World Health Organization

GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION

MARCH 2015

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WHO Library Cataloguing-in-Publication Data

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.

1.Hepatitis B – prevention and control. 2.Hepatitis B – diagnosis. 3.Hepatitis B – drug therapy. 4.Guideline. I.World Health Organization.

ISBN 978 92 4 154905 9 (NLM classification: WC 536)

Printed in France.

Design and layout: blossoming.it

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ACKNOWLEDGEMENTS

Many professionals from a range of backgrounds and specialities have contributed to the development of this guidance. WHO is sincerely grateful for their time and support.

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We appreciate the contribution from Grammati Sarri and Jill Parnham (National Clinical Guideline Centre [NCGC], Royal College of Physicians, UK) for providing technical presentations and sharing their network meta-analyses with the Guidelines Development Group.

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We extend our gratitude to the following consultants and interns for excellent support to the steering committee and the Guidelines Development Group: Ioannis Hodges-Mameletzis, Sarah Hess, and Zainab Hussain. We also thank other WHO staff for peer review of the guidelines: Karen Hennesey (Expanded Programme on Immunization), Selma Khamassi (Injection Safety), Jessica Markby, Vincent Habiyambere, Francoise Renaud, Oyuntungalag Namjilsuren (HIV Department) Annabel Baddeley, Haileyesus Getahun (TB Department), Anita Sands (Essential Medicines & Health Products), Vason Pinyowiwat (WHO Regional Office for South-East Asia), Masaya Kato, Amitabh Suthar (WHO Country Office Viet Nam), Nick Walsh (WHO Regional Office for the Western Pacific).

Funding

Funding for the development of these guidelines was provided by the United States Centers for Disease Control and Prevention.

ABBREVIATIONS AND ACRONYMS

AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBe	antibody to hepatitis B e antigen
anti-HBs	antibody to hepatitis B surface antigen
ARFI	acoustic radiation force impulse
BMI	body mass index
CAPD	continuous ambulatory peritoneal dialysis
cccDNA	covalently closed circular DNA
CG	Cockcroft–Gault
CHB	chronic hepatitis B
CI	confidence interval
CrCl	creatinine clearance
DART	Development of AntiRetroviral Therapy in Africa (trial)
DTP	diphtheria–tetanus–pertussis (vaccination)
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FDA	(US) Food and Drug Administration
FIB-4	fibrosis-4 score
GAVI Alliance	The Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization)
GFR	glomerular filtration rate
gGT	gamma glutamyl transpeptidase
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

HDV	hepatitis D virus
HIV	human immunodeficiency virus
HR	hazard ratio
IFN	interferon
INR	international normalized ratio
IVD	in-vitro diagnostic devices
LMICs	low- and middle-income countries
MDRD	modification of diet in renal disease
MRD	multidrug resistance-associated protein
NA	nucleos(t)ide analogue
NAT	nucleic acid testing
NICE	National Institute of Health and Care Excellence
NIT	non-invasive test
NMA	network meta-analysis
OAT	organic anion transporter
OR	odds ratio
ORF	open reading frame
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PI	protease inhibitor
PICO	population, intervention, comparison, outcomes
PICOT	population, intervention, comparison, outcomes, time
PWID	people who inject drugs
RNA	ribonucleic acid
RCT	randomized controlled trial
RR	relative risk
RUP	reuse prevention
SAGE	(WHO) Strategic Advisory Group of Experts
SIGN	Safe Injection Global Network
SIP	sharp injury prevention
siRNA	short-interfering RNA
STD	sexually transmitted disease
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
WHO ASSIST	Alcohol, Smoking and Substance Involvement Screening Test

ABBREVIATIONS AND NAMES OF ANTIVIRAL DRUGS

3TC	lamivudine
ADV	adefovir
EFV	efavirenz
ETV	entecavir
FTC	emtricitabine
TAF	tenofovir alafenamide fumarate
TBV	telbivudine
TDF	tenofovir disoproxil fumarate

GLOSSARY OF TERMS

NATURAL HISTORY OF 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 (antibodies to hepatitis B surface antigen), usually within 3 months.
Chronic HBV infection	Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV. Throughout the guidelines, the term chronic hepatitis B (CHB) has been used to indicate chronic HBV infection.
Immune-tolerant phase	High replicative phase of infection seen 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 anti-HBe (antibody to hepatitis B e antigen)
Inactive phase (or immune-control phase)	Low replicative phase of chronic hepatitis B 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 chronic hepatitis B (immune-escape phase)	HBeAg-negative but anti-HBe-positive disease with variable levels of HBV replication and liver injury
HBsAg seroconversion	Loss of HBsAg and development of anti-HBs
HBeAg reversion	Reappearance of HBeAg in a person who was 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 chronic hepatitis B infection
Hepatitis B core antigen (HBcAg)	HBV core protein. The core protein is 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 antibody (anti-HBs)	Antibody to HBsAg. Develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity
Anti-HBe	Antibody to HBeAg. Detected in persons with lower levels of HBV replication but also in HBeAg-negative disease (i.e. HBV that does not express HBeAg)
Hepatitis B core antibody (anti-HBc)	Antibody to hepatitis B core (capsid) protein. Anti-HBc antibodies are not neutralizing antibodies and are detected in both acute and chronic infection
IgM anti-HBc	Subclass of anti-HBc. Detected in acute hepatitis B but can be detected by sensitive assays in active chronic HBV
IgG anti-HBc	Subclass of anti-HBc detected in past or current infection
Occult HBV infection	Persons who have cleared hepatitis B surface antigen, i.e. they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL); most are also anti-HBc positive
Treatment failure	May be primary or secondary. *In settings where HBV DNA testing is available:* Primary antiviral treatment failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by ≥1 x $\log_{10}$ IU/mL within 3 months of initiating therapy. Secondary antiviral treatment failure may be defined as a rebound of HBV DNA levels of ≥1 x $\log_{10}$ IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x $\log_{10}$ 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 barrier to resistance together with documented or suspected poor adherence, laboratory measures such as an increase in serum aminotransferases, and/or evidence of progressive liver disease. *Note:* Elevation in ALT level 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.

TESTS FOR ASSESSMENT AND MONITORING OF HEPATITIS B INFECTION

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes which, as they are released after cell injury or death, reflect liver cell injury
HBV DNA	HBV viral genomes that can be detected and quantified in serum. 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. (i.e. 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.
AFP (alpha-fetoprotein)	A host cellular protein. High levels can occur in persons with hepatocellular carcinoma.
Persistently abnormal or normal ALT level	ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, although local laboratory normal ranges should be applied. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.

ASSESSMENT OF LIVER FIBROSIS BY NON-INVASIVE TESTS

APRI	Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. A formula for calculating the APRI is given: APRI = * (AST/ULN) x 100) / platelet count (10^9/L). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
FIB-4	A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. Formula for calculating FIB-4: FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)$^{1/2}$]). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
FibroTest (FibroSure)	Commercial biomarker test that uses the results of six blood markers to estimate hepatic fibrosis
Transient elastography (FibroScan)	A technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver

PERFORMANCE OF DIAGNOSTIC TESTS

Positive predictive value (PPV)	The probability that when a person's test result is positive, they truly have the infection/disease. Predictive values are influenced by the prevalence of the disease in the population.
Negative predictive value (NPV)	The probability that when a person's test result is negative, they truly do not have the infection/disease
Sensitivity of a test	The ability of a test to correctly identify those with the infection or disease (i.e. true positives/true positives + false negatives)
Specificity of a test	The ability of a test to correctly identify those without the infection or disease (i.e. true negatives/true negatives + false positives)
True negative (TN)	When a person's test is negative and they truly do not have the infection or disease
True positive (TP)	When a person's test is positive and they truly have the infection or disease
False negative (FN)	When a person's test is negative, but they do have the infection or disease. Such misclassifications are generally due to assay or test inaccuracy.
False positive (FP)	When a person's test is positive but they do not have the infection or disease. Such misclassifications are generally due to assay or test inaccuracy.

EXECUTIVE SUMMARY

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic, progressive disease. Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more – is a major public health problem. Worldwide, there are an estimated 240 million chronically infected persons, particularly in low- and middle-income countries (LMICs). The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20% and 30% of those who become chronically infected will develop these complications, and an estimated 650 000 people will die annually due to CHB. The majority of people are unaware of their HBV infection, and therefore often present with advanced disease. Universal hepatitis B immunization programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction.

Antiviral agents active against HBV are available, and have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. However, currently available treatments fail to eradicate the virus in most of those treated, necessitating potentially lifelong treatment. In addition, these drugs are not widely available or used in LMICs, and therefore timely intervention to prevent the onset of advanced liver disease does not occur.

These are the first World Health Organization (WHO) guidelines for the prevention, care and treatment of persons living with CHB infection, and complement similar recent published guidance by WHO on the prevention, care and treatment of infection due to the hepatitis C virus (HCV). In contrast to several recent international guidelines on the management of CHB infection from the United States, Europe, Asia-Pacific and the United Kingdom (UK), the primary audience for these WHO guidelines is country programme managers in all settings, but particularly in LMICs to help plan the development and scale up of hepatitis B prevention, care and treatment. These guidelines are also intended for health-care providers who care for persons with CHB in these settings.

The recommendations are structured along the continuum of care for persons with CHB[a], from initial assessment of stage of disease and eligibility for treatment, to initiation of first-line antiviral therapy and monitoring for disease progression, toxicity and HCC, and switch to second-line drugs in persons with treatment failure. They are intended for use across age groups and adult populations.

The recommendations in these guidelines are covered in Chapters 5 to 10, and promote the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment; prioritize treatment for those with most advanced liver disease and at greatest risk of mortality; and recommend the preferred use of nucleos(t)ide analogues with a high barrier to drug resistance (tenofovir and entecavir, and entecavir in children aged 2–11 years) for first- and second-line treatment. These guidelines also recommend lifelong treatment in those with cirrhosis; and regular monitoring for disease progression, toxicity of drugs and early detection of HCC. An additional chapter highlights management considerations for specific populations, including those coinfected with HIV, HCV and hepatitis D virus (HDV); children and adolescents; and pregnant women.

Recommendations for the treatment of HBV/HIV-coinfected persons are based on the WHO 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, which will be updated in 2015. The use of interferon or pegylated interferon as antiviral therapy was excluded from consideration in these guidelines, as their use is less feasible in LMICs due to their high cost and significant adverse effects requiring careful monitoring.

Existing recommendations for the prevention of HBV transmission from relevant WHO guidelines are summarized in Chapter 10. These include prevention of perinatal and early childhood HBV infection through infant hepatitis B vaccination; catch-up vaccination and other prevention strategies in key affected populations, including persons who inject drugs, men who have sex with men, and sex workers; as well as prevention of HBV transmission in health-care settings. The use of alcohol reduction interventions to reduce progression of liver disease in those with CHB is also highlighted.

Several key topics were not included in the scope of work for these guidelines, but will be covered in future guidelines as well as planned consolidated guidelines on persons with chronic hepatitis B and C infection for publication in 2016. These include hepatitis B and C testing algorithms and strategies on who to screen; updated recommendations on hepatitis C treatment; diagnosis and management of acute hepatitis B and C; and management of advanced liver disease. Updated recommendations on the use of hepatitis B vaccination will be considered and issued by the WHO Strategic Advisory Group of Experts on Immunization (SAGE)

[a] Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The term chronic hepatitis B (CHB) is used to mean chronic infection with HBV throughout these guidelines.

in 2015. There will also be a need for future operational guidance on strategies to improve retention in care and adherence to antiviral therapy as well as delivery of hepatitis care, including opportunities to integrate with maternal and child health clinics, tuberculosis clinics, and services that treat HIV and drug dependence.

The development of these guidelines was conducted in accordance with procedures established by the WHO Guidelines Review Committee. Clinical recommendations in the guidelines were formulated by a regionally representative Guidelines Development Group at a meeting held in June 2014, and are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations. This includes assessment of the quality of evidence, consideration of the overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resource use, cost–effectiveness and feasibility.

As with other WHO guidelines on the use of antiretroviral therapy, these guidelines are based on a public health approach to the use of antiviral drugs for the treatment of CHB, which considers feasibility and effectiveness across a variety of resource-limited settings, including where access to specialized tests such as measurement of HBV DNA viral load or liver biopsy for staging of liver disease is limited. The process has also identified key gaps in knowledge that will guide the future research agenda. Most of the evidence was based on studies in adults from Asia, North America and western Europe, and there is a striking lack of data to inform management from sub-Saharan Africa, and in children.

