, HIV and ART, maternal and child health, sexual and reproductive health (sexually transmitted infection clinics), harm-reduction programmes and prisons. Integrating HCV and HIV testing is especially important for populations with high-risk behaviour that are at higher risk for all three infections, such as people who inject drugs, men who have sex with men and incarcerated people, who have a high prevalence of HIV, hepatitis C and hepatitis B.

Integrating the diagnosis of hepatitis B with diagnostic platforms and laboratory services used for other infections

Combination integrated multi-disease serological tests

Combination integrated blood- or oral-based multi-disease assays enable integrated testing for HIV, HBV and HCV. Using a single specimen improves the efficiency of testing programmes, especially in populations with a high prevalence of HIV and HCV or HBV and HCV coinfection. Although these assays are not yet fully validated, the preliminary results appear promising *(27)*.

Shared use of HIV or TB multi-disease platforms for HBV DNA testing

Introducing multi-disease testing devices (also called polyvalent testing platforms) brings new opportunities for collaboration and integration and can both increase access and provide significant system efficiency, with cost-savings. Countries with existing multi-disease platforms for HIV viral load or TB testing or those that are planning to introduce them can consider collaborating on and integrating HBV DNA and HCV viral load testing *(28)*. This includes both high-throughput laboratory-based instruments for HIV RNA viral load measurement and POC instruments such as GeneXpert for HIV, TB and COVID-19.

Integrated service delivery of care, prevention and treatment

Increasing access and rapidly scaling up of hepatitis B treatment and care will require significant change in how services are delivered. When possible, hepatitis B services (testing and antiviral therapy) can integrate the public health system. In many cases, this integration extends to primary health care facilities. It makes use of existing HIV or prison health services to increase access, especially for people who inject drugs. Integrating services means not only providing related services at a single setting but also linking reporting systems to share information between settings and providers.

5. Decentralizing services

Decentralizing services means delivering them at peripheral health facilities, community-based venues and locations beyond hospital sites, bringing care nearer to patients' homes. This may reduce transport costs and the waiting time experienced at central hospitals and thereby improve linkage to treatment and follow-up. Most of the evidence to inform simplified approaches such as decentralizing care to primary care facilities and task sharing with nurses, non-specialist doctors and is based on the HIV *(8)* and HCV *(6)* literature. In low- and middle-income countries with a high burden of HIV, decentralizing HIV treatment services was a key factor in successful global scale-up, improving the uptake of both testing and treatment and reducing loss to follow-up. A large systematic review in 2021 showed that testing and treatment at peripheral health facilities improved the uptake of HCV viral load testing and treatment *(4)*. There are now multiple examples of successful models of decentralized viral hepatitis C testing and treatment services, both in primary care for the general population and at harm-reduction sites for people who inject drugs *(4)*. In 2022, WHO recommended delivering HCV testing and treatment at peripheral health or community-based facilities, and ideally at the same site, to increase access to diagnosis, care and treatment *(6)*. These facilities may include primary care, harm-reduction sites, prisons and HIV clinics as well as community-based organizations and outreach services, and HCV testing and treatment should be integrated with existing services at these sites.

In contrast, the delivery of hepatitis B testing and treatment has continued to rely mainly on specialist-led centralized care models in hospital settings. The evidence from the review shows that additional education and training among health-care workers is needed to improve outcomes for hepatitis B care at the primary care level. Decentralizing testing services will require access to quality-assured RDTs or collecting and analysing dried blood spot specimens, good specimen referral networks, enhanced connectivity for return of results and an electronic results system. Decentralized provision of care and treatment will be facilitated by using a simplified algorithm (see the summary algorithm in the executive summary), access to tenofovir, entecavir or dual therapy (tenofovir + lamivudine or emtricitabine) and a programme for training and supervising health-care workers. There are still only a few examples of successful models of decentralized hepatitis B testing and treatment services in countries with a high burden, including Mongolia, Pakistan and Rwanda. Decentralizing services, however, may not always be appropriate for all settings or people with CHB (see approach 7 on differentiated hepatitis B care and treatment), and the relative benefits should be assessed according to the context.

6. Task sharing

Many countries affected by CHB face shortages of trained health-care workers and specialists in managing hepatitis. Task sharing is a pragmatic response to shortages of the health-care workforce to support decentralized care. WHO strongly recommends it in HIV care based on a comprehensive evidence base; it has been widely adopted to expand access to HIV testing and treatment globally *(1,8)* and is now also recommended for HCV care *(6)*. Effective task sharing with non-specialists or nurses requires providing appropriate training at the decentralized site

and access to additional support or referral to tertiary or specialist sites for more complex cases (see Table 15.1). Delivery of hepatitis B testing and treatment has continued to rely mainly on specialist-led centralized care models in hospital settings.

7. Differentiated hepatitis B care and treatment

Differentiated care is defined as a client-centred approach that simplifies and adapts services across the cascade in ways that better serve the needs of those with more complex problems requiring prompt or specialized clinical care but also relieves overburdened hepatitis clinics in central hospitals. Differentiated care is recommended by WHO and widely adopted in HIV treatment and care programmes and now also for HCV programmes *(6)*. Currently, most hepatitis B care and treatment is facility based and not differentiated according to individual needs.

Broadly, three groups of people with hepatitis B with specific needs can be identified. Table 15.1 and Box 15.5 summarizes these three groups, their anticipated care needs, the most appropriate setting to deliver care and the type of health-care provider required.

Box 15.5 Groups of HBV-infected persons with specific needs

1. **Persons clinically well and stable:** this represents the majority of persons diagnosed, and includes those with no evidence of cirrhosis, serious comorbidities, mental health issues or active drug use; and the ability to comprehend issues of long-term adherence and prevention messages.
2. **Persons requiring more intensive clinical support:** this includes persons presenting to care with advanced liver disease, HCC or serious comorbidities, that requires either a more intensive or fast-tracked clinical and care package to manage life-threatening clinical problems and initiate treatment with more intensive monitoring.
3. **Persons requiring more intensive psychosocial/mental health support, or intercultural or language support:** this may include those with mental health issues, with alcohol misuse, or adolescents requiring additional support and counselling. Migrant populations and Indigenous peoples may also require more intensive intercultural or language support.

Most people with CHB will have early-stage liver disease and can be treated at facility level or potentially even in the community. Only a few require more intensive clinical support. However, this will vary considerably according to the epidemic profile of the country and the maturity of the treatment response and diagnosis rate.

Table 15.1 Potential differentiated care needs and approaches to managing CHB

Who? Category of people with hepatitis B	What? Care needs	Where? Site	By whom? Caregiver
Clinically well and stable on treatment. Clinically well and not yet requiring treatment	Standard care package: counselling, adherence support, treatment initiation and monitoring	Facility-based, including primary care or community-based settings, and mobile or outreach	Physician or nurse
Advanced liver disease or serious comorbidities, HCC or previous treatment failure	Requiring more intensive clinical support and follow-up: management of liver-related complications (for example, variceal bleed, ascites, encephalopathy and regular HCC surveillance or treatment)	Facility-based: hospital	Physician
Mental health problems, people who inject drugs or engage in alcohol misuse, adolescents and migrants	Requiring more intensive psychosocial or mental health support or intercutural and language support	Can be facility-based or community-based, harm-reduction site	Physician and counsellor or peer support

8. Community engagement and peer support, including addressing stigma and discrimination in the general population

Peer-led interventions have been effective in increasing access, care and treatment and supporting adherence to treatment for both hepatitis B and C and other infectious diseases such as HIV and TB *(15,29)*. In addition to providing services, peers can act as role models and offer non-judgemental support that may contribute to reducing stigma and improving the acceptability of services.

15.4 Research gaps

More methodologically rigorous studies are needed to compare packages of different service delivery models and interventions, focusing on different steps in the care cascade, especially in low- and middle-income countries. Studies should fully describe the service delivery model, and evaluation should capture the effectiveness of different interventions across the entire continuum of care, including uptake of HBV testing, linking to assessment, initiating treatment and retention in care.

These should include the following.

- Evaluation of interventions already well established for use in HIV care for adapting to hepatitis B care settings and the general population in various settings. These include strategies to promote and sustain adherence to long-term antiviral therapy (such as peer counsellors, mobile text reminders, cognitive behavioural therapy, behavioural skills training and medication adherence training); strategies to promote retention in care and track and re-engage those disengaged from care, including those not yet receiving treatment (such as lay counsellors and peer and family support).
- Evaluation of various models of decentralized testing and treatment services in primary care clinics or HIV clinics to promote access to care; various models of integrating hepatitis testing, care and treatment with other services (such as HIV services and primary care); task sharing of activities by different cadres of health-care workers and peer workers, supported by training and mentoring programmes; and a range of differentiated assessment, care and referral strategies in various settings.
- Further evaluation of already recommended strategies to promote the uptake of testing and strengthen linkage to care, treatment and prevention in various settings and populations (such as dried blood spots for serological and virological testing; peer and lay health worker support in community-based settings; and electronic reminders and clinician prompts for facility-based testing).
- Costing and cost–effectiveness data for decentralized and integrated models of care should be collected to enable comparative analysis.

16. Monitoring for treatment response among people with CHB receiving treatment or not yet receiving treatment

16.1 Recommendations

Existing and maintained recommendations from the 2015 hepatitis B guidelines

Monitoring for people receiving treatment

For people receiving treatment, the following are recommended to be monitored at least annually:

- non-invasive tests (APRI score or transient elastography) to assess stage of disease and progression of fibrosis or cirrhosis; and
- ALT levels[a] (and AST for APRI), HBV DNA levels (when HBV DNA testing is available), HBsAg[b] and HBeAg/anti-HBe.[c]
- Treatment adherence should be monitored regularly and at each visit.

(strong recommendation, moderate-certainty evidence)

More frequent on-treatment monitoring (every 3–6 months for the first year) may be performed for: people with more advanced disease (compensated or decompensated cirrhosis[d]); during the first year of treatment to assess treatment response and adherence; if treatment adherence is a concern; for people coinfected with HIV; and for people with renal impairment.

(conditional recommendation, very-low-certainty evidence)

Monitoring for people not yet receiving treatment

People who do not currently meet the criteria for antiviral therapy (persistently normal serum aminotransferase results and HBV DNA levels below 2000 IU/mL (when HBV DNA testing is available) or who have expressed a desire to defer treatment may be monitored annually for disease progression and ALT and HBV DNA levels (when HBV DNA testing is available).

(conditional recommendation, low-certainty evidence)

a ALT levels fluctuate among people with CHB, and longitudinal monitoring is required to determine the trend. The ULN for ALT has been defined as below 30 U/L for men and boys and 19 U/L for women and girls. For people not yet on treatment: persistently abnormal or normal may be defined as two ALT determinations above or below the ULN at unspecified intervals during a 6- to 12-month period or predefined intervals during a 12-month period.

b Among people receiving treatment, monitor for HBsAg loss (although this occurs rarely) and for seroreversion to HBsAg positivity after discontinuing treatment. Quantitative HBsAg, if available, can be used to determine whether HBsAg concentrations are declining.

c Monitoring of HBeAg and anti-HBe mainly applies to those who are initially HBeAg positive. However, those who have already achieved HBeAg seroconversion and are HBeAg negative and anti-HBe positive may subsequently serorevert.

d Decompensated cirrhosis is defined by the development of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease or cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

Box 16.1 Goals of monitoring

Among people receiving treatment

The aim of monitoring people receiving treatment is to evaluate the effectiveness of treatment response, treatment adherence, adverse effects of treatment, progression of liver disease and development of HCC. HBV DNA testing is important for monitoring treatment response, even when HBV DNA measurement was not part of initial assessment for treatment eligibility. Very rarely it can indicate the potential for ending treatment. If antiviral therapy is discontinued, liver function should be monitored closely, since severe acute exacerbations of hepatitis have been reported, and antiviral therapy may need to be resumed.

Among people who do not meet the criteria for antiviral therapy or want to defer therapy

The aim of monitoring in people not on antiviral therapy is to identify an early change in clinical status (levels of HBV DNA or serum ALT or increasing APRI or transient elastography score) that indicates a risk of progressive liver disease and need for antiviral therapy, but before advanced hepatic fibrosis or cirrhosis develops.

16.2 Background

CHB is a dynamic disease that requires monitoring before and during antiviral therapy for treatment response and side-effects, disease progression, advancing fibrosis and development of HCC. Before treatment, the goal of monitoring is to assess treatment eligibility *(1)*. Even in high-income countries, many people are not receiving the requisite monitoring and testing *(2-8)*. For the people who may not meet the criteria for treatment or who express a preference to defer treatment, identifying changing patterns that indicate either improvement or progression of disease is critical. This can be ascertained by longitudinal monitoring of serum aminotransferases and HBV DNA levels as well as serological markers, especially HBeAg, anti-HBe and, in some cases, quantitative HBsAg concentrations.

Fluctuating or persistently abnormal serum ALT and HBV DNA levels >2000 IU/mL can indicate progressive disease and the need for treatment. Conversely, spontaneous improvement may occur with a decline in HBV replication, with normalization of ALT levels and seroconversion from HBeAg-positive to anti-HBe. Continued monitoring during treatment (regardless of whether ETV, TDF or TAF is used) is also required to evaluate the effectiveness of treatment response, treatment adherence and potential adverse effects *(9,10)*. The optimal timing and frequency of monitoring of serological markers (HBeAg and anti-HBe, serum ALT and HBV DNA) to ascertain alterations in disease patterns before treatment and to assess treatment response are not well established, since the evidence base is limited, but most guidelines and reviews suggest six-monthly testing or at least annual monitoring *(10)*. Chapter 18 addresses the exceptional criteria for both stopping nucleos(t)ide analogue therapy and for retreatment, since relapse is common. The decision to stop any nucleos(t)ide analogue therapy must be weighed carefully. Continued monitoring after treatment ends among the few meeting the criteria for stopping is also required to monitor for reactivation and to restart treatment early if required *(9,10)*.

The lack of access to HBV DNA testing in many low- and middle-income countries compromises appropriate assessment and monitoring of disease before and during treatment and in the occasional cases when treatment ends. Newer biomarkers such as HBV RNA and HBcrAg may provide additional predictive profiles at different stages of CHB and endpoints, such as during antiviral therapy, when HBV DNA is not detected *(11,12)*, but these biomarkers not yet widely available *(13,14)*. High-sensitivity quantitative HBsAg may also be used as an alternative to HBV DNA measurement for monitoring *(15)*. Measuring liver stiffness for those with persistently normal or minimally elevated ALT can identify fibrosis progression *(16)*. People with CHB also require surveillance monitoring for the development of HCC (see Chapter 18).

16.3 Summary of the evidence review for the 2015 hepatitis B guidelines

For the 2015 hepatitis B guidelines *(17)*, evidence was reviewed to determine the optimal timing and frequency of monitoring for treatment response among those receiving treatment, and for disease progression among those not yet receiving antiviral therapy and to detect relapse after treatment ends. No studies were identified that had directly compared monitoring approaches or frequency of monitoring to assess disease progression or treatment response. The evidence summary was therefore based on indirect evidence from cohort studies that had examined disease progression and predictors of future reactivation among people not yet receiving treatment *(18,19)*. In addition, four systematic reviews *(20–23)*, two clinical trials *(24,25)* and three retrospective observational studies *(26–28)* assessed outcomes at different times before or during the course of antiviral therapy. No new evidence was identified in 2023 that would further inform or change monitoring approaches and frequency during treatment. Most guidelines advise six-monthly testing or at least annual monitoring *(10)*.

16.3.1 Monitoring on antiviral therapy

The evidence from the previous 2015 review suggests that about 80% of HBeAg-positive people (and 50–70% of HBeAg-negative people) achieved treatment response (both undetectable levels of HBV DNA and normalized ALT levels) with potent nucleos(t)ide analogues (ETV and TDF) by week 48 of treatment, even people with decompensated cirrhosis *(20–23)*. Chapter 6 summarizes more recent data on treatment responses to nucleos(t)ide analogues, including studies with dual TDF + FTC or 3TC regimens or TAF. However, the findings are based on monitoring regimens during Phase 3 trials and may not reflect routine clinical practice or be feasible in low- and middle-income countries, where HBV DNA monitoring is not widely available. Monitoring treatment with PEG-IFN is demanding but not covered in these guidelines *(29,30)*.

16.3.2 Monitoring among those who do not meet treatment criteria

Studies to investigate the monitoring of ALT levels among those who have HBeAg-negative CHB (formerly known as "inactive carriers") to predict future ALT flares or elevation *(31)* suggest that a minimum period of monitoring of three months would identify about 90% of people with flares, but the evidence did not consider people lost to follow-up. Less than 3% of those with an HBV DNA level of less than 2000 IU/mL had elevated ALT at six or 12 months. However, definitions of normal serum ALT are highly heterogeneous (see Chapter 5) *(32)*.

16.3.3 Monitoring after antiviral therapy ends

The observational studies provided very limited evidence on the frequency of monitoring for reactivation, and the evidence was therefore rated as low or very low quality because of both indirectness (no study directly investigated different frequencies of monitoring) and imprecision because of few events or risk of bias. A rise in HBV DNA typically precedes the increase in ALT, in this setting, and a rise to 10 000 to 100 000 IU/mL would prompt rapid reinstitution of nucleos(t)ide analogue therapy to avoid a severe flare. People who stop TDF therapy may experience a rise in serum aminotransferases earlier than those who stop ETV *(33)*. Newer biomarkers such as HBV RNA and HBcrAg can predict the severity of relapse but are not widely available *(13,14)* (see Chapter 17).

16.4 Rationale for the recommendations

16.4.1 Balance of benefits and harm

Monitoring people who do not yet meet the criteria for antiviral therapy

Among people who do not meet the criteria for antiviral therapy or who want to defer therapy (see Chapter 5), the aim of periodic monitoring is to enable ongoing assessment of disease stability and to detect early progression to active disease. Lack of monitoring may result in undetected progression to end-stage liver disease and associated complications that might have been prevented with early detection of progressive disease and timely antiviral therapy.

The Guidelines Development Group recognized that the evidence base to guide the optimal frequency of monitoring to track alterations in disease patterns is limited. The frequency of monitoring needs to be appropriate to the stage of disease (and estimated rate of progression) and frequent enough to detect evidence of significant progression and any transient flares in ALT requiring treatment but not result in overinterpreting any fluctuation in serum ALT, especially in the absence of concomitant measurement of HBV DNA levels, which may be rising or falling or may not be measurable in some regions.

Although measuring both serum aminotransferase levels and HBV DNA level are key measures, monitoring HBeAg may be helpful in some situations (indicating the presence of active HBV replication and high infectivity, and spontaneous improvement may occur following HBeAg to anti-HBe seroconversion in association with a decline in HBV replication and normalization of ALT levels, which confers a good prognosis).

In the future, newer biomarkers such as HBcrAg and HBV RNA may add precision to the assessment of anti-HBe positive people when these become available. HBV genotyping and resistance testing are not required to guide or monitor therapy.

The Guidelines Development Group therefore recommended at least annual monitoring of non-invasive tests, serum ALT and HBV DNA levels and also HBeAg and anti-HBe for people not receiving treatment to determine any persistent abnormality in ALT, to quantify HBV DNA levels (based on the thresholds of raised HBV DNA and ALT levels specifying a subsequent risk of disease progression) and to monitor fibrosis progression based on non-invasive testing (see Chapter 4). More frequent monitoring was recommended conditionally, based on limited evidence for those who already have fluctuating elevated ALT or HBV DNA levels (≥2000 IU/mL), since this indicates a higher risk of progression and need for treatment.

Monitoring people receiving antiviral therapy

People receiving treatment (whether ETV, TDF, TDF + FTC or 3TC or TAF) need to be monitored to assess the effectiveness of treatment response (based on sustained viral suppression if HBV DNA level can be measured), treatment adherence and potential adverse effects and to check for evidence of progression of liver disease. Monitoring can also identify reactivation early after treatment ends and the need to restart treatment *(10)*. In the future, newer markers such as a sensitive test for HBcrAg could be adapted for POC use to monitor hepatitis B when HBV DNA testing is not available *(34)*.

Data from multiple clinical trials show that potent nucleos(t)ide analogues with a high genetic barrier to resistance (TDF, ETV and TAF) suppress HBV DNA replication to low or undetectable levels for most people by 24–48 weeks of treatment, with low rates of resistance (but with limited success in achieving loss of HBeAg for HBeAg-positive people or loss of HBsAg). Although the minimum and optimal frequency for monitoring treatment response during therapy has not been directly evaluated in clinical trials, these data suggest that, if good adherence can be confirmed, monitoring can be relatively infrequent.

The Guidelines Development Group therefore recommended at least annual monitoring of ALT, HBeAg (for seroconversion to anti-HBe) and preferably HBV DNA levels and also non-invasive tests such as APRI to assess improvement for those receiving treatment or progression. For people receiving antiviral therapy, a decrease in liver stiffness measurements may reflect the remission of liver inflammation, and to a degree, improvement of fibrosis *(35)*.

More frequent and careful monitoring was recommended conditionally based on limited evidence for the following groups: those with more advanced disease (compensated or decompensated cirrhosis or advanced fibrosis), because treatment reduces but does not eliminate the risk of HCC and because of their higher risk of adverse events; during the first year of treatment to assess treatment response; when adherence to therapy is a concern; for people with impaired renal function or bone mineral disease; and after discontinuation of therapy. The Guidelines Development Group noted that overly infrequent monitoring risks loss to follow-up, or treatment interruption. Monitoring adherence is especially important in resource-limited settings if HBV DNA levels cannot be measured during treatment (see Box 6.2). Chapter 17 summarizes approaches to monitoring side-effects during treatment.