These recommendations provide opportunities to save lives, improve clinical outcomes of persons living with CHB, reduce HBV incidence and transmission, and stigma due to disease, but they also pose practical challenges to policy-makers and implementers in LMICs. Chapter 12 covers implementation considerations across the health system for national programmes in adopting the key recommendations. These address the necessary decision-making and planning for the development of hepatitis treatment programmes in the context of HBV epidemiology, health systems capacity, laboratory services and supply systems for drugs and other commodities, as well as available financial resources, and ethical and human rights considerations. There are particular challenges to the implementation of lifelong care and treatment programmes for persons with CHB in LMICs, particularly in sub-Saharan Africa, where there is currently very limited access to diagnostic assays, antiviral therapies and appropriate infrastructure.

Summary of recommendations for persons with chronic hepatitis B infection[a]

CHAPTER 4: NON-INVASIVE ASSESSMENT OF LIVER DISEASE STAGE AT BASELINE AND DURING FOLLOW UP	
	• APRI (aspartate aminotransferase [AST]-to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g. FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. *(Conditional recommendation, low quality of evidence)*

CHAPTER 5: WHO TO TREAT AND WHO NOT TO TREAT IN PERSONS WITH CHRONIC HEPATITIS B	
Who to treat	• **As a priority**, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. (*Strong recommendation, moderate quality of evidence*) • Treatment is recommended for adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), **and** have persistently abnormal ALT levels **and** evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status. (*Strong recommendation, moderate quality of evidence*) › *Where HBV DNA testing is not available*: Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status. (*Conditional recommendation, low quality of evidence*)
Existing recommendation for HBV/HIV-coinfected persons[1]	• In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all those with a CD4 count ≤500 cells/mm^3, regardless of stage of liver disease. (*Strong recommendation, low quality of evidence*) [1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.
Who not to treat but continue to monitor	• Antiviral therapy is **not** recommended and can be deferred in persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), **and** with persistently normal ALT levels **and** low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age. (*Strong recommendation, low quality of evidence*) › *Where HBV DNA testing is not available:* Treatment can be deferred in HBeAg-positive persons aged 30 years or less **and** persistently normal ALT levels. (*Conditional recommendation, low quality of evidence*) • Continued monitoring is necessary in all persons with CHB, but in particular those who do not currently meet the above-recommended criteria for who to treat or not treat, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. These include: - persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/mL **but** persistently normal ALT levels; - HBeAg-negative persons without cirrhosis aged 30 years or less, with HBV DNA levels that fluctuate between 2000 and 20 000 IU/mL, **or** who have intermittently abnormal ALT levels; › *Where HBV DNA testing is not available:* Persons without cirrhosis aged 30 years or less, with persistently normal ALT levels, regardless of HBeAg status.

[a] Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more.
All recommendations in these guidelines apply to persons with CHB infection.

CHAPTER 6: FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B	
	• In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)* • NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. (*Strong recommendation, moderate quality of evidence*)
Existing recommendation for HBV/HIV-coinfected persons [1]	• In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. (*Strong recommendation, moderate quality of evidence*) [1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

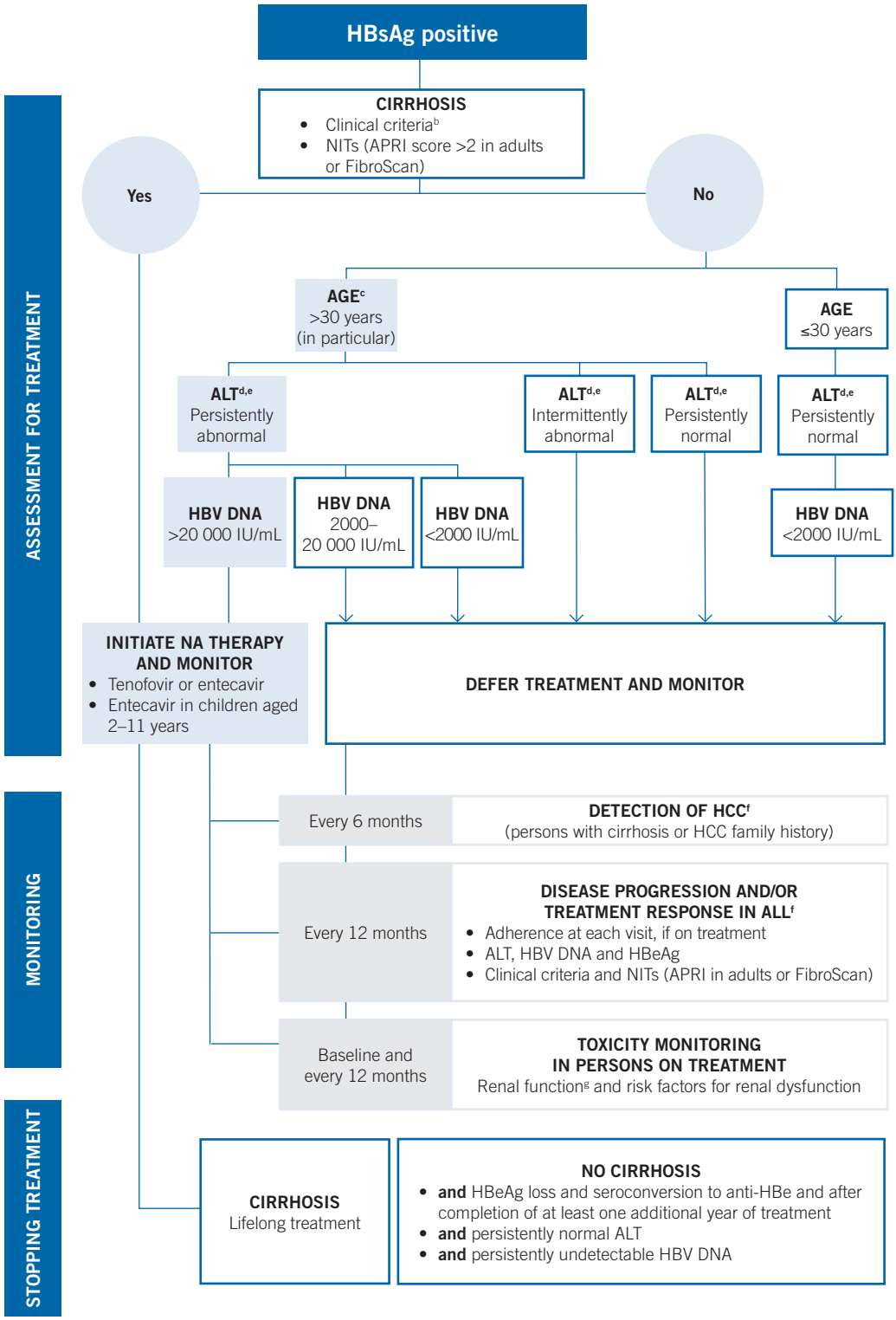
CHAPTER 7: SECOND-LINE ANTIVIRAL THERAPIES FOR THE MANAGEMENT OF TREATMENT FAILURE	
	• In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended. (*Strong recommendation, low quality of evidence*)

CHAPTER 8: WHEN TO STOP TREATMENT	
Lifelong NA therapy	• All persons **with cirrhosis** based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analogues (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (*Strong recommendation, low quality of evidence*)
Discontinuation	• Discontinuation of NA therapy may be considered exceptionally in: - persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults); - **and** who can be followed carefully long term for reactivation; - **and** if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and after completion of at least one additional year of treatment; - **and** in association with persistently normal ALT levels **and** persistently undetectable HBV DNA levels *(where HBV DNA testing is available).* › *Where HBV DNA testing is not available*: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. *(Conditional recommendation, low quality of evidence)*
Retreatment	• Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) *(where HBV DNA testing is available).* (*Strong recommendation, low quality of evidence*)

CHAPTER 9: MONITORING	
9.1: Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment	
	• It is recommended that the following be monitored at least annually: - ALT level (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels (*where HBV DNA testing is available*) - Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline; - If on treatment, adherence should be monitored regularly and at each visit. (*Strong recommendation, moderate quality of evidence*)
More frequent monitoring	• ***In persons who do not yet meet the criteria for antiviral therapy:*** More frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20 000 IU/mL *(where HBV DNA testing is available)*, and in HIV-coinfected persons. (*Conditional recommendation, low quality of evidence*) • ***In persons on treatment or following treatment discontinuation:*** More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons 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 persons; and in persons after discontinuation of treatment. (*Conditional recommendation, very low quality of evidence*)
9.2: Monitoring for tenofovir and entecavir toxicity	
	• Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy. • Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children. (*Conditional recommendation, very low quality of evidence*)
9.3: Monitoring for hepatocellular carcinoma	
	• Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for: - persons with cirrhosis, regardless of age or other risk factors *(Strong recommendation, low quality of evidence)* - persons with a family history of HCC *(Strong recommendation, low quality of evidence)* - persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL *(where HBV DNA testing is available). (Conditional recommendation, low quality of evidence)*

CHAPTER 10: PREVENTION	
10.1: Infant and neonatal hepatitis B vaccination	
Existing recommendations in infants and neonates[1]	• All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses. [1] WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.
10.2: Prevention of mother-to-child HBV transmission using antiviral therapy	
	• In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.
Existing recommendations in HIV-infected pregnant and breastfeeding women[2]	• In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped. (*Strong recommendation, low to moderate quality of evidence*) [2] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]



NITs non-invasive tests, ALT alanine aminotransferase, APRI aspartase aminotransferase-to-platelet ratio index

[a] Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The algorithm does not capture all potential scenarios, but the main categories for treatment or monitoring. Recommendations for settings without access to HBV DNA testing are provided in the relevant chapters.

[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, and oedema.

[c] The age cut-off of >30 years is not absolute, and some persons with CHB less than 30 years may also meet criteria for antiviral treatment.

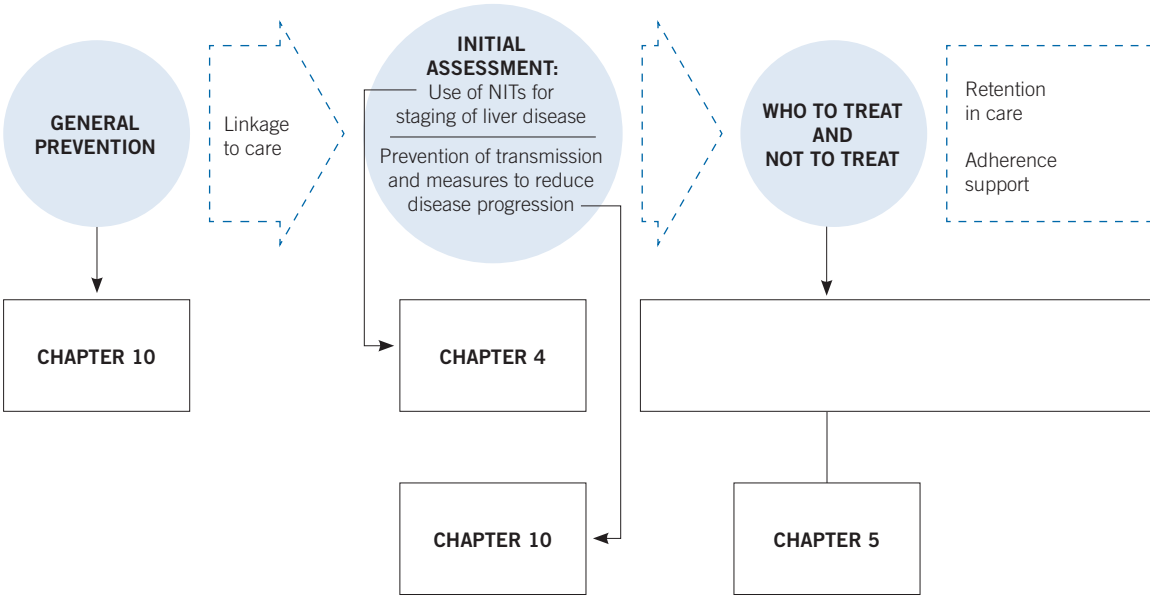
[d] ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied. Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12–month period or predefined intervals during 12-month period.

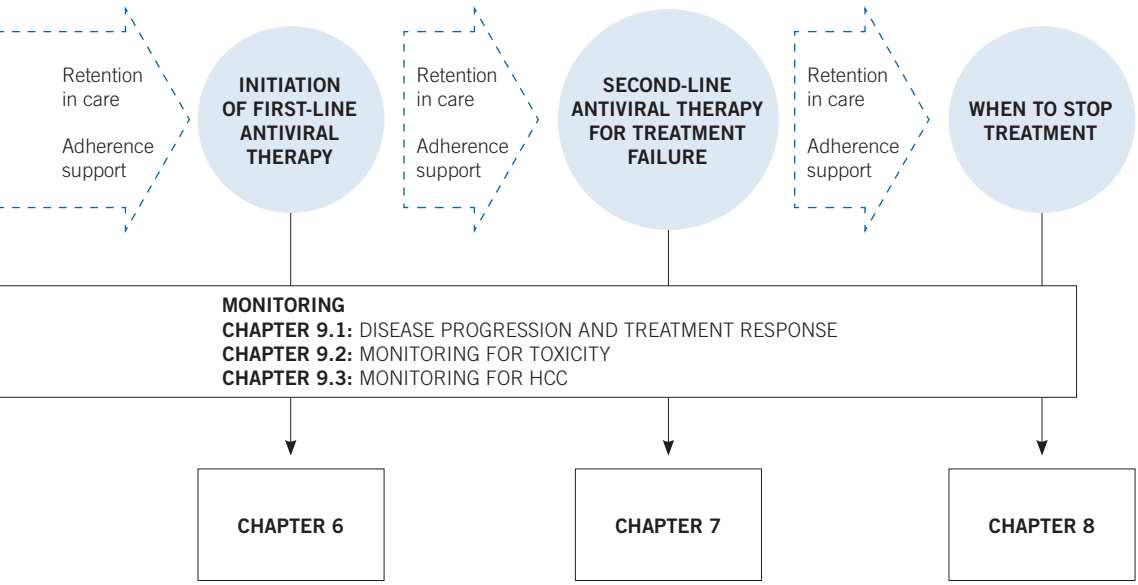
[e] Where HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.