Monitoring after stopping antiviral therapy (see Chapter 19)

The decision to stop any nucleos(t)ide analogue therapy must be weighed carefully *(36)*. Frequent close monitoring is required in the first year. Although the evidence base for monitoring is very limited, ALT and HBV DNA can be measured monthly for the first three months and then every three months during the first year to detect severe exacerbations. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase or HBV DNA becomes detectable again). Biochemical relapse has been variously defined but includes an ALT elevation to >2 times the ULN. A hepatitis flare has been defined as an ALT elevation >5 times the ULN, and severe hepatitis flare has been defined as ALT level >1000 U/L or ALT <1000 U/L plus a total bilirubin ≥3.5 mg/dL or an international normalized ratio ≥1.5. Viral relapse has been defined as HBV DNA >2000 IU/mL. Quantitative HBsAg at the end of treatment predicts HBsAg loss or relapse after nucleos(t)ide analogues are stopped, with lower levels predicting relapse for Asian versus Caucasian people.

16.5 Implementation considerations

Monitoring of adherence and completeness of HBV DNA suppression requires periodically measuring HBV DNA levels. There are cost implications to regular ALT and HBV DNA monitoring for those receiving treatment or who do not yet meet criteria for treatment.

- The introduction of multi-disease testing platforms, both high-throughput laboratory-based and POC devices, represents an additional opportunity for integration that may further expand access and achieve significant system efficiency and cost savings.
- There is potential for adopting differentiated care models with primary or community care and nurse-led services for people with stable disease receiving treatment and specialist referral and care for people with advanced disease and cirrhosis.
- Additional training of health-care workers will be required for interpreting laboratory results and decision-making, especially when non-specialist physicians or nurses provide care and follow-up (see Chapter 15).

17. Monitoring the safety of nucleos(t)ide analogues

17.1 Recommendations

Existing and maintained recommendations from the 2015 hepatitis B guidelines

- Before initiating antviral therapy, people's baseline risk for renal dysfunction[a] may be assessed and baseline renal function[b] measured.
- People receiving long-term tenofovir disoproxil fumarate therapy may be monitored annually for renal function and children's growth monitored carefully.

(conditional recommendation, very-low-certainty evidence

Note: In the 2021 WHO consolidated HIV guidelines *(1)*, baseline measurement of creatinine is not required before initiating ART for people living with HIV with the preferred tenofovir-based regimen.

a Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age >60 years, body mass index (BMI) <18.5 kg/m^2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV and solid organ transplantation.

b Measurement of baseline renal function includes: serum creatinine levels and calculation of CrCl/estimated glomerular filtration rate (eGFR) using the MDRD formula.

MDRD formula: eGFR = 175 × (serum Cr)$^{-1.154}$ × (age)$^{-0.203}$ × 1.212 if the person is Black) × 0.742 (if the person is female).

Table 17.1 Recommended dosage for adults with renal impairment and decompensated cirrhosis and recommended dose reduction or dosing interval

Drug	CrCl (mL/min)[a]			
	>50	30–49	10–29	<10 Haemodialysis or continuous ambulatory peritoneal dialysis
TDF[b,c]	One 300-mg tablet every 24 hours (7.5 scoops of	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 seven 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)
ETV[d]	0.5 mg once daily	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
ETV (decom-pensated 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
TAF	25 mg orally once a day	25 mg orally once a day	25 mg orally once a day CrCl at least 15 mL/min: no adjustment recommended. 25 mg once daily	CrCl less than 15 mL/ min) not receiving chronic haemodialysis: not recommended.

a Calculated using lean body weight.

b Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

c TDF is also available in a granule formulation (33 mg/g in a 60-g pack) for ease of swallowing. Dosing is the same for oral granules and tablets.

d For ETV doses less than 0.5 mg, oral solution is recommended. ETV is not recommended for those with 3TC resistance.

17.2 Background

Box 17.1 Assessing and monitoring renal function

1. For people initiating treatment with an estimated CrCl or glomerular filtration rate (eGFR) <50 mL/min or with risk factors for renal dysfunction, including older age, long-term diabetes, uncontrolled hypertension or severe osteopaenia or osteoporosis, consider either using ETV instead or avoiding TDF or reducing the dose of TDF (guided by Table 17.1).

2. Use of TDF should be avoided with concurrent nephrotoxic drugs (such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, vancomycin and cidofovir) because of the increased risk of reducing renal function.

3. Monitoring renal function during nucleos(t)ide analogue therapy may include: urine dipsticks for proteinuria and glycosuria (in the absence of diabetes or if blood glucose is well controlled), serum creatinine, estimated eGFR decline, serum phosphate, urine protein-to-creatinine ratio (or fractional excretion of phosphate, if available) as well as growth of children receiving TDF. For individuals with normal renal function, a minimum monitoring package could include annual urine dipstick testing and creatinine measurement for eGFR if possible.

4. The frequency of renal monitoring during nucleos(t)ide analogue therapy depends on the presence of risk factors for renal dysfunction and should be more frequent among people at higher risk.

    a. People at high risk of renal toxicity: every six months unless there is evidence of worsening. Closer renal monitoring is advisable among people with CrCl <50 mL/min.

    b. People at low risk of renal toxicity: either no routine monitoring of renal function or every 12 months unless there is evidence of worsening.

5. During treatment, if the CrCl falls below 50 ml/min or in case of progressive decline of renal function, consider adjusting the dosing interval of TDF or switching to ETV or TAF (guided by Table 17.1) and closely monitoring renal function.

6. If low bone mineral density is detected or suspected because of a fracture, then appropriate consultation should be obtained, with a switch from TDF to ETV or TAF.

The nucleos(t)ide analogues TDF, ETV and TDF are the preferred options for antiviral therapy for people with CHB, with ETV or TAF recommended for people with established osteoporosis and/or impaired kidney function and also TAF in adolescents for those 12 years or older, and ETV in children for those 2 years or older (see Chapter 6).

TDF is mainly eliminated via the kidney and has a side-effect profile characterized by proximal tubular cell dysfunction. The range of severity is from mild renal tubular dysfunction and hypophosphataemia with subclinical decline in renal function to classical Fanconi syndrome and impaired glomerular filtration *(2–5)*. Small decreases in bone mineral density with osteopaenia or osteoporosis during the early phases of treatment have also been reported *(6–9)* and, more rarely, lactic acidosis or severe hepatomegaly with steatosis. Known risk factors for developing TDF-induced nephrotoxicity include underlying renal dysfunction, low CD4 count for people living with HIV and low body weight and comorbid hypertension, diabetes, HIV-associated kidney disease, hepatitis B or C coinfection and TDF in combination with a ritonavir-boosted protease inhibitor. Management of these comorbid conditions should be given priority *(10–12)*. Genetic variability within the MRP7 gene may influence renal tubular transport of TDF and contribute to the development of toxicity *(13)*. Although tubular dysfunction is reversible in most cases after withdrawal of TDF, persistent renal dysfunction has been reported *(5,14)*.

ETV is also mainly eliminated via the kidney, but proximal tubular dysfunction is less common. In addition to the effects of antiviral therapy, hepatitis B may also affect renal function *(15,16)*. TAF is a prodrug of TDF with reduced systemic exposure and improved safety. TAF has been shown to reduce how the antiviral drug affects proximal renal function because of the much lower plasma concentration of tenofovir. Numerous clinical trials have demonstrated that TAF affects renal function and structural bone integrity less strongly than TDF while suppression of viral load is maintained *(17–21)*. ETV may be associated with a higher risk of renal function decline than observed for TAF *(22)*. However, TAF may also result in weight gain and an increase in BMI *(23)*. Because of the overall improved renal safety of TAF, it is preferred to other nucleos(t)ide analogues for people at risk of bone or renal complications, older people and people with evidence of impaired renal function *(24)*.

17.3 Summary of the evidence

An initial evidence review was undertaken for the 2015 hepatitis B guidelines to assess the optimal type and frequency of monitoring for toxicity among adults, adolescents and children receiving TDF or ETV treatment for CHB *(25)*. No studies had compared monitoring strategies for people receiving TDF, such as routine toxicity monitoring versus no monitoring or targeted monitoring in case of perceived clinical need. The original 2015 review focused on the long-term adverse renal effects related to TDF and ETV for both nucleos(t)ide-naive and -experienced people. There have been no key new data and therefore no changes to the existing monitoring recommendations. However, several recent systematic reviews have further informed the safety of TAF versus TDF *(24)* (see Chapter 7 and Web annex C 6.1).

The review included eight studies of adults who had received TDF treatment, with two including people with both hepatitis B and HIV, and four studies among those who had received ETV *(10,26–32)*. Since the data came from non-controlled observational studies, the certainty of evidence was rated very low. Several prospective studies have also reported renal function at between two and five years of TDF treatment *(16,27,29)*. Overall, a higher percentage (9%) of people with CHB had an increase in serum creatinine (usually defined as >0.5 mg/dL) during the first year of treatment, but this was lower over longer periods of follow-up: 0.8% in the second year and 0% at three years. At five years of follow-up, 1% or less of individuals had either a serum creatinine level above baseline values or a decrease in CrCl or serum phosphate *(29)*. For people with decompensated liver disease, 9% of those treated with TDF for 48 weeks had an increase in serum creatinine concentrations, but treatment discontinuation was rare *(30)*. The long-term (3–5 years) effectiveness studies of ETV had limited reporting of adverse outcomes *(33–39)*. In one RCT, 1.6% of the people receiving ETV monotherapy had an increase in serum creatinine through 96 weeks *(40)*. The Development of AntiRetroviral Therapy in Africa clinical trial involving people living with HIV compared laboratory with clinical monitoring and showed that individuals receiving TDF had an increased risk of reduced eGFR but no increased risk of renal failure over a median five years of follow-up (rated as low-certainty evidence) *(41)*.

Children and adolescents

TDF-related decreases in bone mineral density have been observed for children, although it remains uncertain how reduced bone mineral density might affect future growth patterns or the risk of bone fracture. In an RCT of TDF among adolescents (12–17 years old), none met the safety endpoint of a 6% decrease in spine bone mineral density at week 72 *(42)*. There is also uncertainty as to how best to measure and monitor children for TDF-related bone toxicity. Dual-energy X-ray absorptiometry testing is not possible in most settings and will not detect osteomalacia, but careful growth monitoring is recommended while children are receiving treatment with TDF. Recent data from the CHAPAS trial support the safety of TAF for children living with HIV *(43,44)*. The safety profile of ETV for children was consistent with that observed for adults, with no reported renal adverse events over 48 weeks in an ongoing ETV trial reported in an FDA application (AI463289 trial).

In pregnancy

TAF has been evaluated in clinical trials of hepatitis B in late pregnancy and appears to be safe and effective *(45–47)*. However, although no major safety concerns have arisen in cohort studies, TAF has not yet been approved for PMTCT of hepatitis B *(48,49)*.

Assays to monitor nephrotoxicity

There are limited data on the optimal assay to monitor TDF-related renal toxicity. Data suggest that some people may have normal serum creatinine levels but impaired renal function, so overreliance on absolute serum creatinine values may lead to TDF administration among people with pre-existing kidney disease. A high frequency of glycosuria has also been found among people without diabetes who underwent a biopsy for TDF nephrotoxicity, with increased serum creatinine compared with TDF-treated people with a normal GFR, suggesting that dipstick testing for glycosuria may be a cost-effective screening test for serious TDF-induced kidney injury *(50)*.

17.4 Rationale for the recommendations

Balance of benefits and harm

Although TDF is associated with a risk of nephrotoxicity, hypophosphataemia (especially noted for children), bone mineral loss and osteopaenia, the 2015 evidence review showed a low risk of these adverse effects (ranging from 0.3% to 2% for nephrotoxicity) with long-term TDF or ETV, even among people living with HIV, but especially in the absence of established risk factors (such as HIV-associated kidney disease, hypertension and diabetes) *(25)*. Switching from TDF to TAF maintained or improved suppression of HBV replication and improved bone and renal safety, especially for those with stage 2 chronic kidney disease. Because of the overall improved renal safety of TAF, the drug is preferred to other nucleos(t)ide analogues for people at risk of bone or renal complications, older people and people with evidence of impaired renal function *(24)*.

In 2015, the Guidelines Development Group conditionally recommended annual monitoring of renal function, growth monitoring in children, baseline assessment of renal function and categorization of baseline risk of renal dysfunction based on limited evidence. TAF is now recommended in special circumstances for people with established osteoporosis and/or impaired kidney function and also as an alternative regimen for adolescents (aged 12 years or older) (see Chapter 6).

The indications for TAF could be extended to people with an eGFR higher than 60 mL/min. Switching to TAF led to improved kidney function, especially for those with stage 2 chronic kidney disease, since treatment with nucleos(t)ide analogues will be extended over many decades for most people. More people treated with TAF than TDF achieve normal ALT, but the mechanism for this remains unknown *(51)*.

Baseline assessment

In the 2021 WHO consolidated HIV guidelines *(52)*, a baseline measurement of creatinine was not considered an absolute requirement for initiating antiviral therapy among people living with HIV with the preferred TDF-based regimen. This applies also to initiating antiviral therapy for CHB. Use of TAF is recommended for people with established osteoporosis and/or impaired kidney function and for adolescents or children (aged 12 years or greater).

Monitoring

The incidence of progression to moderate or severe kidney dysfunction was low among TDF users, and there was limited comparative evidence of the benefits and cost-effectiveness of routine monitoring versus no monitoring or incidental monitoring among people with CHB. Among people at low risk of renal toxicity, periodic monitoring of renal function is advised. The use of TAF or ETV is recommended among people with impaired eGFR at baseline (<50 mL/min) and other people at higher risk of renal toxicity (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension or are receiving concomitant therapy with boosted protease inhibitors or nephrotoxic drugs) or those with evidence of worsening of renal function during treatment. Most cases of tubular dysfunction are reversible, and the risk of renal impairment can also therefore be reduced if the dose is appropriately adjusted based on renal function monitoring. People switching from TDF to TAF will require ongoing monitoring of their renal function, bone mineral density, lipid profile and weight and for metabolic syndrome.

Assays

The Guidelines Development Group recognized the limited evidence available to guide what tests should be used to monitor for kidney disease, especially in resource-limited settings. The renal toxicity of TDF is usually directed at the tubules; glomerular function tests do not adequately measure tubular dysfunction, but there are currently no other simple tests to detect renal tubular toxicity. In addition, some people may have normal serum creatinine levels but impaired renal function, and relying on absolute serum creatinine values may lead to administering TDF to people with pre-existing kidney disease. Monitoring may include a range of tests, including serum creatinine and, where available, estimated GFR using the MDRD formula for estimation, serum phosphate and urine dipsticks for proteinuria and glycosuria. The growth of children and adolescents using TDF should be monitored.

Resource considerations

Measurement and long-term monitoring of serum creatinine and bone mineral density scanning increases the costs of care and treatment. Access to testing for creatinine may be limited in some settings, and simple urine dipstick testing is a simpler and cheaper alternative in low- and middle-income countries. There are also challenges in providing appropriate laboratory infrastructure and human resources for lifelong therapy and follow-up.

17.5 Implementation considerations

- Known risk factors for developing TDF-induced nephrotoxicity include underlying renal dysfunction, low CD4 count, low body weight and comorbid hypertension, diabetes, HIV-associated kidney disease, HIV or C coinfection and TDF in combination with a ritonavir-boosted protease inhibitor in people with HIV infection *(10–12)*. Managing these comorbid conditions should be given priority.
- People receiving TAF should be monitored for weight gain and lipid rises as well as metabolic syndrome.
- Age and advanced liver disease are additional contributing factors that can help identify those at greatest risk of osteoporotic fracture. Dual-energy X-ray absorptiometry can be used to monitor bone mineral density changes for people receiving TDF. The frequency of monitoring will depend on each person's age and health status. The accuracy of the Fracture Risk Assessment Tool (as an alternative to dual-energy X-ray absorptiometry) has also been evaluated *(53)*. TDF-containing regimens may be replaced with non-TDF-containing regimens for those at higher risk of fragility fracture.

17.6 Research gaps

- Evaluate the relative impact and cost–effectiveness of routine laboratory screening and monitoring of renal function for all people receiving long-term TDF and ETV or only for people at higher risk, such as those with hypertension or diabetes or those using boosted protease inhibitors.
- Develop and evaluate (including cost–effectiveness studies) simplified monitoring tools, such as a combination of serum creatinine–based GFR estimates and a urine dipstick, to identify people who have the greatest risk of TDF-related toxicity.
- Establish the long-term safety, efficacy and toxicity of TAF versus TDF for people including children and adolescents with HBV monoinfection and HIV and HBV coinfection and those treated with anti-TB drugs.

18. Surveillance for hepatocellular carcinoma (HCC) among people with CHB

18.1 Recommendations

Existing and maintained recommendations *(1)*

Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:

- people with cirrhosis, regardless of age or other risk factors;

(strong recommendation, moderate-certainty evidence)

- people with a family history of HCC; and

(strong recommendation, moderate-certainty evidence)

- if there is no family history of HCC or evidence of cirrhosis, people older than 40 years (a lower age may apply depending on the regional incidence of HCC[a]) and with HBV DNA level >20,000 IU/mL (if HBV DNA testing is available).

(conditional recommendation, low-certainty evidence)

a The GLOBOCAN project of the International Agency for research on Cancer (IARC) (http://globocan.iarc.fr/ia/World/atlas.html) provides current estimates of the incidence of, mortality and prevalence of major types of cancer, including HCC, at the national level, for 185 countries. The GLOBOCAN estimates are presented for 2020, separately for each sex. One-, three- and five-year prevalence data are available for adults only (15 years and older).

18.2 Background

CHB leads to an increased risk of death from liver cirrhosis and liver cancer. The Global Cancer Observatory project of the International Agency for Research on Cancer (https://gco.iarc.fr) provides estimates of the incidence, mortality and prevalence of major types of cancer, including primary liver cancer, at the national level, for 185 countries. The most recent estimates available are for 2020. Time trends and projection data are available as well as data on cancer attributable to infections, including hepatitis B (https://gco.iarc.fr/causes/infections/home). According to the Global Cancer Observatory, primary liver cancer is the seventh most common type of cancer globally (fifth for men) and the fourth leading cause of annual cancer deaths worldwide (second for men) *(2–12)*. Men develop liver cancer more than twice as frequently as women. In settings with limited resources and a high burden of hepatitis B, people are often diagnosed with hepatitis B at an advanced stage of disease (decompensated cirrhosis or HCC) *(13,14)*.

Although 80–90% of people with hepatitis B–associated HCC already have cirrhosis when diagnosed, HCC may occur without cirrhosis. A further challenge is that HCC may be asymptomatic until it presents clinically at an advanced stage. In sub-Saharan Africa, HCC also develops at a significantly younger age (median age 46 years), and more than one third of the people in Africa who develop HCC are diagnosed before the age of 40 years *(15)*. This increased risk is maintained among African populations migrating to high-income settings. Dietary exposure to aflatoxin and aristolochic acid are known cofactors for HCC for people with hepatitis B *(16–18)*. Despite the long latency between infection and cancer, universal newborn HBV vaccination programmes implemented decades ago in Asia have already led to significant declines in HCC incidence *(19)*. Although about 40% of the people with HCC in high-income countries are diagnosed at an early stage, when interventions with curative intent are feasible, 95% of those with HCC in sub-Saharan Africa present with advanced disease. Although the reported overall five-year survival rates approach 70% in the few high-income countries with comprehensive national surveillance programmes for people at risk of HCC *(19)*, the survival rate in sub-Saharan Africa is extremely poor.

Treatment options for advanced HCC are limited, and overall survival is extremely poor. The prognosis of HCC is affected by the size and number of tumours and underlying liver function and is improved if treatment can begin at an early stage of the disease, when the tumour is small. Surveillance is therefore required to detect HCC at an early stage (a single nodule or up to three nodules, with the largest tumour size ≤3 cm in diameter) and thereby increase the chances of effective treatment. Effective surveillance programmes require a means for implementing such treatment for small HCC in low- and middle-income countries, recognizing that access to liver transplantation or resection remains limited, even in high-income settings. These treatments would include microwave ablation, radiofrequency ablation or percutaneous ethanol injection of small tumours. Current surveillance is with ultrasound and AFP measurement but with a consensus that people with CHB should be monitored for HCC every six months. Surveillance detects HCC at an earlier stage and improves survival. Continued surveillance is a substantial financial burden, even in high-income countries, and surveillance strategies therefore need to be developed that are more sensitive, specific and cost-effective *(20)*.

18.3 Summary of the evidence

18.3.1 Approaches to surveillance for HCC

An evidence review was undertaken to identify the most effective surveillance strategy among those with CHB for early detection of HCC, to inform the 2015 hepatitis B guideline recommendations *(1)*. These recommendations remain largely unchanged in these updated guidelines, but are further supported by new studies. The more recent references elaborate the potential methodologies required for a complex screening process, the epidemiology of and surveillance for HCC, gaps in surveillance, the frequency and outcomes of abnormal imaging for people enrolled in HCC surveillance, for whom HCC surveillance is cost effective, current best practice elucidated in updated guidelines and potential harm of HCC surveillance *(21–31)*. Overall, the data showed an effect on disease-specific mortality of six-monthly ultrasonography and AFP versus no intervention (OR 0.57, 95% CI: 0.37–0.89) or six-monthly ultrasonography and AFP versus more often than six-monthly (OR 0.63, 95% CI: 0.40–0.98) but not for six-monthly AFP alone versus no intervention. In addition, five-year survival favoured six-monthly screening versus no intervention (31% versus 23%; P = 0.03). Although there was no statistically significant difference in the number of new cases of HCC detected, HCC was detected significantly earlier in terms of stage and smaller lesion size (<3 cm or <5 cm in diameter) with either six-monthly ultrasonography and AFP screening (OR 11.2, 95% CI: 6.7–18.7) or more often than six-monthly screening (OR 2.1, 95% CI: 1.4–3.2) and with six-monthly AFP alone versus no intervention.