[f] All persons with CHB should be monitored regularly for disease activity/progression and detection of HCC, and after stopping treatment for evidence of reactivation. More frequent monitoring maybe required in those with more advanced liver disease, during the first year of treatment or where adherence is a concern, and in those with abnormal ALT and HBV DNA levels >2000 IU/mL, not yet on treatment.

[g] Before initiation, assessment should be done of renal function (serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria, and risk factors for renal dysfunction (decompensated cirrhosis, CrCl <50 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation, older age, BMI <18.5 kg/m^2 (or body weight <50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV). Monitoring should be more frequent in those at higher risk of renal dysfunction.

STRUCTURE OF THE GUIDELINES ALONG THE CONTINUUM OF CARE





1. INTRODUCTION

1.1. Goals and objectives

Existing guidelines for the treatment of chronic hepatitis B and C infection have been developed by national and international medical organizations, but relate mainly to the treatment of persons living in high-income countries. In 2014, the World Health Organization (WHO) issued its first evidence-based treatment guidelines for persons living with hepatitis C virus (HCV) infection in low- and middle-income countries (LMICs) (1). The present guidelines are the first WHO guidelines on the prevention, care and treatment of persons with chronic hepatitis B virus (HBV) infection – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. They provide a framework for the development or strengthening of hepatitis B treatment programmes in LMICs, but are also of relevance to some high-income countries (2). Although most of the recommendations are related to treatment, there are also recommendations across the continuum of care on assessment, monitoring and general care. These recommendations will be updated and revised as appropriate.

Several key topics were not included in the scope of work for this guideline, but will be covered in future guidelines as well as in planned consolidated guidelines on the management of persons with chronic hepatitis B and C for publication in 2016. In addition to incorporating the current treatment recommendations, these will include hepatitis B and C testing algorithms and strategies on who to screen; management of advanced liver disease; and diagnosis and management of acute hepatitis B and C. The use of interferon (IFN) or pegylated interferon (PEG-IFN)[a] as antiviral therapy was not considered in these guidelines. Although there are some advantages of IFN therapy, such as a finite duration of therapy and possibly a higher rate of HBsAg loss, IFN is less feasible for use in resource-limited settings, as it requires administration by injection, is expensive, inconvenient to use, less well tolerated, and requires careful monitoring. IFN also cannot be used in infants less than 1 year and in pregnant women.

[a] Throughout these guidelines, IFN and PEG-IFN refer to IFN alpha or PEG-IFN alpha.

1.2. Related WHO materials and guidelines

These guidelines on the management of CHB are intended to complement existing WHO guidance on the primary prevention of hepatitis B through both hepatitis B vaccination and by improving blood and injection safety, as well as guidance among persons who inject drugs (PWID) and other vulnerable groups, including those living with human immunodeficiency virus (HIV) infection. The existing WHO guidance includes: prevention of perinatal and early childhood HBV infection through infant hepatitis B vaccination (3); treatment of HBV/HIV-coinfected persons in the consolidated antiretroviral (ARV) guidelines (which will be updated in 2015) (4); prevention measures, including catch-up vaccinations in key affected populations (5), including PWID, men who have sex with men and sex workers (6–8), and prevention of HBV infection in health-care settings (9–11). The use of alcohol reduction interventions to reduce progression of liver disease was recommended in the recent WHO HCV treatment guidelines (1). New WHO recommendations on the use of auto-disable syringes in immunization services, and safety-engineered injection devices, including reuse prevention (RUP) syringes and sharp injury prevention (SIP) devices for therapeutic injections, will be published in early 2015.

1.3. Target audience

These guidelines are primarily targeted at policy-makers in ministries of health working in LMICs to assist in developing national hepatitis B prevention and treatment plans and policy, and country-specific treatment guidelines. In addition, 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 a useful resource for clinicians who manage persons with CHB.

1.4. Guiding principles

The overarching objective of WHO is to achieve the highest possible level of health for all people. These guidelines have been developed with this principle in mind and that of the United Nations Universal Declaration of Human Rights (12). People infected with viral hepatitis may come from vulnerable or marginalized groups with poor access to appropriate health care, and be subject to discrimination and stigma. It is therefore essential that these guidelines and the policies derived from them incorporate basic human rights, including the right to confidentiality and informed decision-making when considering whether to be screened and treated for HBV infection.

The public health approach

In accordance with existing WHO guidance on HIV, these guidelines are based on a public health approach to scaling up the use of antiviral therapy for HBV infection (13). 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.

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 gender, 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. Persons with HBV infection may also come from vulnerable groups because of low socioeconomic status, poor access to appropriate health care, or because they belong to groups that are marginalized or stigmatized such as PWID, 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 persons with most advanced disease who need it most, as well as pregnant women, children and vulnerable groups, 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.

Some countries may face significant challenges as they seek to implement these recommendations for the care and treatment of persons with CHB, in the context of constraints in resources and health systems. A key challenge may involve the need to give priority to ensuring access to treatment for those who have the most advanced disease. Each country will need to plan its own approach to ensuring that other care and treatment programmes such as ARVs for HIV infection are not disrupted, and that expanded access is fair and equitable.

Service provision

Provision of quality screening, care and treatment for persons with CHB requires the involvement of appropriately trained individuals as well as facilities suitable for regular monitoring, especially for those on therapy. Facility requirements for providing treatment for HBV will depend on the setting, but will require access to appropriate laboratory facilities for monitoring treatment response, and adequate supplies of medication. Operating testing services under quality management systems is essential for the provision of quality testing results. The protection of confidentiality and a non-coercive approach are fundamental principles of good clinical practice.

Implementation based on 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 anticipated cost–effectiveness of the various interventions. Chapter 12 in these guidelines addresses decision-making and planning for the development of hepatitis treatment programmes, and implementation considerations for the key recommendations relevant to country programme managers.

2. METHODOLOGY AND PROCESS OF DEVELOPING THE GUIDELINES

2.1. WHO guideline development process

These WHO guidelines were developed following the recommendations for standard guidelines as described in the WHO Handbook for Guideline Development, 2012 (1). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was followed for this process (2–11) (Tables 2.1 and 2.2). A Guidelines Development Group was formed, ensuring representation from various stakeholder groups, including members of organizations that represent persons living with chronic hepatitis, advocacy groups, researchers, clinicians and programme managers. Geographical representation and gender balance were also considerations in selecting Group members. There was an initial scoping and planning process to formulate questions across the continuum of hepatitis B care and treatment most relevant to LMICs and determine patient-important outcomes. These questions were structured in PICO format (population, intervention, comparison, outcomes) and patient-important outcomes were identified for each research question *(see Web appendix 1 for PICO questions)*. These outcomes were refined and ranked based on their importance for the patient population (3).

Systematic reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g. study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions. Search strategies and summaries of evidence are reported in Web appendix 2.

The quality of the evidence was assessed and either rated down or rated up based on the following criteria: *rated down* based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool), including publication bias; (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration); or (iv) imprecision. Conversely, the quality of the evidence was *rated up* if there was no reason to rate it down, and if it met any of the following three criteria: (i) large effect size; (ii) dose–response; or (iii) plausible residual confounders (i.e. when biases from a study might be reducing the estimated apparent intervention effect). Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low or very low (Table 2.1). Summaries of the quality of evidence to address each outcome were entered in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler software (GRADEpro 3.6) *(see Web appendix 2)*.

BOX 2.1 Approach to rating the quality of evidence and strength of recommendations using the GRADE system

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

The **quality 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 quality of evidence as high, moderate, low and very low (4–10). Randomized controlled trials (RCTs) are initially rated as high-quality evidence but may be downgraded for several reasons, including the risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if multiple studies show the same effect, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect (10). The higher the quality 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 strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of the intervention (Table 2.2).

The GRADE system classifies the strength of a recommendation in two ways: "strong" and "conditional" (11). 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. 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 Guidelines Development Group is not confident about these trade-offs. 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, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

TABLE 2.1 GRADE categories of the quality of evidence (4–10)

Level of evidence	Rationale
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

TABLE 2.2 Key domains considered in determining the strength of recommendations

Domain	Rationale
Benefits and risks	Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation will be made.
Values and preferences (acceptability)	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation will probably be made. If there are strong reasons that the recommended course of action is unlikely to be accepted, a conditional recommendation is more likely to be made.
Costs and financial implications (resource use)	Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is more probable.

At the June 2014 meeting of the Guidelines Development Group, for each of the PICO questions *(see Web appendix 1)*, the results of the systematic reviews and the evidence profiles *(see Web appendix 2)* were presented, and reviewed to ensure that there was understanding and agreement on the scoring criteria. Drug availability and costs of diagnostics and drugs were also considered based on the available evidence and presentations from invited external expert speakers. Recommendations were then formulated based on the overall quality of the evidence, in addition to other considerations, including the balance between benefits and harms, values and preferences, and resource implications (Table 2.2). However, no formal survey of acceptability of the proposed interventions among patients or health-care workers was undertaken for these guidelines. These were assessed through discussions among members of the Guidelines Development Group. The strength of the recommendations was rated as either strong (the panel was confident that the benefits of the intervention outweighed the risks) or conditional (the panel considered that the benefits of the intervention

probably outweighed the risks). Recommendations were then formulated and the wording finalized by the entire Group. Implementation needs were subsequently evaluated, and areas and topics requiring further research identified.

The final recommendations were agreed on by consensus during a teleconference in July 2014. After all of the comments and questions from members of the Guidelines Development Group were addressed, a draft document was prepared and circulated to the members of the Guidelines Development Group. Suggested changes were incorporated into a second draft, which was circulated again to the Guidelines Development Group, as well as to the WHO Steering Group, and external peer reviewers. This document was further revised to address their comments, but modifications to the recommendations or to the scope were not considered.

2.2. Roles

The Guidelines Development Group helped formulate the PICO questions *(see Web appendix 1)*, reviewed the evidence profiles *(see Web appendix 2)*, formulated and agreed upon the wording of the recommendations, and reviewed all drafts of the guidelines document. The peer reviewers reviewed the draft guidelines document and provided comments and suggested editorial changes.

The guideline methodologist ensured that the GRADE framework was appropriately applied throughout the guidelines development process. This included a review of the PICO questions, ensuring the comprehensiveness and quality of the systematic reviews, and preparation of 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.

2.3. Management of conflicts of interest

In accordance with WHO policy, all members of the Guidelines Development Group and peer reviewers were required to complete and submit a WHO Declaration of Interest form (including participation in consulting and advisory panels, research support and financial investment) and, where appropriate, also provide a summary of research interests and activities. The WHO Secretariat then reviewed and assessed the declarations submitted by each member and, at the June 2014 meeting of the Guidelines Development Group, presented a summary to the Guidelines Development Group *(see Web appendix 3)*. The WHO Secretariat considered significant and predominant funding from a single company whose drug was being considered for use in the treatment of HBV (e.g. tenofovir by Gilead Sciences). The Secretariat found no case where there

was exclusive membership of an advisory panel, receipt of consulting fees or financial support through research grants from one pharmaceutical company. One member had received a research grant from Gilead, but this was for a community-based screening project, and unrelated to treatment. The Secretariat therefore concluded that no member should be excluded from actively taking part in formulating the recommendations during the meeting. For the peer review group, the WHO Secretariat was satisfied that there had been a transparent declaration of financial interests, and no case necessitated exclusion from the review process.

2.4. Disseminating and monitoring implementation of the guidelines

The guidelines will be launched in March 2015 at the annual meeting of the Asian Pacific Association for the Study of the Liver, which brings together approximately 5000 persons involved in hepatitis care. The guidelines will also be accessible on the WHO website with links to other related websites, and translated into the official UN languages. The Secretariat staff will work with the hepatitis points of contact in the WHO regional offices to ensure dissemination to WHO country offices and ministries of health, as well as key international, regional and national collaborating centres (e.g. civil society, foundations, donors), and national programmes. Additional tools will be developed to support country implementation.