An observational study also found that six-monthly AFP screening (versus no intervention) was effective in detecting most HCC tumours at a resectable stage and significantly prolonged survival *(32)*. A systematic review *(33)* included three additional relevant observational studies *(34,35)* – one that compared ultrasonography plus AFP versus no screening *(34)* and the other ultrasonography versus no screening *(35)*. Both showed an overall survival benefit of screening versus no screening, consistent with the findings of the main review.

Of the three economic evaluation studies *(36–39)*, two found screening every six months using both AFP level and ultrasonography to be the most cost-effective strategy *(37,38)*. The third study conducted in rural Alaska reported that restricting ultrasonography to people with raised AFP levels was less costly and more cost-effective than ultrasonography alone every six months for everyone *(36)*. Existing evidence suggests that semiannual surveillance detects HCC at an earlier stage and improves survival *(21)*. Several subsequent meta-analyses and observational studies have shown higher rates of HCC detection at early stages and improvement in three-year survival rates for people under active surveillance *(23,39,40)*. Although the role of AFP has been debated, recent updates recommend a combination of ultrasound and AFP since ultrasound plus AFP achieves a sensitivity of 63% for early-stage HCC (95% CI: 48–75%) *(41)*. Additional blood-based biomarkers are being actively developed that could prove useful for HCC screening, including DNA methylation based (OncoGuard Liver), proteomic, glycomic (GlycoTest) or metabolomic biomarkers and combination assays based on combinations of these various analytes.

18.3.2 Who should have surveillance for HCC?

The key evidence for risk factors (or combinations of factors) specific for developing HCC (see Table 5.1) have been derived from the large population-based REVEAL-HBV cohort from Taiwan, China *(24-26,42)*, several other prospective *(27-30,43)* and retrospective cohort studies *(44-46)*, including studies among people with both hepatitis B and HIV *(47)*, and one systematic review *(48)*. These longitudinal cohorts show that the most important risk factors for developing HCC are the presence of cirrhosis, HBeAg positivity, persistently high HBV DNA levels, family history of HCC, age >40 years (as a surrogate reflecting the duration of infection and extent of accumulated liver damage), ALT levels >45 U/L and HIV and HCV coinfection.

In the REVEAL cohort, the RR for HCC was 3.6 (95% CI 2.0–6.4) for those 40–49 years old versus those <40 years old, RR 5.1 (2.0–8.9) for those 50–59 years and RR 8.3 (4.6–15.0) for those >60 years; and RR 4.3 (3.2–5.9) for HBeAg positivity *(42)*. In the same cohort, the incidence of HCC increased consistently and linearly with baseline HBV DNA over 2000 IU/mL, regardless of the presence of cirrhosis. Those with a family history of HCC had a threefold higher risk, and this was greatest among those who were also HBeAg-positive (HR 45.5; 95% CI: 22.9–90.6) (Table 18.1) *(42)*. Other factors associated with an increased risk of developing HCC are ethnicity (the risk of HCC is greater for people of African or Asian family origin), duration of infection (the risk is higher for those with neonatal or perinatal and childhood infection), those with genotype C, A1 and F and core promoter mutants and those with a history of aflatoxin exposure, HDV coinfection or superinfection, smoking, high alcohol intake and diabetes *(49,50)*.

Table 18.1 Cumulative incidence of HCC among people with CHB according to family history of HCC, baseline HBV DNA level and HBeAg status *(31,42)*

	Cumulative incidence (%)	Adjusted HR (95% CI)
No family history	7.5	Reference
Family history of HCC	15.8	2.4 (1.6–3.7)
No family history HBV DNA <2000 IU/mL	2.5	Reference
HBeAg positive, family history of HCC	40	45.5 (22.9–90.6)
HBeAg positive, no family history	19.1	13.9 (9.3–20.8)
HBeAg negative, family history of HCC HBV DNA >2000 IU/mL	17.6	9.9 (4.5–21.4)
HBeAg negative, no family history HBV DNA >2000 IU/mL	10.3	4.4 (3.0–6.5)
HBeAg negative, family history of HCC HBV DNA <2000 IU /mL	5.4	Not significant

18.3.3 Risk calculators for HCC surveillance

Since the 2015 guidelines, risk calculators to support targeting of screening have expanded further. Risk calculators were developed that provide easy-to-use formulas to predict the risk of HCC in CHB based on models *(51-53)* using clinical and/or laboratory data (age, sex, levels of albumin, bilirubin and ALT, HBeAg status, HBV DNA levels and presence of cirrhosis) to stratify the risk of HCC (low, intermediate and high risk). A recent systematic review summarized 23 models for predicting future HCC risk in CHB (12 of which were derived for treatment-naive individuals) *(54,55)*. These include the Barcelona Clinic Liver Cancer staging system – one of the most widely validated risk scores *(31,54,55)* – and the GAG-HCC risk score, developed from a cohort of 820 people with CHB in China based on age, sex, HBV DNA levels, presence of cirrhosis and core promoter mutations *(52)*. Since cirrhosis is a major risk factor for developing HCC, transient elastography has also been incorporated into recent risk scores as a substitute for HBV DNA levels such as the pre-existing CU-HCC and REACH-B scores *(56)*, resulting in improved performance of the LSM-HCC and mREACH-B, respectively *(56–58)*. More recent studies have shown that HBcrAg, a good surrogate for cccDNA concentrations, may also be able to contribute to risk assessment for developing HCC *(59–61)*. Most models have been developed in Asian populations, although some of these have now been recently validated for Caucasians *(14,55,62,63)*. A further recent simplified risk score (aMAP score) has shown excellent discrimination and calibration in assessing the five-year HCC risk among 17 000 both Asian and Caucasian people with CHB. This score only requires data on age, sex, albumin, bilirubin and platelet counts, without the need for HBV DNA or transient elastography, which is relevant to low- and middle-income countries.

18.4 Rationale for the recommendations and balance of benefits and harm

Approaches to surveillance for HCC

Overall, intervention studies, RCTs and economic evaluation evidence reviewed in 2015, and supported by findings from more recent studies favoured routine surveillance using the combination of ultrasound and AFP at approximately six-monthly intervals to detect HCC in earlier stages and improve overall survival through early and more effective treatment. The overall benefits of screening high-risk people with CHB considerably outweighed any potential harm. The potential benefits were based on the following considerations.

1. Affected individuals develop HCC in mid-to-late adulthood, and deaths from HCC drain health-care resources and productive capacity in low- and middle-income countries, where hepatitis B is prevalent. HCC is generally silent until symptomatic (typically when large: >10 cm in size), and the prognosis is extremely poor among people with symptomatic tumours and underlying hepatic dysfunction.

2. The additional benefit of integrating routine monitoring for HCC alongside routine monitoring for disease progression is that it provides a further opportunity to detect fibrosis or other evidence of disease progression and so to initiate antiviral therapy to prevent progression to HCC or liver failure.

3. Antiviral therapy reduces the risk of HCC *(64)* and has benefits even among people with HCC, including decreased risk of recurrence following curative treatment, decreased necroinflammation and reduced risk of hepatic decompensation.

4. HCC surveillance for people with asymptomatic CHB is cost-effective if the annual incidence is at least 0.2% *(34)*.

Potential harm of routine surveillance includes false-positive AFP and ultrasound detection of small lesions other than HCC, such as regenerative nodules in cirrhotic livers, which may not progress to HCC, resulting in unnecessary and costly interventions and the inconvenience of attending additional visits. There is also a trade-off in the duration of intervals between screenings. If the intervals are too long, this may delay the detection of HCC, especially for non-cirrhotic people. Alternatively, more frequent HCC surveillance is associated with an increase in cost per diagnosis.

The Guidelines Development Group for the 2015 hepatitis B guidelines had recognized that routine surveillance as described above would be effective in improving survival only if low- and middle-income countries also plan for how to treat small HCC. This may include microwave or radiofrequency ablation, percutaneous ethanol injection or resection, complemented by antiviral therapy and managing the complications of advanced liver disease. At present, access to such interventions remains very limited in these settings

Who should have surveillance for HCC?

CHB increases the risk of HCC by 15- to 20-fold versus uninfected individuals. Longitudinal studies provide moderate-certainty evidence showing that the most important risk factors for developing HCC (associated with an approximately fourfold increased risk) are the presence of cirrhosis, HBeAg positivity and a family history of HCC. Most people (80–90%) have cirrhosis when HCC is diagnosed, and the Guidelines Development Group therefore recommended that those with cirrhosis and those with a family history of HCC are the most important high-risk groups to target for screening. Although age >40 years is associated with an increased risk of HCC in Asian populations, the Guidelines Development Group considers that the optimal age at which surveillance for HCC should begin cannot be established with certainty, since the incidence of HCC varies with age according to region and occurs at a younger mean age for Africans versus Asians (see http://globocan.iarc.fr/ia/World/atlas.html, IARC GLOBOCAN). Therefore, no specific age threshold for screening is recommended.

The certainty of evidence was rated as moderate that screening (surveillance) for HCC should be performed among at-risk individuals with CHB, targeting those at greater risk who would be eligible for curative treatment that can improve survival *(31,54)*.

18.5 Implementation considerations

- Surveillance for HCC needs to be integrated into existing monitoring systems for disease progression and treatment response for those receiving antiviral therapy. Additional training in the use and expert interpretation of ultrasound imaging for small HCC will also be required.
- Incorporating risk stratification algorithms that help to differentiate the people at high risk of developing HCC from those at low risk may enable more cost-effective implementation of surveillance programmes. In parallel, using abbreviated magnetic resonance imaging sequences and artificial intelligence–based methods for identifying and characterizing new masses in ultrasound, computed tomography and magnetic resonance imaging may reduce the cost and improve the performance of imaging for early HCC detection.
- Liver cancer detection is now also built into multi-cancer early detection assays (such as the GRAIL Galleri® test) that are being developed for regular population-based detection of multiple cancer types and are already available in some countries. If these newer assays can be deployed at lower cost, they may transform the landscape of early detection of liver cancer by removing key barriers to participation with large-scale HCC surveillance and facilitate regular surveillance of those at high risk.
- Surveillance can only improve survival if low- and middle-income countries develop the capacity to find, diagnose and treat small HCC. Effective surveillance programmes require an organized system for regular liver imaging and blood testing, recall programmes and radiology service capacity. In low- and middle-income countries, HCC is usually diagnosed based on specific imaging criteria rather than histology and therefore requires imaging capability and experience.