Implementation of these guidelines will be assessed by the number of countries that incorporate them into their national treatment guidelines. This will be monitored through the biannual survey that forms the basis for the WHO Global policy report on the prevention and control of viral hepatitis. In the future, the impact of the guidelines would be measured by monitoring the number of persons treated for CHB. However, at present, there is no monitoring system that can collect this information at a national level.

3. BACKGROUND

3.1. Epidemiology and burden

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver and causes hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and may range from asymptomatic infection or mild disease to severe or rarely fulminant hepatitis (1). Acute hepatitis B is usually a self-limiting disease marked by acute inflammation and hepatocellular necrosis, with a case fatality rate of 0.5–1% (1). Chronic hepatitis B (CHB) infection[a] encompasses a spectrum of disease, and is defined as persistent HBV infection (the presence of detectable hepatitis B surface antigen [HBsAg] in the blood or serum for longer than six months), with or without associated active viral replication and evidence of hepatocellular injury and inflammation (1). Age is a key factor in determining the risk of chronic infection (Figure 3.1). Chronicity is common following acute infection in neonates (90% of neonates born to hepatitis B e antigen [HBeAg]-positive mothers) and in young children under the age of 5 years (20–60%), but occurs rarely (<5%) when infection is acquired in adulthood (2,3). Worldwide, the majority of persons with CHB were infected at birth or in early childhood.

The spectrum of disease and natural history of chronic HBV infection are diverse. In some people, CHB is inactive and does not lead to significant liver disease. In others, it may cause progressive liver fibrosis, leading to cirrhosis with end-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC), independent of the presence of cirrhosis – usually many years after initial infection (4). Longitudinal studies of untreated persons with CHB show an 8–20% cumulative risk of developing cirrhosis over five years (2–6). In those with cirrhosis, there is an approximately 20% annual risk of hepatic decompensation (7) and the annual incidence of hepatitis B-related HCC is high, ranging from <1% to 5% (7). Untreated patients with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years (5,7,8). Several host and viral factors, especially coinfections with HIV, HCV and hepatitis D virus (HDV), together with other cofactors such as alcohol use, may increase the rate of disease progression and risk of developing HCC (2,3,5,6) .

It is estimated that worldwide, 2 billion people have evidence of past or present infection with HBV, and 240 million are chronic carriers of HBV surface antigen (HBsAg) (9). Age-specific HBsAg seroprevalence varies markedly by geographical region, with the highest prevalence (>5%) in sub-Saharan Africa, East Asia, some

[a] The term chronic hepatitis B (CHB) has been used throughout the guidelines to denote chronic hepatitis B infection.

parts of the Balkan regions, the Pacific Islands and the Amazon Basin of South America. Prevalence below 2% is seen in regions such as Central Latin America, North America and Western Europe (Figure 3.2) (9). Overall, almost half of the global population lives in areas of high endemicity. Updated WHO estimates of the burden of CHB will be available in 2015. Infection with HBV may present as either hepatitis B "e-antigen" (HBeAg)-positive or -negative disease. The prevalence of HBeAg-negative disease has been increasing over the past decade as a result of ageing of the HBV-infected population, and accounts for the majority of cases in some regions, including Europe (10).

Worldwide, it is estimated that around 650 000 people die each year from the complications of CHB (11). Overall, HBV accounts for around 45% of cases of HCC and 30% of cirrhosis, with much higher proportions in LMICs (11,12). HCC is ranked among the top three causes of death in males, especially in South-East Asia (13). In Asia and most other regions, the incidence of HCC and cirrhosis is low before the age of 35–40 years but then rises exponentially (12). However, in Africa (13), rural western Alaska and the Amazon, the incidence of HCC is also high in infected children and young male adults (12,13). HBV infection also causes a significant economic burden in terms of years of life lost from liver disease in high-income settings as well as LMICs, and accounts for 5–10% of liver transplants (4,5).

Many countries in the world administer hepatitis B vaccine starting at birth or in early childhood (15). Although this strategy has been effective in reducing the incidence and prevalence of hepatitis B in most endemic regions over the past few decades (9,12), it will not have a large impact on the rates of end-stage liver disease or HCC for 20–40 years after the introduction of universal infant immunization.

FIGURE 3.1 Outcome of hepatitis B infection by age at infection

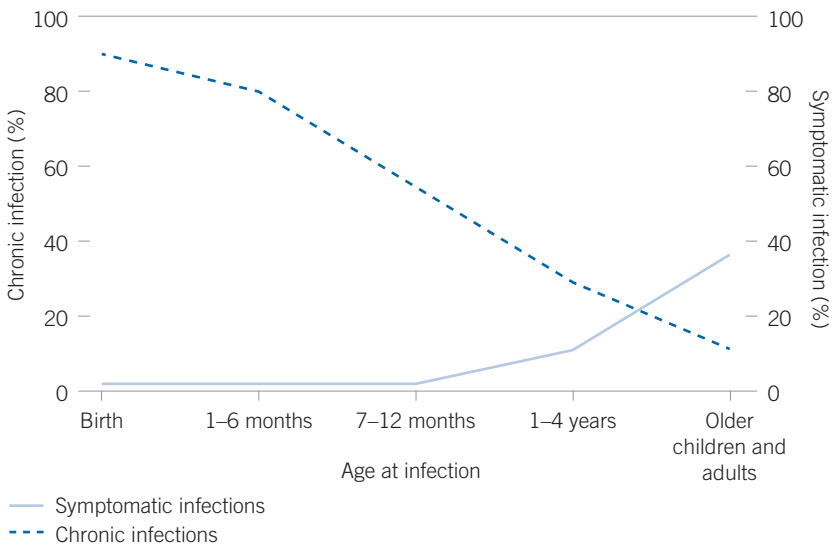
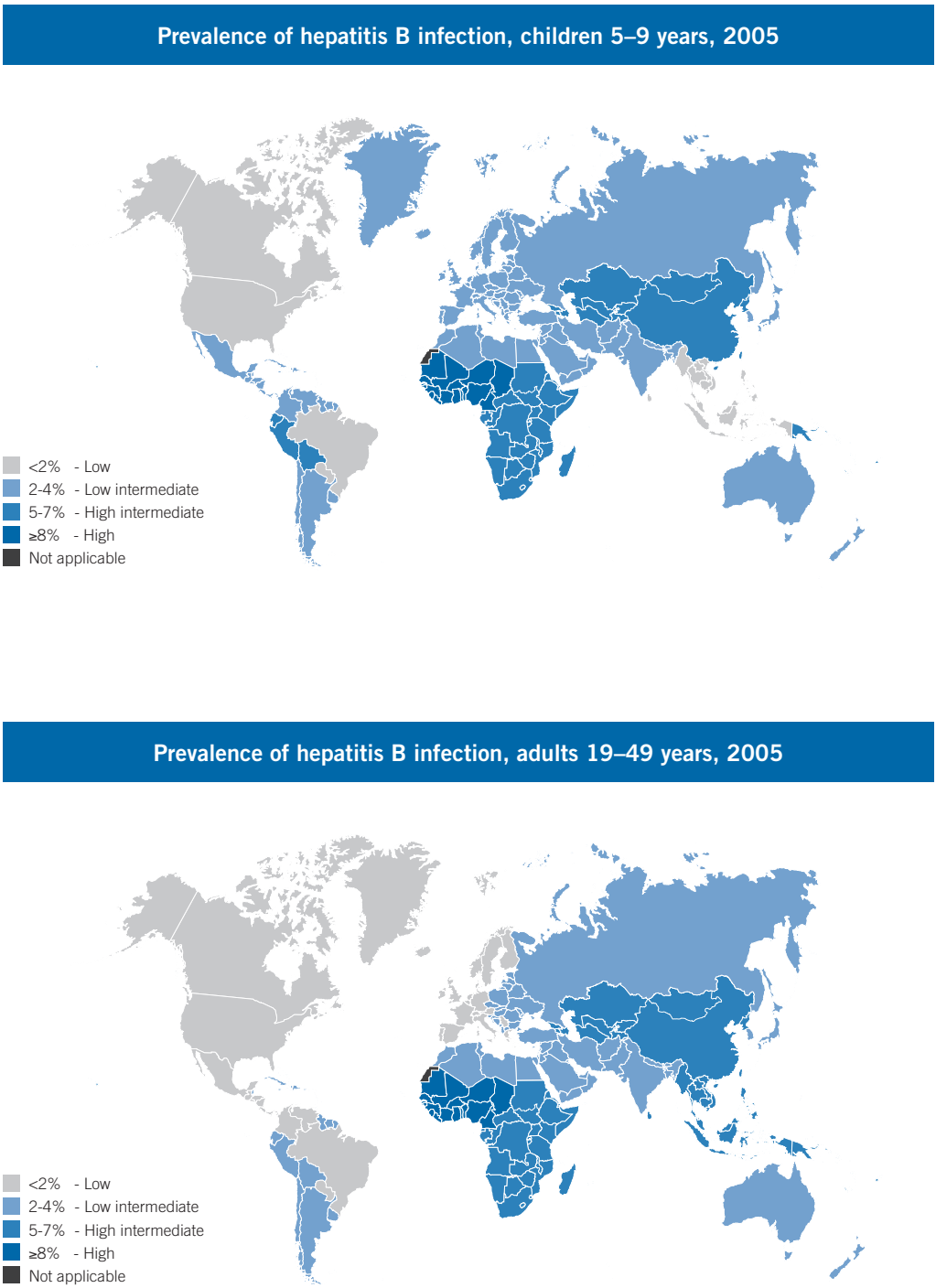


FIGURE 3.2 Geographical distribution of hepatitis B infection worldwide (9)



3.2. Virology

HBV is one of the smallest viruses known to infect humans, and belongs to the hepadnavirus family. It is a hepatotropic virus, and liver injury occurs through immune-mediated killing of infected liver cells. HBV is also a recognized oncogenic virus that confers a higher risk of developing HCC. The genome encodes HBsAg, HBcAg, the viral polymerase and the HBx protein (16). The virus circulates in serum as a 42-nm, double-shelled particle, with an outer envelope component of HBsAg and an inner nucleocapsid component of hepatitis B core antigen (HBcAg). HBV DNA can be detected in serum and is used to monitor viral replication. HBeAg, unlike HBsAg and HBcAg, is not particulate, but rather is detectable as a soluble protein in serum.

Worldwide, at least nine genotypes of HBV (A through I) have been identified on the basis of more than 8% difference in their genome sequences (16–18). Higher rates of HCC have been found in persons infected with genotypes C and F (compared with genotypes B or D), and in those infected with certain subtypes of genotype A found in southern Africa, although aflatoxin exposure may play a role in sub-Saharan Africa. Antiviral therapy is equally effective, and the HBV vaccine protective against all HBV genotypes. A number of naturally occurring mutations in the pre-core region *(pre-core mutants)*, which prevent HBeAg synthesis, have been identified in HBeAg-negative persons with CHB (19). The HBV genotype influences the prevalence of pre-core mutations, but the functional role of this mutation in liver disease is unclear.

3.3. 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 (20). 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. Infection in adulthood leads to chronic hepatitis in less than 5% of cases. Transmission of the virus may also result from accidental inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures, or from razors and similar objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture.

Perinatal transmission: Perinatal transmission is the major route of HBV transmission in many parts of the world, and an important factor in maintaining the reservoir of the infection in some regions, particularly in China and South-East Asia. In the absence of prophylaxis, a large proportion of viraemic mothers, especially those who are seropositive for HBeAg, transmit the infection to their

infants at the time of, or shortly after birth (21). The risk of perinatal infection is also increased if the mother has acute hepatitis B in the second or third trimester of pregnancy or within two months of delivery. Although HBV can infect the fetus in utero, this appears to be uncommon and is generally associated with antepartum haemorrhage and placental tears. The risk of developing chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20–60% between the ages of 6 months and 5 years (21,22) (Figure 3.1).

Horizontal transmission, including household, intrafamilial and especially child-to-child, is also important. At least 50% of infections in children cannot be accounted for by mother-to-infant transmission and, in many endemic regions, prior to the introduction of neonatal vaccination, the prevalence peaked in children 7–14 years of age (23).

3.4. Natural history of chronic hepatitis B

The natural history of CHB is dynamic and complex, and progresses non-linearly through several recognizable phases (Table 3.1). The terms "immune-tolerant", "immune-active", "immune-control" and "immune-escape" have been commonly used to describe these different phases, but it is increasingly recognized that these descriptions are not fully supported by immunological data (24). The phases are of variable duration, are not necessarily sequential, and do not always relate directly to criteria and indications for antiviral therapy.