- For surveillance to be effective in improving survival, there must also be staff, facilities and resources to treat small HCC. This includes, especially in low- and middle-income countries, access to expertise in ablation resection (and transplantation), management of advanced liver disease and provision of antiviral therapy to prevent the development of HCC or tumour recurrence following resection.

18.6 Research gaps

- Assess understudied risk factors and the role of synergistic risk factors that increase risk of HCC in high-, low- and middle-income countries, including metabolic dysfunction–associated steatotic liver disease, diabetes mellitus, alcohol and smoking and environmental carcinogens.
- Further assess newer biomarkers such as HBcrAg and HBV RNA in predicting the risk of HCC for people with CHB being treated to refine risk stratification and screening policy.
- Refine HCC predictive models in different regions and populations with CHB, and according to different genotypes and use of antiviral therapy, to inform HCC surveillance programmes. Validate emerging HCC risk calculators in different regions, especially sub-Saharan Africa, and in regions with high HDV prevalence.
- Evaluate the efficacy and feasibility of low-cost treatment strategies, including ablation and percutaneous ethanol injection for small HCC, in low- and middle-income countries.
- Evaluate how nucleos(t)ide analogue therapy affects tumour-free survival after resection or ablation of small HCC.
- Evaluate simplified risk scores for HCC in low- and middle-income countries, especially in sub-Saharan Africa.

19. When to stop and restart antiviral therapy

19.1 Recommendations

Existing and maintained recommendations from the 2015 hepatitis B guidelines

Lifelong nucleos(t)ide analogue therapy

All people with cirrhosis[a] based on clinical evidence (or APRI or transient elastography score) require lifelong treatment with nucleos(t)ide analogues and should not discontinue antiviral therapy because of the risk of reactivation, which can cause an acute hepatitis flare.

(strong recommendation, moderate-certainty evidence)

Discontinuation

Antiviral therapy is lifelong. Discontinuing nucleos(t)ide analogue therapy may be considered exceptionally for:

- people without clinical evidence of cirrhosis (or based on a non-invasive test score – APRI or transient elastography;

and

- who can be followed carefully after discontinuation and long term for reactivation;

and

- if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment;

and

- in association with persistently normal ALT levels[b] and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

If HBV DNA testing is not available: discontinuing nucleos(t)ide analogue therapy may be considered for people who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of previous HBeAg status.

(conditional recommendation, low-certainty evidence)

Retreatment

Relapse is common after stopping therapy with nucleos(t)ide analogues. Retreatment is recommended if there are consistent signs of reactivation: HBsAg or HBeAg becomes positive, ALT levels increase or HBV DNA becomes detectable again (if HBV DNA testing is available).

(strong recommendation, low-certainty evidence)

a Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease or cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

b The ULN for ALT has been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.

19.2 Background

The main goals of antiviral therapy in CHB are to improve survival and quality of life by preventing progression to severe liver disease (decompensated cirrhosis and liver failure), HCC and death. This can be achieved by suppressing HBV DNA to undetectable levels. HBsAg loss and/or seroconversion to anti-HBs is considered to be the optimal goal of antiviral therapy and a marker of sustained treatment response for both HBeAg-positive and HBeAg-negative people but is achieved for only a minority of HBeAg-positive people or HBeAg-negative people. HBeAg seroconversion among HBeAg-positive people may also be considered as a potential stopping point to guide treatment cessation but, again, is infrequent even with potent nucleos(t)ide analogues.

Although nucleos(t)ide analogues are potent inhibitors of HBV DNA replication, they do not result in cure, because nucleos(t)ide analogue therapy does not eliminate the replicative template cccDNA in the nucleus or integrated viral genomes. Therefore, although finite nucleos(t)ide analogue therapy has considerable advantages, both for people with hepatitis B and policy-makers, especially in low- and middle-income countries, long-term maintenance of suppressive therapy is generally required. A finite duration of treatment may be possible for some HBeAg-positive people who achieve anti-HBe seroconversion and a sustained undetectable HBV DNA viral load and for HBeAg-negative anti-HBe-positive people with low HBsAg concentrations and for whom evidence (using newer biomarkers) indicates low cccDNA transcriptional activity *(1)*. However, in resource-limited settings where access to HBV DNA monitoring is limited, it remains unclear under what conditions nucleos(t)ide analogue therapy may be safely stopped *(2–8)*. New data also show that HBsAg can be persistently transcribed for people with low levels of HBV replication, from integrated viral genomes, accounting for detectable HBsAg in serum even for HBeAg-negative people with low HBV DNA levels *(9,10)*.

19.3 Summary of the evidence

The previous evidence review for the 2015 hepatitis B guidelines *(11)* assessed what criteria should be used to stop treatment, evidence for the durability of treatment response after antiviral therapy ends for both HBeAg-positive and HBeAg-negative people and factors that predict a durable response. The outcomes were HBeAg seroconversion, HBsAg loss, undetectable HBV DNA levels, liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease and HCC), progression of liver disease, reversion of fibrosis stage and mortality, severe adverse effects and antiviral resistance.

No systematic reviews or RCTs directly compared the durations of different types of antiviral therapy (ending treatment at defined time points versus continuing treatment). Instead, the search identified 26 prospective and retrospective observational studies and one RCT, which reported relapse rates after ending therapy with antiviral drugs – 3TC *(12–16)*, adefovir *(9)*, ETV *(17)* and multiple antiviral drugs *(18–21)* following varying treatment durations and responses. The heterogeneity of treatment duration, varying follow-up after treatment ends and criteria for discontinuing treatment and assessing relapse precluded pooled analysis of outcomes.

In general, viral responses were not durable, and relapse rates after treatment ended (with different definitions) at one year ranged from 40% to 95% if the duration of consolidated treatment was less than one year *(20)*. Relapse rates were also high based on the few studies stopping therapy with nucleos(t)ide analogues with a higher barrier to resistance (three with ETV but none with TDF). Only 3% of HBeAg-negative viral responders treated with ETV for about one year had a sustained response (HBV DNA level <300 copies/mL) six months after therapy ended *(22)*. In a further prospective study, the one-year relapse rates (rise in HBV DNA and ALT levels) were 53% and 29%, respectively *(17)*. Most relapses occurred more than six months after treatment ended. Overall, the data show that most people experience biochemical or viral relapse after therapy ends, and increases in serum aminotransferases and HBV DNA concentrations occur earlier after stopping TDF versus ETV *(7)*.

More recent data suggest that HBsAg concentrations when therapy ends strongly predict HBsAg seroclearance, but the concentrations associated with HBsAg seroclearance vary from <100 IU/L for Asian people to <1000 IU/L for Caucasian people. Off-treatment HBsAg seroclearance varies from 4% to 19% for HBeAg-negative people *(23-27)*.

Although the risk of decompensation is low, the consequences of discontinuation can be hazardous, and ensuring the safety of ending therapy requires careful criteria *(28)*. Moreover, repetitive silent flares in serum aminotransferases are a manifestation of hepatic injury and could lead to progressive hepatic fibrosis.

Independent factors associated with an increased probability of relapse after therapy ends included the presence of cirrhosis, older age, shorter nucleos(t)ide analogue therapy duration and higher pretreatment HBV DNA levels *(29)*. The overall certainty of evidence from these studies on relapse rates and risk factors after stopping antiviral therapy was rated as low to moderate. Although their clinical relevance requires further evaluation in various populations, recent data suggest that HBV RNA and HBcrAg identify active cccDNA transcription and have the potential to identify people at higher risk of relapse after stopping nucleos(t)ide analogues *(30,31)*.

19.4 Rationale for the recommendations

19.4.1 Balance of benefits and harm

The advantages of stopping nucleos(t)ide analogue therapy are a finite duration of treatment, reduced costs and minimizing renal and bone toxicity. The disadvantages are the risk of reactivating previously suppressed disease after discontinuing therapy, resulting in an unpredictable worsening of disease even for people without cirrhosis and possible development of acute-on-chronic liver failure *(32)* or, more commonly, repeated hepatic injury and fibrosis. Stringent criteria should be met before stopping treatment. People who discontinue therapy also require careful immediate and long-term follow-up for early detection of relapse (see Chapter 16).

Overall, the evidence shows that treatment even with potent nucleos(t)ide analogues (ETV or TDF) infrequently leads to HBeAg seroconversion and loss of HBsAg for HBeAg-positive people and (even more rarely) HBsAg loss or anti-HBs seroconversion for HBeAg-negative people *(33)*. In addition, relapse occurs for many after ending treatment, even with the potent nucleos(t)ide analogues and following HBeAg seroconversion. The Guidelines Development Group previously recognized that uncontrolled HBV replication could be harmful, and stopping therapy could prove to be a poor alternative to uninterrupted treatment. No clear evidence indicates that relapse rates after discontinuation are lower with TDF than with ETV, but the timing is delayed after ETV. Newer biomarkers such as HBV RNA and HBcrAg can predict the severity of relapse but are not widely available *(34)*. A decline in HBV RNA can predict fibrosis regression among people being treated *(35)*.

The Guidelines Development Group in 2015 *(11)* strongly recommended that people with cirrhosis never discontinue antiviral therapy. Since they have much less hepatic reserve, life-threatening hepatic decompensation may occur after exacerbation based on moderate to low-certainty evidence. People with both hepatitis B and HIV initiating therapy should also remain on long-term HBV suppressive therapy. Given the limited access to monitoring of HBV DNA levels as well as regular monitoring of HBsAg or HBeAg serology in resource-limited settings, the Guidelines Development Group had previously considered that long-term antiviral suppressive therapy will be necessary for the majority and recommended a very conservative approach to stopping therapy – only for a few carefully selected people with evidence of sustained HBsAg loss, without cirrhosis.

Everyone who stops treatment should be closely monitored with serum ALT and preferably HBV DNA. Although the evidence base is limited, ALT and HBV DNA could be measured monthly for the first three months and then every three months during the first year to avoid severe exacerbations because of the high early risk of relapse (defined as a rise in HBV DNA and serum ALT concentrations or seroreversion to HBeAg positivity), and the need to reinstitute treatment for active disease. Later reactivation will require occasional testing for HBsAg.

Newer biomarkers such as HBV RNA and HBcrAg can predict the severity of relapse but are not widely available. Retreatment is required for elevated HBV DNA concentrations (HBV DNA>2000 IU/mL) and/or persistently abnormal serum aminotransferases. In a multicentre cohort study of HBeAg-negative people, the cumulative incidence of hepatic decompensation at 60 months after stopping treatment among the total cohort was 1.8% and 1.1% for the subgroup without cirrhosis *(5)*. Although the risk of decompensation is relatively rare, the outcome can be severe. Less clinically obvious flares may also injure the liver. People with cirrhosis or HBeAg positive when starting therapy require careful assessment to prevent hepatic decompensation. Despite recent clinical trials and evidence from large observational databases, there is considerable controversy as to whether withdrawing nucleos(t)ide analogues is an appropriate therapeutic strategy to induce HBsAg loss *(7,23,36–41)*. Several recent trials, observational studies and systematic reviews provide updated evidence *(36,38,42–51)*. Several safety considerations apply to prevent severe flares in subgroups, to appropriate risk stratification protocols for post-treatment monitoring and to indications for resuming treatment *(28)*. More recent data suggest that HBsAg seroclearance is restricted to people with low HBsAg concentrations: <100 IU/mL or preferably less than 10 IU/mL for Asians and <1000 IU/mL or preferably <100 IU/mL for Caucasians *(7,25–27,52–54)*.

19.4.2 Values, preferences and acceptability

Finite treatment is preferable to long-term or indefinite treatment for people with hepatitis B, health-care workers and national policy-makers but is currently not possible for most people receiving nucleos(t)ide analogues. Initial treatment success may be reversed among people who reactivate disease that was previously stable while being treated after treatment ends. Those who do stop therapy (in addition to those who continue therapy) after HBeAg seroconversion or suppression of HBV DNA but remain HBsAg positive require continued long-term follow-up and careful monitoring (see Chapter 16). Given the more limited access to monitoring in low- and middle-income countries, both people with hepatitis B and caregivers need access to regular serum ALT and HBV DNA monitoring to determine reactivation and the need to restart treatment.

19.4.3 Resource and access considerations

The ability to monitor the resumption of HBV replication for everyone after stopping therapy requires HBV DNA monitoring. HBV DNA testing is relatively costly and is not available in most low- and middle-income countries. The evidence base for monitoring with liver enzymes alone, which is less expensive, is limited, and this is not recommended currently for disease relapse. Long-term TDF or ETV therapy also has cost implications, especially if paid out of pocket. Generic TDF is widely available at low cost in many low- and middle-income countries (about US$ 30–50 per person per year) and also as part of national ART programmes. The costs are currently higher for ETV, but it can be manufactured at lower cost since it is both off patent and the daily dose is low.

19.5 Implementation considerations

- The decision to stop any nucleos(t)ide analogue therapy must be weighed carefully. Biochemical relapse has been variously defined but includes ALT elevation to >2 times the ULN. A hepatitis flare has been defined as ALT elevation >5 times the ULN and severe hepatitis flare has been defined as ALT level >1000 U/L or ALT <1000 U/L plus a total bilirubin ≥3.5 mg/dL or an international normalized ratio ≥1.5. Viral relapse has been defined as HBV DNA >2000 IU/mL. Quantitative HBsAg at the end of treatment predicts HBsAg loss or relapse after stopping nucleos(t)ide analogues, but the levels predicting relapse are lower for Asian versus Caucasian people.
- Stopping nucleos(t)ide analogues before HBsAg loss should only be considered if HBsAg seroclearance is likely based on prediction with current biomarkers, especially HBsAg levels, at the time of stopping.
- People with hepatitis B should be educated about the importance of long-term monitoring to ensure adherence to monitoring and care. The benefits versus the disadvantages of stopping treatment should be also clearly explained.
- The ability to monitor everyone for safety after stopping therapy for resumption of HBV replication requires HBV DNA monitoring and recall policies. Both laboratory-based and POC DNA testing remain relatively costly and less available in low- and middle-income countries.
- Postpartum, women who have started nucleos(t)ide analogue prophylaxis to prevent vertical transmission should be strongly advised to continue treatment if indicated for their own health and especially if multiple subsequent pregnancies are anticipated. This would also avoid the risk of liver flare when treatment ends after each pregnancy and delivery.
- Monitoring for and managing relapse: HBV DNA concentrations typically rise rapidly before serum ALT concentrations. Treatment should be reinstated if concentrations rise to >4 log10 IU/mL before any rise in serum aminotransferases to circumvent the immune-mediated flare *(32)*. The findings of the unpublished REEF-2 study provide strong support for this approach, which has now been incorporated into the clinical trials of new agents. Delayed resumption of therapy may have severe outcomes for these people.
- An array of immunosuppressive agents may induce HBV reactivation. These include cancer chemotherapy, checkpoint inhibitors, immunosuppressive therapy, bone marrow and stem cell treatment, anti-tumour necrosis factor and novel immunobiologics, including tyrosine kinase inhibitors, chimeric antigen receptor T-cell treatment and after treatment for comorbid hepatitis C. Since the composite risk can be difficult to determine, pre-emptive antiviral therapy is recommended *(55)*.

19.6 Research gaps

- Examine rates of hepatic flares (including biochemical and viral flares) in populations stopping treatment and the clinical event rate.
- Conduct studies to examine HBsAg concentrations and utility of new biomarkers, including pgRNA (HBV RNA) and HBcrAg to guide the safety of discontinuation in various population groups.
- Conduct longitudinal studies to identify subgroups of African HBeAg-negative people at low risk of reactivation after discontinuing nucleos(t)ide analogue therapy based on quantitative HBsAg levels.
- Evaluate lower-cost and POC assays for HBsAg quantification as potential markers to determine rules for stopping therapy and monitoring for relapse.

20. Management considerations for specific populations

A comprehensive approach to management of CHB includes measures to prevent the onward transmission of hepatitis B, screening for HIV, hepatitis C and D coinfection and co-morbidites, providing HBV vaccination and general care and treatment. Management also needs to address the needs of specific populations with CHB, including people coinfected with HIV, HDV or HCV, those with advanced or decompensated liver disease as well as extrahepatic manifestations, and children and adolescents, pregnant women and people who inject drugs. This chapter summarizes the key considerations in treatment and care for these populations for implementing the recommendations covered in Chapters 4 to 19.

20.1 Coinfections

HBV, HIV, HCV and HDV share similar although not identical transmission routes. Coinfection with these other infections usually results in more severe and progressive liver disease and a higher incidence of cirrhosis, HCC and mortality. Coinfection is therefore one of the eligibility criteria for antiviral therapy regardless of HBV DNA or ALT levels.

In general, the dominant hepatitis virus causing the liver disease should be identified and initial treatment targeted towards this.

20.1.1 HBV and HIV coinfection

Current estimates are that between 5% and 25% of the 34 million people living with HIV worldwide also have CHB (about 2 million–8 million). The burden of coinfection is greatest in low- and middle-income countries, especially in South-East Asia and sub-Saharan Africa, where more than 3 million people with both hepatitis B and HIV live *(1)*. CHB is usually acquired perinatally or during early childhood and precedes HIV infection in most cases. The prevalence of CHB among people living with HIV is therefore close to what is observed in the general population. In countries with an intermediate hepatitis B prevalence (2–8%, Mediterranean region, South America and the Caribbean), routes of transmission are mixed and the prevalence of coinfection may vary.

In the absence of treatment, HIV coinfection profoundly affects almost every aspect of the natural history of HBV infection and includes more rapid progression to cirrhosis and HCC, higher liver-related mortality, higher rates of chronicity after acute HBV infection, rates of reactivation and rates of occult HBV (HBV DNA positivity in the absence of HBsAg-positivity) and reduced treatment response compared with people without HIV coinfection *(2-8)*. Previous challenges with coinfection include cross-resistance between HIV and HBV drugs *(9,10)*, increased liver

injury, either due to direct hepatoxicity *(11,12)* or ART-related immune reconstitution hepatitis, with elevation of ALT and even fulminant hepatitis if ART does not cover both HIV and hepatitis B adequately *(12–14)*. However, improved access of people with both HIV and hepatitis B to ART active against hepatitis B has considerably improved the outcome in recent years *(13,14)*.

People living with HIV may have a higher risk of hepatitis B, and all people newly diagnosed with HIV should therefore be screened for HBsAg, anti-HBs and anti-HBc to identify those with CHB and vaccinated if not immune, especially among high-risk groups such as people who inject drugs and men who have sex with men. The response to HBV vaccination is lower among people living with HIV, especially those with a low CD4 cell count. A meta-analysis has shown that a schedule of four double (40 µg) doses of the vaccine provides a higher protective anti-HBs titre than the regular three 20-µg dose schedules *(15)*. Knowing the HBsAg status of people living with HIV is important before initiating ART or switching regimens and before initiating PrEP.

The recommended NRTI drugs as part of ART regimens are TDF with 3TC or FTC which are also active against HBV. WHO guidelines recommend using TDF or ETV or TDF + FTC or 3TC for the long-term treatment of people with CHB (see Chapter 6). All people coinfected with HIV and HBV should therefore receive a TDF-based ART regimen in combination with 3TC (or FTC) as the NRTI backbone of an ART regimen, regardless of stage of disease or HBV DNA level. If ARV drugs need to be switched because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs *(16)*. If TDF cannot be safely used, the alternative recommended hepatitis B therapy is ETV in addition to a fully suppressive ARV drug regimen. TAF may be an option for specific clinical situations in which renal or bone problems are a concern and for adolescents. DTG in combination with an NRTI backbone is the preferred first-line drug regimen for adults, adolescents and children living with HIV and initiating ART, including those with HIV and HBV coinfection. EFV at low dose (400 mg) is an alternative to DTG for adults and adolescents.

HIV treatment among people coinfected with HBV without using TDF in the regimen may lead rarely to flares of HBV because of ART-associated immune reconstitution. Similarly, abrupt treatment discontinuation of TDF or 3TC may be associated with HBV reactivation, hepatic flares and, in rare cases, hepatic decompensation.

This treatment strategy has achieved high rates of HBV DNA suppression (90%), HBeAg loss (46%) and HBsAg loss (12%) among HBeAg-positive people after five years of treatment without major evidence of resistance and reduced progression to cirrhosis, with no significant differences in response between those with and without HIV coinfection *(16)*. To date, no definitive viral resistance to TDF in vivo has been described, although resistant strains have been identified *(17,18)*. Although the risk of developing cirrhosis is negligible for people with both hepatitis B and HIV receiving long-term tenofovir combined with FTC or 3TC, the risk of HCC persists but is lower.

Specialty care was independently associated with higher-quality hepatitis B care for people with both hepatitis B and HIV and those with just hepatitis B *(19,20)*. Using HIV infrastructure (laboratory and pharmacy capacity, staff, procurement and supply chain) provides an opportunity to expand care and treatment to people with HBV monoinfection and coinfection in many low- and middle-income countries *(21,22)*.

20.1.2 HBV and HDV coinfection

See Chapters 12, 13 and 14 *(23)*.