TABLE 3.1 Phases of chronic hepatitis B

Phase	HBeAg serological status	Pattern	Indications for treatment
1. "Immune tolerant"	HBeAg positive	• Stage seen in many HBeAg-positive children and young adults, particularly among those infected at birth • High levels of HBV replication (HBV DNA levels >200 000 IU/mL)) • Persistently normal ALT • Minimal histological disease	Treatment not generally indicated, but monitoring required
2. "Immune active" (HBeAg-positive[a] chronic hepatitis)	HBeAg positive; may develop anti-HBe	• Abnormal or intermittently abnormal ALT • High or fluctuating levels of HBV replication (HBV DNA levels >2000 IU/mL) • Histological necroinflammatory activity present • HBeAg to anti-HBe seroconversion possible, with normalization of ALT leading to "immune-control" phase	Treatment may be indicated
3. Inactive chronic hepatitis "Immune control" (previously called inactive carrier)	HBeAg negative, anti-HBe positive	• Persistently normal ALT • Low or undetectable HBV DNA (HBV DNA levels <2000 IU/mL) • Risk of cirrhosis and HCC reduced • May develop HBeAg-negative disease	Treatment not generally indicated, but monitoring required for reactivation and HCC
4. "Immune escape" (HBeAg-negative chronic hepatitis)	HBeAg negative, with or without being anti-HBe positive	• HBeAg negative and anti-HBe positive • Abnormal ALT (persistent or intermittently abnormal) • Moderate to high levels of HBV replication (HBV DNA levels >20 000 IU/mL) • Older persons especially at risk for progressive disease (fibrosis/cirrhosis)	Treatment may be indicated
5."Reactivation" or "acute-on-chronic hepatitis"	HBeAg positive or negative	• Can occur spontaneously or be precipitated by immunosuppression from chemo– or immunosuppressive therapy, HIV infection or transplantation, development of antiviral resistance, or withdrawal of antiviral therapy • Abnormal ALT • Moderate to high levels of HBV replication • Seroreversion to HBeAg positivity can occur if HBeAg negative • High risk of decompensation in presence of cirrhosis	Treatment indicated

ALT alanine aminotransferase, anti-HBe antibody to hepatitis e antigen, HBeAg hepatitis B e antigen, HCC hepatocellular carcinoma

[a] Not all persons after HBeAg seroconversion enter the inactive phase. Up to 20% may progress directly from HBeAg immune active to anti-HBe immune escape phase

Phases of chronic hepatitis B (3–7)

1. The *immune-tolerant* phase occurs most commonly in HBsAg-positive children and young adults infected in the perinatal or early childhood period. It usually persists into young adulthood and may last 10–30 years after perinatal infection. Typically, serum HBeAg is detectable, HBV DNA levels are high (usually more than 200 000 IU/mL), and alanine aminotransferase (ALT) levels may be normal or only minimally raised. There is minimal liver inflammation, no or slow progression to fibrosis, and low spontaneous HBeAg loss.

2. This is usually followed by an HBeAg-positive *immune-active phase* of active inflammatory disease. Serum ALT may be abnormal or fluctuate and is accompanied by variable decreases in HBV DNA levels. Symptoms of hepatitis may be present and there is more severe, histologically evident hepatitis and fibrosis. This phase may last from several weeks to years, and may result in successful seroconversion from an HBeAg-positive to an anti-HBe state. Seroconversion rates are higher in those with raised serum aminotransferases and those infected with genotypes D, A, F and (in Asia) B.

3. The non-replicative or inactive *immune-control phase* (previously called the inactive carrier phase) follows successful seroconversion from an HBeAg-positive to anti-HBe state, which occurs in approximately 10–15% of HBeAg-positive persons per year. Once HBeAg is cleared, the disease may remit, with minimal progression of fibrosis, and serum ALT levels revert to normal with low or undetectable levels of HBV DNA (less than 2000 IU/mL). HBeAg seroconversion at a young age, prior to the onset of significant liver disease, confers a good prognosis, with a substantially reduced risk of cirrhosis and liver cancer. However, active viral replication can reappear in a proportion of persons.

4. In addition to HBeAg-positive chronic hepatitis, *HBeAg-negative ("immune escape-mutant") active chronic hepatitis* occurs in approximately 5–15% of HBeAg-negative, anti-HBe-positive persons in the inactive carrier state (8,25,26). HBeAg is undetectable (and anti-HBe detectable) in these persons because mutations in the pre-core or basal core promoter region of the viral genome result in HBV variants that do not express HBeAg. This represents a later phase of disease, generally in older persons, and 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%).

5. 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 (NA) therapy is therefore used. *Occult HBV infection* (defined as persistence of HBV DNA in the liver in persons in whom HBsAg is not detectable in the blood) may also be reactivated through prolonged chemo- or immunosuppressive therapy. Subjects with occult infection may also represent an important source of new infections in blood transfusion services in HBV-endemic LMICs where HBsAg is used as the sole marker of infection in donor populations. Persons who have cleared HBsAg and who are negative for HBV DNA but anti-HBc positive may reactivate if given potent immunosuppressive drugs.

3.5. Diagnosis and staging

Routine assessment of HBsAg-positive persons is needed to guide management and indicate the need for treatment (27,28). This generally includes assessment of: additional serological markers of HBV infection (HBeAg); measuring aminotransferase levels to help determine liver inflammation; quantification of HBV DNA levels; and stage of liver fibrosis by non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest.

HBV serological markers

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. CHB is defined as the persistence of HBsAg for more than 6 months. Recently, quantitative HBsAg level determination has been proposed to differentiate inactive HBsAg carriers from persons with active disease (29).

HBeAg: It also needs to be established whether the person is in the HBeAg-positive or HBeAg-negative phase of infection (Table 3.1), though both require lifelong monitoring, as the condition may change over time. In persons with CHB, a positive HBeAg result usually indicates the presence of active HBV replication and high infectivity. Spontaneous improvement may occur following HBeAg-positive seroconversion (anti-HBe), with a decline in HBV replication, and normalization of ALT levels. This confers a good prognosis and does not require treatment. HBeAg can also be used to monitor treatment response, as HBeAg (anti-HBe) seroconversion in HBeAg-positive persons with a sustained undetectable HBV DNA viral load may be considered a potential stopping point of treatment. However, this is infrequent even with potent NA therapy. Some HBeAg-negative persons have active HBV replication but are positive for anti-HBe and do not produce HBeAg due to the presence of HBV variants or pre-core mutants.

Virological evaluation of HBV infection

Serum HBV DNA concentrations quantified by real-time polymerase chain reaction (PCR) correlate with disease progression (27,28,30) and are used to differentiate active HBeAg-negative disease from inactive chronic infection, and for decisions to treat and subsequent monitoring. Serial measures over a few months or longer are preferable, but there remains a lack of consensus regarding the level below which HBV DNA concentrations are indicative of "inactive" disease, or the threshold above which treatment should be initiated (28). HBV DNA concentrations are also used for optimal monitoring of response to antiviral therapy, and a rise may indicate the emergence of resistant variants. WHO standards are now available for expression of HBV DNA concentrations (31,32). 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 (i.e. 10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). The same assay should be used in the same patient to evaluate the efficacy of antiviral therapy. Access to HBV DNA testing remains very poor in resource-limited settings.

Assessment of the severity of liver disease

A full assessment includes clinical evaluation for features of cirrhosis and evidence of decompensation, and measurement of serum bilirubin, albumin, ALT, AST, alkaline phosphatase (ALP), 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 in persons with cirrhosis.

Liver enzymes: Aminotransferase levels may fluctuate with time, and single measurements of ALT and AST do not indicate disease stage. Usually, the ALT concentrations are 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 (27,28). A progressive decline in serum albumin concentrations, rise in bilirubin and prolongation of the prothrombin time are characteristically observed as decompensated cirrhosis develops.

Liver biopsy: Liver biopsy has been used to ascertain the degree of necroinflammation and fibrosis, and to help guide the decision to treat. There are several established methods of scoring histology and measuring activity (necroinflammation) separately from stage (fibrosis). However, limitations of biopsy include sampling error, subjectivity in reporting, high costs, the risks of bleeding and pneumothorax, discomfort to the patient, and the need for training and infrastructure in LMICs. The pathological features of CHB on liver

biopsy depend upon the stage of the disease, host immune response and degree of virus replication.

Non-invasive tests (NITs) (see also Chapter 4: Non-invasive assessment of stage of liver disease): Non-invasive methods for assessing the stage of liver disease are supplanting liver biopsy and have been validated in adults with CHB. 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 to rule out advanced fibrosis (33–35).

3.6. Screening

Most international guidelines recommend that several 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 persons with CHB, HIV-infected persons, persons who inject drugs (PWID), men who have sex with men, sex workers, as well as other groups such as indigenous peoples, persons who are incarcerated, and persons of transgender. Blood and organ donors should also be screened for HBsAg and other bloodborne pathogens in accordance with WHO recommendations (36) to prevent HBV transmission, especially in LMICs. In the United States and Europe, population-based screening is also recommended for migrants from endemic countries (37,38). There is currently limited guidance on screening for HBsAg in LMICs (39). WHO is developing consolidated guidelines on hepatitis B and C for publication in 2016, which will include testing algorithms and strategies on who to screen for hepatitis B and C infection.

3.7. Prevention through vaccination *(see also Chapters 10.1 Infant and neonatal hepatitis B vaccination* and *10.2 Prevention of mother-to-child HBV transmission using antiviral therapy)*

Recombinant DNA-derived vaccines against HBV have been available for more than two decades. The primary hepatitis B immunization series conventionally consists of three doses of vaccine. Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by at least two other doses. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth (15). This strategy has resulted in a dramatic decrease in the prevalence of CHB among young children in regions of the world where universal infant vaccination programmes have been implemented. A proportion of vaccinated children (5–10%) have a poor response to vaccination, and will remain susceptible as adults to acquisition of HBV infection.

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 as well as other preventive strategies include young adolescents; household and sexual contacts of persons who are HBsAg-positive; and persons at risk of acquiring HBV infection, such as PWID, men who have sex with men, and persons with multiple sex partners.

3.8. Antiviral therapy

Although HBV infection can be prevented by vaccination, it is important to treat persons with CHB at high risk of progression to reduce the considerable morbidity associated with CHB. Over the past three decades, treatment outcomes have improved, first with conventional and then pegylated (PEG) interferon (IFN) and, more recently, with the advent of NAs. Currently, seven antiviral agents (lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine, standard and PEG-IFN) are approved for the treatment of CHB in high-income countries, and have been shown to delay the progression of cirrhosis, reduce the incidence of HCC and improve long-term survival (Table 3.2). Although all NAs act on HBV polymerase, their mechanism of action differs; adefovir inhibits the priming of reverse transcription; lamivudine, emtricitabine and tenofovir inhibit the synthesis of the viral (-) strand DNA; and entecavir inhibits three major stages of HBV replication. In addition to their variable mechanisms of action, their pharmacokinetics, inhibitory capacity and resistance patterns vary (40). Although NAs are effective inhibitors of HBV replication, they seldom result in cure, and clearance of HBsAg is rare. Therefore, at present, long-term (potentially lifelong) NA therapy is required in the majority.

The advantage of NA therapy over IFN includes few side-effects and a one-pill-a-day oral administration. The main advantages of IFN over NAs are the absence of resistance, and achievement of higher rates of HBeAg and HBsAg loss. However, the disadvantages of IFN are that less than 50% of persons treated will respond, its high cost, administration by injection and common side-effects, which precludes its use in many persons, particularly in resource-limited settings. A number of relative and absolute contraindications to IFN also exist, which include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant disease, pregnancy, seizures and psychiatric illness, concomitant use of certain drugs, retinopathy, thrombocytopenia and leucopenia. IFN also cannot be used in infants less than 1 year and in pregnant women.

Several international organizations have developed guidelines for the treatment of CHB (39–41), but the optimal timing of treatment is still debated. In general, treatment is targeted at persons with CHB and moderate or severe liver inflammation, and/or fibrosis and high viral replication, who are at high risk of

disease progression to cirrhosis and HCC. The benefits of treatment for those with mild inflammation or fibrosis are less certain. If HBV replication can be suppressed, the accompanying reduction in chronic liver inflammation reduces the risk of cirrhosis and HCC, but generally lifelong treatment is required. Extrahepatic manifestations of hepatitis B such as glomerulonephritis or polyarteritis nodosa may also respond to treatment.

New treatment strategies: Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir that enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes, so that the dose of tenofovir can be reduced and toxicities minimized (42,43). TAF has been evaluated in recent and ongoing clinical trials (44). Research is also ongoing to develop and test new agents that can "cure" HBV by eliminating all replicative forms, including covalently closed circular DNA (cccDNA). 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. New molecules under investigation include entry inhibitors and short-interfering RNAs (siRNAs), and capsid inhibitors (45).

Planned consolidated guidelines on hepatitis care and management for 2016 will include recommendations for the management of advanced and decompensated liver disease in LMICs.

TABLE 3.2 Antiviral agents active against hepatitis B virus infection (in order of potency and barrier to developing resistance)

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

3.9. Special populations

Coinfection with HIV, HDV, HCV and TB *(see also Chapter 11.1: Management considerations for specific populations: Coinfections)*

HBV, HIV, HCV and HDV share similar transmission routes. In general, concurrent or sequential infection with these viruses usually results in more severe and progressive liver disease, and a higher incidence of cirrhosis, HCC and mortality.

HBV/HIV coinfection *(see also Chapter 11.1.1: HBV/HIV coinfection)*

HIV coinfection has a profound impact on almost every aspect of the natural history of HBV infection based on data from Western cohorts. The consequences include higher rates of chronicity after acute HBV infection, higher level of HBV replication and rates of reactivation, less spontaneous clearance, higher rates of occult HBV (i.e. detectable HBV DNA positivity in the absence of HBsAg seropositivity), more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection (46–50). In Western cohorts, liver disease has emerged as a leading cause of death in HIV-infected persons coinfected with either hepatitis B or C, as mortality due to other HIV-related conditions has declined following the introduction of antiretroviral therapy (ART) (51–54). While earlier studies found no consistent evidence for a significant effect of HBV on HIV disease progression (55,56), recent longitudinal cohort studies have found that coinfection with HBV also can lead to increased progression to AIDS-related outcomes and all-cause mortality (57,58).

It is estimated that between 5% and 15% of the 34 million HIV-infected persons worldwide are coinfected with CHB (59–62), and the burden of coinfection is greatest in LMICs, particularly in South-East Asia and sub-Saharan Africa. In countries where HBV prevalence is high (>5%), as in Africa and Asia, infection is usually acquired perinatally or during early childhood, and precedes HIV infection in most cases. In these settings, the prevalence of CHB in HIV-infected persons is close to that observed in the general population. In contrast, in countries where HBV prevalence is low (<2%), as in Europe, the United States and Australia, HBV infection is acquired during adulthood mainly through sexual intercourse, injecting drug use and nosocomial exposure.

HBV/HDV coinfection *(see also Chapter 11.1.2: HBV/HDV coinfection)*

Hepatitis D virus (HDV) is a small defective RNA virus that requires HBV for its transmission (63,64). The routes of HDV transmission are the same as for HBV but vertical transmission is rare. It is estimated that globally, 5% of HBsAg-positive carriers, or approximately 15 million people, are coinfected with HDV and the distribution is worldwide (63,64). High-prevalence areas include the Mediterranean, Middle East (the Gulf States, Saudi Arabia and Turkey), Pakistan (65–67), Central and northern Asia, Japan, Taiwan, Greenland and parts of Africa

(mainly horn of Africa and West Africa), the Amazon Basin and certain areas of the Pacific. The prevalence is low in North America and northern Europe, South Africa and eastern Asia. Vaccination against HBV prevents acute HDV coinfection, and expansion of childhood hepatitis B immunization programmes has resulted in a decline in hepatitis D incidence worldwide. However, in some settings, an increase has been observed (68–71), attributed to infections among PWID, or as a result of migration from areas where HDV is endemic. Outbreaks of fulminant HDV hepatitis with a high mortality have also been reported in many countries.

Severe or fulminant hepatitis is more frequently observed in HBV/HDV coinfection compared to HBV monoinfection (64,72–74). Two major types of HDV infection are seen. In *acute coinfection*, persons are infected simultaneously with both HBV and HDV, leading to a mild-to-severe or even fulminant hepatitis. Recovery is usually complete and chronic infection is rare (around 2%) (73). In *superinfection*, there may be HDV superinfection of a person who already has CHB, leading to a more severe disease course and accelerated progression to cirrhosis in all ages (74,75), including children (76,77), with occurrence of complications almost a decade earlier (78).

HBV/HCV coinfection *(see also Chapter 11.1.3: HBV/HCV coinfection)*

Coinfection with HCV is commonly found in HBV-endemic countries in Asia, sub-Saharan Africa and South America. In some populations, especially PWID, up to 25% of HCV-infected persons may be coinfected with HBV (79–81). Persons with coinfection are at higher risk of developing HCC (82), both a more aggressive form and at a younger age (83,84). Management of HCV infection is discussed in detail in the 2014 WHO guidelines for the screening, care and treatment of persons with hepatitis C infection (85).

HBV/tuberculosis coinfection *(see Chapter 11.1.4: HBV/TB coinfection)*

Children and adolescents *(see also Chapter 11.5: Children and adolescents)*

CHB is generally benign and asymptomatic in children, as they are usually in the immune-tolerant phase. Children with minimal histological disease have not usually been considered for treatment because of the relatively low immediate risk of progression, low response rates to treatment, and concerns over long-term safety and risks of drug resistance. However, children with severe ongoing necroinflammatory disease or cirrhosis may require antiviral therapy. Conventional IFN, lamivudine and adefovir have been evaluated for safety and efficacy in children, with similar response rates to that in adults (86–89). The US Food and Drug Administration (FDA) has approved tenofovir as treatment for HBV in adolescents and children above the age of 12 years, and entecavir for children above 2 years of age.

Other populations *(see also Chapter 11: Management considerations for specific populations)*

These include pregnant women *(see Chapter 11.6)*; persons who inject drugs *(see Chapter 11.7)*; dialysis and renal transplant recipients *(see Chapter 11.8)*; health-care workers *(see Chapter 11.9)*; and indigenous peoples *(see Chapter 11.10)*.

4. RECOMMENDATIONS: NON-INVASIVE ASSESSMENT OF LIVER DISEASE STAGE AT BASELINE AND DURING FOLLOW UP

Recommendations

APRI (aspartate aminotransferase [AST]-to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g. FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. *(Conditional recommendation, low quality of evidence)*

[a] This recommendation was formulated assuming that liver biopsy is not a feasible option.

4.1. Background

The spectrum of liver disease in persons with CHB ranges from minimal fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis, which is associated with the potentially life-threatening complications of ascites and spontaneous bacterial peritonitis, oesophageal varices and bleeding, hepatic encephalopathy, sepsis and renal failure. Persons with cirrhosis, including those with clinical decompensation, need antiviral therapy as a priority in order to prevent further disease progression. While the diagnosis of decompensated cirrhosis is based on clinically obvious features, this is not always the case for compensated cirrhosis. Identifying persons with cirrhosis or advanced CHB in need of treatment is generally based on a combined assessment of clinical features (including hepatomegaly and splenomegaly), the level and ratio of aminotransferases, and other relevant tests, such as albumin and platelet counts, HBV DNA viral load, the degree of fibrosis and/or necroinflammation on liver biopsy or NITs, and liver imaging.

Liver biopsy: Liver biopsy is considered the gold standard method to stage liver disease and assess for the degree of fibrosis, but it is not widely used in resource-limited settings because of its high cost, invasiveness, patient discomfort, risk of complications, sampling error, as well as the need for expert histological interpretation. Several liver biopsy scoring systems have been developed, of which the METAVIR system (Table 4.1), Knodell and Ishak scores (1) are the most widely used.

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

Non-invasive tests (NITs): Several non-invasive fibrosis tests based on blood or serum indices (APRI, FIB-4 and a commercial assay – FibroTest,) or ultrasound principles (transient elastography [e.g. FibroScan]) (Table 4.2) are now available and increasingly used for evaluating and staging liver fibrosis, which reduces the need for liver biopsy in persons with an established cause of liver disease. The use of accurate and validated NITs in resource-limited settings could help with the optimal selection of persons with CHB for antiviral therapy.

Blood tests such as the APRI and FIB-4 scores consist of indirect markers of fibrosis such as ALT, AST and platelet count (Figure 4.1), which are more readily available in LMICs, are associated with lower costs, do not require particular expertise in their interpretation, and can be performed in an outpatient setting. Other serum tests such as FibroTest are patented and must be performed in laboratories that meet certain quality standards, and are therefore more expensive and less readily available. Not all of these tests can assess all stages of fibrosis/cirrhosis. For example, APRI has been validated for the diagnosis of both significant fibrosis and cirrhosis, while FIB-4 has not been validated for the diagnosis of cirrhosis. These markers of fibrosis have a high specificity but low sensitivity for significant fibrosis and cirrhosis at their specific cut-off ranges and, therefore, many persons with advanced fibrosis and cirrhosis are missed.

More recently, new techniques that measure liver stiffness have been developed based on ultrasound technology. Of such tests, transient elastography performed with FibroScan (Echosens, Paris) has been the most widely evaluated (Figure 4.2). It is non-invasive, takes less than 10 minutes to perform, can be undertaken in outpatient or community settings, and health-care staff can be easily trained in its use. Factors that limit the use of transient elastography include the high cost of the equipment, the need for preventive and corrective maintenance (regular service/recalibration) and trained operators, and the lack of extensively validated cut-off values for specific stages of fibrosis. Other elastography techniques include 2-D acoustic radiation force impulse imaging (ARFI) and shear-wave elastography. ARFI and shear-wave elastography are similar in principle to transient elastography, and have been incorporated into new ultrasound imaging machines. However, they require more operator training and expertise than FibroScan.

TABLE 4.2 Selected non-invasive tests to assess for stage of liver fibrosis

Test	Components	Fibrosis stages assessed	Requirements	Cost
APRI	AST, platelets	≥F2, F4 (cirrhosis)	Basic haematology and clinical chemistry	+
FIB-4	Age, AST, ALT, platelets	≥F3	Basic haematology and clinical chemistry	+
FibroTest	Gamma glutamyl transpeptidase (gGT), haptoglobin, bilirubin, A1 apolipopotein, alpha2-macroglobulin	≥F2, ≥F3, F4 (cirrhosis)	Specialized tests. Requires testing at designated laboratories. Commercial assay	+ +
FibroScan	Transient elastography	≥F2, ≥F3, F4 (cirrhosis)	Dedicated equipment	+ + +

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

FIGURE 4.1 APRI and FIB-4 calculations

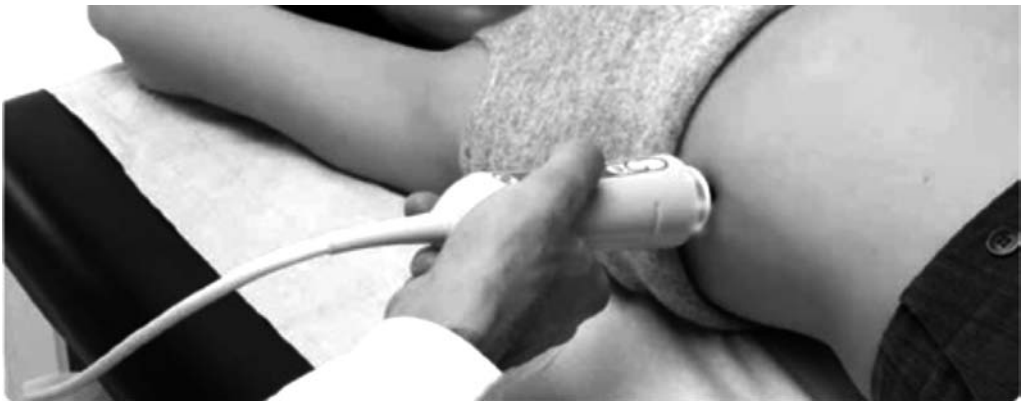
APRI = * (AST/ULN) x 100) / platelet count (10^9/L)

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

For APRI, ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken. For example, in a patient with an AST of 82 IU/L (where laboratory ULN for AST is 40 IU/L) and a platelet count of 90x10^9/L, the APRI would be: (82/40)x100/90 = 2.28. This value is >2 and is consistent with the presence of cirrhosis.

Online calculators can be accessed for APRI at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri, and for FIB-4 at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

FIGURE 4.2 Operation of transient elastography (FibroScan)



Source: http://www.myliverexam.com/en/lexamen-fibroscan.html

4.2. Summary of the evidence

Question: The purpose of the evidence review *(see Web appendix 2: SR4)* was to compare the diagnostic accuracy and performance of different NITs (APRI, FIB-4, FibroTest and transient elastography [e.g. FibroScan]) in diagnosing cirrhosis and significant liver fibrosis in persons with CHB compared to liver biopsy as the reference standard. Outcomes were the sensitivity, specificity, and positive and negative predictive values of NITs, using defined index test cut-off points for the detection of cirrhosis (stage F4) and significant fibrosis (stage ≥F2) based on the METAVIR staging system. As the presence of cirrhosis was considered a priority criterion for initiation of antiviral therapy, the primary outcome assessment in the review was for diagnosis of cirrhosis (F4).