20.1.3 HBV and HCV coinfection

Coinfection with HCV is common in hepatitis B-endemic countries in Asia, sub-Saharan Africa and South America, especially people who inject drugs, where up to 25% of those with HCV may also have HBV. In many instances of coinfection, HCV is the dominant virus and may in fact suppress levels of HBV DNA *(24,25)*. People with both HCV and HBV have a much higher risk of developing HCC *(26,27)*, and this is more likely to be an infiltrating and aggressive form of HCC and to occur at a younger age than those with nodular HCC, suggesting accelerated hepatocarcinogenesis with coinfection *(28,29)*. Treatment for both infections is generally required. IFN can be effective, but treatment for hepatitis B and C is now largely based on treatment with separate direct-acting antiviral drugs for both.

The presence of active or past hepatitis B is not an impediment to HCV therapy *(30,31)*, but those starting HCV direct-acting antiviral therapy should be assessed for current or past HBV infection and monitored for potential post-therapy HBV reactivation. There is a moderate risk of HBV reactivation among HBsAg-positive people receiving HCV direct-acting antiviral therapy, and HBsAg-positive people should therefore be treated with a nucleos(t)ide analogue during and after direct-acting HCV antiviral therapy *(32-36)*. All coinfected people should be monitored by measuring serum ALT and HBV DNA during HCV infection *(37-39)*.

20.1.4 HBV and TB coinfection

Groups with increased risk of hepatitis B are also at risk of infection with TB largely because they live in regions of the world that are endemic for both infections. This can pose a particular challenge for clinical management and warrants additional clinical vigilance *(40)*. People who inject drugs and prisoners have a high risk of acquiring HIV, HBV and HCV and also have increased risk of coinfection with TB, and should be considered for screening for alll infections *(41)*. In the absence of cough, weight loss, fever and night sweats, active TB can be confidently ruled out. Further investigations for TB and other diseases may be indicated *(42,43)*. Drug-induced liver injury with elevated aminotransferases is three- to six-fold higher among people coinfected with HBV, HCV or HIV who are receiving anti-TB drugs because of hepatic toxicity with isoniazid, rifampicin and pyrazinamide *(44)*.

20.1 Comorbidities such as diabetes and steatotic liver disease

The influence of hepatitis B infection on necroinflammation and progression of fibrosis among people with metabolic dysfunction-associated steatotic liver disease remains unclear but indicates that treatment and appropriate management of hepatic steatosis should be considered *(45–48)*. Diabetes is thought to increase the risk of progression to HCC *(49)*. Although these risk factors are imperfectly understood, if metabolic dysfunction-associated steatotic liver disease is considered to contribute to significant liver inflammation and fibrosis in a person with CHB, antiviral therapy fibrosis, treatment for hepatitis B is indicated. Tenofovir may increase serum lipid levels *(50)*.

20.2 Decompensated cirrhosis and advanced liver disease

Older people are more likely to present with cirrhosis and complications of chronic liver disease and HCC. Liver failure and HCC are rare in the initial 20 years after acquiring infection. Compensated cirrhosis may progress over time to decompensated cirrhosis with associated weight loss, weakness, wasting, oedema, dark urine, jaundice, ascites, hepatomegaly, spontaneous bacterial peritonitis, oesophageal varices or encephalopathy, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. With progressive disease and the development of cirrhosis, the laboratory tests become progressively more abnormal. There is generally an increase in the ratio of AST to ALT; a low platelet count (suggesting the development of portal hypertension); an increase in alkaline phosphatase and gamma glutamyl transpeptidase; a decline in serum albumin; and prolongation of prothrombin time, with worsening hepatocellular function. Hyperbilirubinaemia with depressed albumin and prolonged prothrombin time are poor prognostic findings in CHB and associated with an increased risk of liver-related death.

Regular clinical examination and monitoring (every 6–12 months) of serum bilirubin, albumin, international normalized ratio and liver ultrasound before and during treatment are an essential part of the ongoing care of people with hepatitis B–related cirrhosis to detect further disease progression, including decompensation and evidence of HCC.

All people with compensated or decompensated cirrhosis should receive and indefinite antiviral therapy with TDF or ETV, even if the HBV DNA level is low or undetectable, to improve clinical outcomes and to prevent flares and reactivation (see Chapter 5). Suppressing HBV DNA will also decrease the risk of hepatitis B recurring after liver transplantation. Those with deteriorating renal function can use ETV at a recommended dosage of 1 mg daily and should be monitored for lactic acidosis. These people have a high risk of developing HCC, even with effective nucleos(t)ide analogue therapy, and long-term HCC surveillance is therefore mandatory. IFN therapy is generally contraindicated because of significant adverse effects from serious bacterial infections and possible exacerbation of liver disease, even at low doses.

Managing people with complications of cirrhosis and advanced liver disease from hepatitis B, such as assessing and managing oesophageal varices and prophylaxis to prevent variceal bleeding and spontaneous bacterial peritonitis, also requires care by appropriately trained personnel *(51)*. End-stage liver disease from CHB should be treated urgently. Immediate suppression of viraemia confers benefit for people with cirrhosis, reducing (but not obviating) the risk of progression to decompensated cirrhosis and HCC *(52)*. Adequate suppression of viraemia stabilizes people with cirrhosis and advanced liver disease and reduces the need for transplantation. Prophylactic therapy with a nucleos(t)ide analogue (and generally, hepatitis B immune globulin prophylaxis) is recommended for people undergoing liver transplantation.

20.3 Extrahepatic manifestations

About 20% of people with CHB develop major extrahepatic manifestations, including polyarteritis nodosa, non-rheumatoid arthritis, non-Hodgkin lymphoma, cryoglobulinaemic vasculitis and glomerulonephritis, which can influence their quality of life and mortality. The extrahepatic manifestations of hepatitis B and their management have been recently reviewed *(53,54)*. The renal diseases most commonly linked to HBV infection include membranous nephropathy, membranoproliferative glomerulonephritis and polyarteritis nodosa.

Effective antiviral therapy for the primary liver disease can improve extrahepatic signs or symptoms. Treatment with nucleos(t)ide analogues has improved the management of HBsAg-positive glomerulonephritis, kidney transplant recipients and people receiving dialysis, resulting in improved survival while not compromising renal allograft outcome. Nucleos(t)ide analogues are cleared by the kidneys, which requires dose adjustment for those with impaired renal function *(55,56)*. Plasma exchange has been used for acute-on-chronic liver failure, aggressive cryoglobulinaemic vasculitis, glomerulonephritis and progressive peripheral neuropathy *(57-59)*. Careful use of rituximab can be considered together with nucleos(t)ide analogue treatment in refractory cases *(53)*.

20.4 Reactivation of hepatitis B

The exacerbations associated with either a decline in viral replication or reactivation of viral replication and recurrence of disease can also be severe and life-threatening *(60,61)*. The pattern of recurrent reactivation with multiple remissions and recurrences is an especially severe form of CHB, frequently leading to cirrhosis and ultimately liver failure *(62)*. Many cancer chemotherapeutic agents, checkpoint inhibitors, immunosuppressive therapy, bone marrow and stem cell treatment, anti-tumour necrosis factor and newer classes of immunobiologics may reactivate hepatitis B *(63,64)*. Anti-CD20 monoclonal antibody (rituximab) treatment of non-Hodgkins lymphoma poses a particular high risk. Pre-emptive antiviral therapy is generally recommended if a risk is considered.

20.5 Acute hepatitis B

Antiviral therapy is not necessary for uncomplicated symptomatic acute hepatitis B, since >95% of immunocompetent adults will spontaneously clear HBV infection *(65)*. People with fulminant or severe acute hepatitis may benefit from nucleos(t)ide analogue therapy with ETV or TDF, to improve survival and reduce the risk of recurrent hepatitis B *(66)*. The duration of treatment has not been established, but continuing antiviral therapy for at least three months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is generally advised.

20.6 Children and adolescents

See Chapter 9.

20.7 Pregnant women

(see Chapters 5 and 9)

20.8 People who inject drugs

Injecting drug use is prevalent in many countries around the world, affecting people in low-, middle- and high-income countries. People who inject drugs have increased risk of acute and CHB (in addition to HIV and HCV infection) and liver-related disease as well as all-cause morbidity and mortality and therefore require additional care, including hepatitis B vaccination. The central tenets of respect, person-centred approaches and non-discrimination should be followed in caring for people who inject drugs, and additional adherence and psychological support should be provided as required.

20.9 Dialysis and kidney transplant recipients (see Chapter 6 and 17)

Hepatitis B is prevalent among people with end-stage renal disease, including kidney transplant recipients, who should all be screened for hepatitis B, and HBV-seronegative people should be vaccinated. TDF and ETV require dose adjustment and should be used with caution among people with renal impairment and renal transplant recipients. Renal function should be monitored during antiviral therapy. Unexpected deterioration of renal function during antiviral therapy may necessitate a change of treatment or further dose adjustment. IFN-based therapy is not recommended for renal transplant recipients because of the risk of graft rejection. All HBsAg-positive people undergoing renal transplantation should receive prophylactic nucleos(t)ide analogue therapy to prevent HBV reactivation.

20.10 Health-care workers

Health-care workers need special consideration for hepatitis B screening and HBV vaccination; however, this is not widely implemented in low- and middle-income countries. Those who are HBsAg positive and viraemic and undertake exposure-prone procedures (with direct contact between the body fluids of health-care workers, especially blood, and the tissues or mucous membranes of the person with hepatitis B), such as procedures performed by surgeons, gynaecologists, nurses, phlebotomists, personal care attendants and dentists, should be considered for antiviral therapy to reduce direct transmission *(71,72)*, and levels of HBV DNA ideally to undetectable or at least to <2000 IU/mL before resuming exposure-prone procedures. Post-exposure prophylaxis should be considered following needle-stick or other occupational exposure.

20.11 Indigenous peoples

Indigenous peoples are a special population group native to a region but retaining social, cultural, economic and political characteristics that are distinct from those of the dominant societies in which they live. Certain indigenous groups in different parts of the world have a high prevalence of hepatitis B. This includes peoples of the Arctic and the Americas and the Maori and aboriginal peoples of New Zealand and Australia *(73–76)*. These populations also often are excluded or feel excluded from health-care services and, since they may live in remote communities far from hospitals and well-equipped clinics, have poor access to health care. The needs of these communities must be considered as countries plan for hepatitis treatment programmes and implement the management recommendations.

20.12 Migrants

Individuals migrating from a region of high hepatitis B endemicity such as sub-Saharan Africa are at higher risk of hepatitis B and hepatitis D, as well as HIV and HCV, depending on their country of origin *(23,77)*. Migrants should be considered for hepatitis B and D testing (where appropriate). These individuals often face challenges adapting and adjusting to a new health-care system and should be appropriately guided and supported into the health-care system of their new country, taking into consideration linguistic and cultural values and preferences.

Web annexes

Web annex A. Summary of declarations of conflicts of interest

Web annex B. Evidence-to-decision making tables and GRADE tables

Web annex C. Systematic reviews, modelling, and landscape reports

Web annex D. Values and preferences survey reports

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Chapter 1

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Chapter 6

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Chapter 19

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Chapter 20

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