NIT cut-off values for the detection of cirrhosis and significant fibrosis

The optimal cut-off values for different NITs that correlate with specific stages of liver fibrosis have been derived and (in the case of APRI and FIB-4) also validated. APRI and FIB-4 use two cut-off points for diagnosing specific fibrosis stages, as the use of a single cut-off would result in suboptimal sensitivity and specificity. A high cut-off with high specificity (i.e. fewer false-positive results) is used to diagnose persons with fibrosis (i.e. greater than or equal to a particular stage [e.g. ≥F2]), and a low cut-off with high sensitivity (i.e. fewer false-negative results) to rule out the presence of a particular stage of fibrosis. Some persons will fall in the indeterminate range of test results (i.e. their score will be between the low and the high cut-off) and will need future re-testing and evaluation. Transient elastography (FibroScan) has a range of values between 0 and 75 kPa, and although there are no uniformly established and validated cut-offs for specific stages of fibrosis, it uses a single cut-off. Table 4.3 shows the established high and low cut-off values

of APRI, FIB-4, FibroTest, and a range of the most commonly reported cut-offs for transient elastography (FibroScan) for diagnosing cirrhosis (F4) and significant fibrosis (≥F2).

TABLE 4.3 Cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis

	APRI (low cut-off)	APRI (high cut-off)	FIB-4	Fibrotest	Transient elastography (FibroScan)[a]
Cirrhosis (METAVIR F4)	1.0	2.0	--	0.32–0.48	>11–14 kPa
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	1.45 (low) 3.25 (high)	0.58–0.75	>7–8.5 kPa

kPa kilopascal

[a] There are no validated exact cut-offs for specific stages of fibrosis with FibroScan. This table presents the range of the most commonly used cut-offs for F4 and ≥F2 stages of fibrosis in CHB. A mean cut-off of 12.5 kPa may be used to diagnose cirrhosis and guide treatment decisions, after taking into account key limitations.

Separate meta-analyses were performed to evaluate the diagnostic performance of low and high cut-offs of different NITs (APRI, FIB-4, FibroTest and FibroScan) and for each METAVIR stage (F2–F4). There were data from 79 studies (2–80), which included 38 studies from South-East Asia, two from sub-Saharan Africa and the remainder from various countries and geographical regions *(see Web appendix 2: SR4)*. There were two studies in HBV/HIV-coinfected persons (44,80), one in children (61) but none in adolescents or pregnant women. Overall, the quality of evidence was rated as low, because of bias due to the absence of predetermined index test cut-offs, and selection bias in study populations.

Diagnostic accuracy and performance of NITs

Table 4.4 presents the summary sensitivity, specificity, and positive and negative predictive values for the detection of cirrhosis (F4 stage) and significant fibrosis (≥F2 stage) for APRI, FibroTest and transient elastography (FibroScan). Additional data on all NITs, including FIB-4 (not used for diagnosing F4) and FibroTest are available in *Web appendix 2: SR4.* For the diagnosis of cirrhosis (F4), FibroScan had similar sensitivity (86%) to FibroTest (88%), but significantly better sensitivity than the APRI low or high cut-offs (65% and 35%, respectively). FibroScan had similar specificity (87%) to the APRI high cut-off (89%), but significantly better specificity than the FibroTest (73%).

The positive and negative predictive value, number of true-positive, false-positive, true-negative and false-negative results of NITs for the diagnosis of cirrhosis (F4) were also assessed (Tables 4.4 and 4.5). For this analysis, APRI and FibroScan

only were selected, as FIB-4 is not used for diagnosing cirrhosis, and FibroTest is less accurate than FibroScan for diagnosing cirrhosis. The prevalence of cirrhosis and fibrosis in the population under evaluation is a major determinant of the predictive value of these tests in practice. The median prevalence (interquartile range) of fibrosis stages F2–F4 in included studies was: for F4 17% (12–25%) and ≥F2 49% (34–62%), but this was based on a highly selected population who had liver biopsy because of various clinical and laboratory indications. The true prevalence in a clinic setting or at a community level will be lower. Table 4.5 presents the number of true- and false-positive and true- and false-negative results, using APRI (low, high or combined cut-offs) and FibroScan for the detection of cirrhosis (F4) in 1000 persons, assuming a prevalence of 10%.

The positive predictive value (PPV) was low (less than 50%) for all NITs, but FibroScan had a higher PPV (42%) than APRI using either a high or low cut-off (26% and 22%) (Table 4.4). Although using a low APRI cut-off has a much higher sensitivity than the high cut-off, it results in many more false-positive results compared to the high cut-off (225 versus 99 in 1000 persons tested) (Table 4.5). Overall, there would be no significant difference in the number of false-positive and false-negative results between persons tested with FibroScan and those tested using the combined cut-offs of APRI.

Other fibrosis stages

For the diagnosis of fibrosis stages ≥F2, the summary sensitivities of APRI (low cut-off), FibroTest and transient elastography (FibroScan) were 78%, 68% and 76%, respectively, while the summary specificities of APRI (high cut-off), FibroTest and FibroScan were 92%, 92% and 82%, respectively. There were no significant differences between the accuracy of FibroScan and FibroTest in the diagnosis of stages ≥F2 and ≥F3. For the diagnosis of stages ≥F2, the APRI low cut-off had a similar sensitivity and APRI high cut-off had a significantly better specificity than FibroScan.

Overall, there were also no differences in the diagnostic accuracy of the evaluated NITs in relation to ethnicity (South-East Asia versus other ethnicities), but only one study was conducted in sub-Saharan Africa and none in Latin America.

TABLE 4.4 Summary of sensitivity, specificity, and positive and negative predictive values of APRI, FibroTest and transient elastography (FibroScan) for the detection of cirrhosis (F4) and significant fibrosis (≥F2)

		APRI (low cut-off)	APRI (high cut-off)	FibroTest	Transient elastography (FibroScan)
Cirrhosis (METAVIR F4)	Sensitivity (%) (95% CI)	65 (55–73)	35 (22–49)	88 (78–94)	86 (81–90)
	Specificity (%) (95% CI)	75 (70–80)	89 (81–94)	73 (66–79)	87 (83–90)
	Positive predictive value (%) (95% CI)	22 (18–28)	26 (19–34)	27 (22–32)	42 (35-49)
	Negative predictive value (%) (95% CI)	95 (93–97)	92 (91–94)	98 (97–99)	98 (97-99)
Significant fibrosis (METAVIR ≥F2)	Sensitivity (%) (95% CI)	78 (71–84)	36 (28–45)	68 (59–76)	76 (71–80)
	Specificity (%) (95% CI)	60 (50–69)	92 (90–95)	84 (75–90)	82 (75–87)
	Positive predictive value (%) (95% CI)	57 (52–61)	75 (68–81)	74 (69–78)	74 (69–78)
	Negative predictive value (%) (95% CI)	80 (76–84)	68 (65–72)	80 (76–83)	84 (80–87)

Positive and negative predictive values are calculated based on a 10% prevalence of F4 and 49% of ≥F2 stages.

TABLE 4.5 Number of true- and false- positive and -negative results, and indeterminate results using APRI (low, high or combined cut-offs) and transient elastography (FibroScan) for the detection of cirrhosis (F4) in 1000 persons, assuming a prevalence of 10%

	APRI (low cut-off) ≤1 and >1	APRI (high cut-off) ≤2 and >2	APRI combined cut-off >2 and ≤1	Transient elastography (FibroScan)
True positive (TP)	65	35	35	86
False positive (FP)	225	99	99	117
False negative (FN)	35	65	35	14
True negative (TN)	675	801	675	783
Indeterminate results	NA	NA	156	NA

4.3. Rationale for the recommendations

Balance of benefits and harms

The Guidelines Development Group recommended the use of NITs to assist in the assessment of stage of liver disease and diagnosis of cirrhosis, to help prioritize those at greatest risk of morbidity and mortality for antiviral therapy. This avoids the use of liver biopsy, which is an expensive and invasive procedure associated with patient discomfort, carries a small risk of serious bleeding and requires specialist histological interpretation for accurate staging. Based on evidence from the systematic review, the Guidelines Development Group considered that transient elastography (FibroScan) (where resources permit) and APRI were the most useful tests for the assessment of cirrhosis in LMICs. However, the recommendation was conditional because the PPV for detection of cirrhosis was low for all NITs, and in particular for APRI (detecting only one third of persons with cirrhosis), and there has been very limited evaluation of their use in sub-Saharan Africa. FIB-4 was not considered or recommended because it has been developed and validated for the detection of fibrosis stages ≥F3 and not cirrhosis. FibroTest is a commercial assay and less accurate than transient elastography (FibroScan) for diagnosing cirrhosis. Standard ultrasound was also not considered as it only detects advanced cirrhosis, and therefore its use would result in an unacceptably high number of false-negative results.

Potential harms from the use of NITs include treatment decisions based on either false-positive or false-negative APRI test results. A false-positive test result may lead to a patient being treated unnecessarily or prematurely, which would expose them to the inconvenience of long-term treatment, potential drug resistance as well as a small risk of drug toxicities. Conversely, a false-negative result means that a person with cirrhosis would not be identified by NITs, and may therefore not receive prompt antiviral therapy, which might prevent progression to decompensation or decrease the risk of developing HCC.

APRI is based on two indirect markers of fibrosis (AST and platelet count), which are readily available in resource-limited settings. An approach that combined a high and a low cut-off value of APRI would be optimal (a high cut-off with high specificity [i.e. fewer false-positive results] and a low cut-off with high sensitivity [i.e. fewer false-negative results]). However, the Guidelines Development Group recommended the use of a single high cut-off >2 for identifying adults with cirrhosis (F4) and in need of antiviral therapy, and those ≤2 without cirrhosis for several reasons.

1. Although in adults an APRI score of >2 would detect only one third of persons with cirrhosis, this high cut-off of >2 was used, because the low cut-off would result in an unacceptibly high number of false-positive test results (approximately one quarter of those tested).

2. It is also likely that adults with cirrhosis not detected using an APRI score >2 would be identified as being in need of antiviral therapy because of other eligibility criteria (such

as persistently abnormal ALT levels[a] as well as evidence of ongoing HBV replication (HBV DNA >20 000 IU/mL) *(see also Chapter 5: Who to treat and not to treat)*.

3. It is also simpler and more feasible to use a single cut-off in resource-limited settings.

Clinical evidence of cirrhosis or an APRI score >2 are recommended in these guidelines as key criteria for prioritizing initiation of antiviral therapy among adults in resource-limited settings. Conversely, treatment can be deferred in those without clinical features of cirrhosis (or based on APRI score ≤2), who also have persistently normal ALT concentrations and low levels of HBV replication (HBV DNA <2000 IU/mL), and who can be re-evaluated at subsequent visits. For those with an APRI score ≤2, a proportion will fulfil other criteria for treatment such as persistently abnormal ALT or raised HBV DNA levels. Adults with indeterminate APRI scores (i.e. between 1 and 2 based on the combined APRI cut-off) in particular would need retesting and evaluation every one or two years.

Caveats in the use of NITs: Overall, the Guidelines Development Group considered that the benefits of using NITs outweighed these potential harms. The benefits included the potential increase in treatment availability resulting from access to non-invasive monitoring, and reduced risk of adverse events from liver biopsy.

However, a number of very important caveats were noted in the use of NITs. Overall, the PPV of all NITs for the diagnosis of cirrhosis was low, especially for APRI, and many cases of cirrhosis will be missed using NITs alone. It is therefore important that NITs are used alongside clinical criteria and other laboratory criteria (ALT and HBV DNA levels) to identify those in need of treatment. Second, the results of NITs may be impacted by intercurrent diseases that may falsely increase or decrease the scores. For example, heavy alcohol intake (due to AST elevation from alcoholic hepatitis), and conditions such as malaria or HIV (due to a decrease in platelet count), or use of drugs and traditional herbal medicines may also cause falsely high APRI scores. Hepatitis flares or acute hepatitis, congestive heart failure or a recent meal may also cause a high liver stiffness measurement on elastography (81). The impact of different comorbidities on the diagnostic accuracy of the APRI score has not been fully evaluated and, in particular, there has been no evaluation of NITs, particularly APRI in people from sub-Saharan Africa or among children.

Limitations with transient elastography (FibroScan) include the following: it uses a single cut-off and therefore reported sensitivities and specificities of FibroScan may be overestimated across fibrosis stages; there are no uniformly established and validated cut-offs for specific stages of fibrosis; accuracy is diminished in obese persons, in the presence of moderate/severe necroinflammation, right-sided heart failure, and food intake. Examination is not feasible in the presence of ascites and is contraindicated

[a] ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, although local laboratory normal ranges should be applied. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.

in pregnant women. Data on its use in children are limited, and special probes are required.

Although the data on HBV/HIV coinfection were limited, the performance of NITs in such persons is unlikely to be significantly different from that in HBV-monoinfected persons.

Values and preferences

From a patient's perspective, the Guidelines Development Group felt that the APRI test would be acceptable, as it requires only phlebotomy, is routinely available and can be undertaken by untrained staff. Similarly, transient elastography (FibroScan) is non-invasive, takes less than 10 minutes to perform, can be undertaken in outpatient or community settings, and health-care staff can be easily trained in its use. Factors that limit the use of transient elastography include the high cost of the equipment, the need for preventive and corrective maintenance, regular service/recalibration, trained operators, and the lack of extensively validated cut-off values for specific stages of fibrosis.

Resource use

The lower cost of the blood-based NITs compared to transient elastography was a key factor in the recommendation for the use of APRI as the preferred NIT. The blood tests that are needed to calculate APRI score are routinely available at most health-care facilities, even in LMICs, and are inexpensive (less than a few dollars each). The results of APRI using a high cut-off of >2 in adults to diagnose cirrhosis are also relatively straightforward to interpret. Cost considerations were a concern with the FibroTest. It is a patented test that is costly (approximately US$ 73/test) and requires a certified laboratory or the processing of specimens at a centralized laboratory in France.

In contrast to APRI, the cost of acquiring, running and maintaining (requires regular service/recalibration) a transient elastography machine such as the FibroScan is high; the machine costs US$ 50 000 (or US$ 34 000 for the portable machine), and yearly maintenance is US$ 8500/year. However, consumable costs are minimal for FibroScan, and the cost per test could be less than US$ 10 in some settings. FibroScan also requires a trained operator, and the interpretation of the results needs an understanding of the indications and limitations of the method, especially given the lack of well-validated cut-off values for specific stages of fibrosis. However, the training process is relatively straightforward and the inter- and intra-observer variability of the test is low (81). FibroScan in children requires a specially designed probe and a different specific probe for those with a body mass index (BMI) >30 kg/m^2. For these reasons, the use of transient elastography and FibroTest was considered to be less feasible in most LMICs.

Research gaps

- Conduct comparative assessments of NITs for use in high-prevalence resource-limited settings, i.e. APRI, FIB-4, transient elastography, as well as other elastography techniques (e.g. ARFI) to identify persons with cirrhosis and advanced fibrosis (requiring treatment) as well as those with minimal disease (not requiring treatment).
- Evaluate the performance of NITs, especially in populations from sub-Saharan Africa and Latin America, and in other underresearched populations, including persons with HBV/HIV coinfection, HBV/HDV coinfection, pregnant women, children and adolescents, and those with non-alcoholic fatty liver disease. Conduct studies on the cost–effectiveness of NITs in the context of LMICs.
- Evaluate the impact of hepatitis flares and other factors on the diagnostic accuracy and performance of the APRI score.
- Establish and validate FIB-4 cut-offs for the diagnosis of cirrhosis and advanced fibrosis.

5. RECOMMENDATIONS: WHO TO TREAT AND WHO NOT TO TREAT IN PERSONS WITH CHRONIC HEPATITIS B

Recommendations

Who to treat

- **As a priority**, all adults, adolescents and children with CHB[a] and clinical evidence of compensated or decompensated cirrhosis[b] (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. *(Strong recommendation, moderate quality of evidence)*

- Treatment is recommended for adults with CHB[a] who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years[c] (in particular), **and** have persistently abnormal ALT levels[d,e] **and** evidence of high-level HBV replication (HBV DNA >20 000 IU/mL[f]), regardless of HBeAg status. *(Strong recommendation, moderate quality of evidence)*

  › *Where HBV DNA testing is not available:* Treatment may be considered based on persistently abnormal ALT levels alone[e], regardless of HBeAg status.
  (Conditional recommendation, low quality of evidence)

Existing recommendation for HBV/HIV-coinfected persons[1]:

- In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease[b], regardless of CD4 count; and in all those with a CD4 count ≤500 cells/mm^3, regardless of stage of liver disease. *(Strong recommendation, low quality of evidence)*

[1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.

Who not to treat but continue to monitor

- Antiviral therapy is **not** recommended and can be deferred in persons without clinical evidence of cirrhosis[b] (or based on APRI score ≤2 in adults), **and** with persistently normal ALT levels[d,e] **and** low levels of HBV replication (HBV DNA <2000 IU/mL[f]), regardless of HBeAg status or age. *(Strong recommendation, low quality of evidence)*

  › *Where HBV DNA testing is not available:* Treatment can be deferred in HBeAg-positive persons aged 30 years or less **and** persistently normal ALT levels.
  (Conditional recommendation, low quality of evidence)

- Continued monitoring is necessary in all persons with CHB, but in particular those who do not currently meet the above-recommended criteria for who to treat or not treat, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. These include:
  - persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/mL[e] **but** persistently normal ALT;

- HBeAg-negative persons without cirrhosis aged 30 years or less, with HBV DNA levels that fluctuate between 2000 and 20 000 IU/mL, **or** who have intermittently abnormal ALT levels[d,e];

  › *Where HBV DNA measurement is not available:* Persons without cirrhosis aged 30 years or less, with persistently normal or ALT levels, regardless of HBeAg status.

[a] Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more

[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, and oedema.

[c] The age cut-off of >30 years is not absolute, and some persons with CHB aged less than 30 years may also meet criteria for antiviral treatment.

[d] ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women (based on greater sensitivity observed in hepatitis C for histological disease in the liver), though local laboratory normal ranges should be applied (1). Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12- month period or predefined intervals during 12-month period.

[e] Where HBV DNA testing is not available, other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.

[f] WHO has defined an international standard for expression of HBV DNA concentrations. Serum HBV DNA levels should be expressed in IU/mL to ensure comparability; the same assay should be used in the same patient to evaluate antiviral efficacy. All HBV DNA values in the recommendations are reported in IU/mL; values given as copies/mL were converted to IU/mL after 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) (2).

Occasionally, extrahepatic manifestations of hepatitis B, including glomerulonephritis or vasculitis, may be indications for treatment.

BOX 5.1 Key points in the initial assessment of persons with CHB prior to therapy

Assessment of the severity of liver disease should include a history, physical examination, including for the presence of hepatomegaly and splenomegaly, and measurement of ALT, AST, ALP and total bilirubin; full blood count, including platelet count and white cell count. ALT and platelet count measurements allow 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 (INR). Patients should also be questioned about the presence of liver-related symptoms[a], although it is recognized that even advanced disease may be asymptomatic.

Assessment of the level of viral replication: using quantification of serum HBV DNA *(where HBV DNA testing is available)* and HBeAg and anti-HBe serostatus.

Assessment for the presence of comorbidities: evaluation for the presence of other comorbidities, including coinfection with HIV, HCV or HDV, impaired glucose tolerance, dyslipidaemia, non-alcoholic fatty liver disease, alcoholic liver disease, iron overload and drug/toxin-induced injury. All persons with cirrhosis should be screened for the presence of HCC. A review of family history of HCC and medication history are also required.

Preventive measures: HBsAg screening with HBV vaccination of non-immune family members and sexual contacts, and other general measures to reduce HBV transmission *(see also Chapter 10.3: Prevention of hepatitis B transmission).*

Counselling on lifestyle: assessment of alcohol consumption, and advice on lifestyle, including alcohol reduction (WHO ASSIST package (3) [Alcohol, Smoking and Substance Involvement Screening Test]), diet and physical activity. Consider also hepatitis A vaccination *(see also Chapter 10.3: Measures to reduce disease progression in persons with chronic hepatitis B).*

Preparation for starting treatment: patients 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 abrupt cessation of treatment may precipitate acute liver failure); and cost implications.

Measurement of baseline renal function[b] and assessment of baseline risk for renal dysfunction[c] should be considered in all persons prior to initiation of antiviral therapy *(see also Chapter 9.2: Monitoring for tenofovir and entecavir toxicity).*

[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/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

[b] Measurement of baseline renal function includes: serum creatinine levels, and calculation of 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) x (wt in kg) x 0.85 (if female)/(72 x Cr in mg%)

MDRD formula: eGFR = 175 x serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is Black) x 0.742 (if female)
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).

[c] Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, 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 (PI) for HIV, and solid organ transplantation.

5.1. Background

The natural history of chronic HBV infection is dynamic and complex, and progresses non-linearly through several recognizable phases that are of variable duration and not necessarily sequential *(see also Chapter 3.4, Natural history of CHB and Table 3.1)*. The spectrum of disease with CHB is diverse. In some people, CHB is inactive and does not lead to significant liver disease. In others (approximately 10–30%), it may cause progressive liver fibrosis, leading to cirrhosis with end-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC), usually many years after initial infection. Understanding the natural history and phases of chronic infection is important to inform decisions about who requires antiviral therapy, and when treatment can be deferred.

The objective of treatment is to prevent the adverse outcomes of CHB. The decision to initiate antiviral therapy is usually based on a combined assessment of the stage of liver disease (from clinical features, liver histology [where available], and increasingly on blood or ultrasound-based NITs), together with levels of serum ALT and HBV DNA. The decision to treat is usually clear in persons who present with life-threatening or advanced liver disease, such as acute liver failure, and compensated or decompensated cirrhosis and acute-on-chronic liver failure. In persons who have not yet progressed to cirrhosis, decisions are also based on ALT and HBV DNA levels. However, not all persons will have elevated ALT and HBV DNA levels. For example, during the immune-tolerant phase of disease, there will be high levels of HBV DNA but low or normal levels of ALT, and little liver inflammation or progression of fibrosis. Later on, during the immune-active phase, HBV DNA levels will be low, but ALT levels raised, with a much higher risk of progression of fibrosis. It is important that antiviral therapy is targeted to the active phases of CHB when the risks of disease progression (fibrosis) are greatest and, conversely, that persons with minimal fibrosis and low risk of CHB progression are identified, as they do not require antiviral therapy. Prospective studies have identified several predictors of progression of HBV-related liver disease, including the risk of cirrhosis and HCC, and likelihood of exacerbations of CHB. These include age, gender, 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, as well as cofactors such as alcohol use, HIV infection and diabetes.

5.2. Summary of the evidence

Question: The purpose of the evidence review was twofold: (i) to determine what factors/tests among HBsAg-positive persons best identify individuals at the highest risk of progression, as well as those at very low risk of progression;

and (ii) to determine what factors/tests best identify individuals with the greatest and least benefit from treatment, in those with and without access to HBV DNA testing. Potential baseline prognostic factors and stratification included: age (>40 or >30 vs <40 or <30 years); cirrhosis (compensated or decompensated)/ fibrosis (METAVIR stages 1–3) vs no cirrhosis or fibrosis; ALT level (>2x or >5x ULN or >ULN) vs normal): and HBV DNA level (any positive or >2000 IU/mL or >20 000 IU/mL vs undetectable). Key outcomes were liver-related mortality and morbidity (fibrosis, cirrhosis, end-stage liver disease, HCC), and progression of liver disease *(see Web appendix 2: SRs5a and 5b)*.

Identifying individuals at highest and very low risk of progression

We reviewed a comprehensive body of evidence, including a systematic review *(see Web appendix 2: SR5a)*, which incorporated data from one previous systematic review (4) and 22 observational studies (four large population-based prospective cohort studies (5–14), 11 prospective cohort studies (15–25), seven retrospective cohort studies (26–32)). Of the 22 included primary studies, the majority were performed in Asia (6–9,11,17–19,22,24,32–37), four in Europe (23,26,28,29), two in North America (5,14) and one in the Middle/Near East (21). The populations analysed in these studies include HBeAg-positive, HBeAg-negative; and HIV-coinfected persons *(see Web appendix 2: SRs5a and 5b)*. A further systematic review *(see Web appendix 2: SR5b)* of observational studies (17,18,20–23,35,39–43) identified thresholds of HBV DNA and ALT levels and age predictive of hepatitis reactivation among persons in different phases of CHB: HBeAg positive (immune-tolerant and immune-active) or HBeAg negative immune-escape.

Population-based studies and the REVEAL-HBV cohort

The Guidelines Development Group considered that the data from four large population-based prospective cohort studies conducted in Taiwan, China, Korea, and Alaska (5–7,37) provided the highest quality of evidence on predictors of progression (5–7,10,12,14). The REVEAL-HBV cohort, in particular – a large population-based prospective observational study of 23 820 participants, aged from 30 to 65 years, enrolled between 1991 and 1992 from seven townships in Taiwan provides the most comprehensive evidence based on high-quality data on patient-important outcomes of HCC, liver cirrhosis and liver-related deaths, and their association with gender, age, HBV DNA and ALT levels and thresholds, HBeAg positivity, family history, and combinations of these variables (8–10,12,13,15).

For the outcome of HCC, the REVEAL-HBV cohort provides consistent evidence of a significantly increased risk of HCC associated with the following factors: male gender, age above 40 years, baseline HBV DNA more than 10 000 copies/mL (>2000 IU/mL), baseline ALT more than 45 U/L, HBeAg positivity, family history of HCC, as well as combinations of these factors (Table 5.1). A consistent and linear increase in

the incidence of HCC with baseline HBV DNA >10 000 copies/mL (>2000 IU/mL) is also seen in HBeAg-negative persons, irrespective of the presence of cirrhosis or whether ALT levels were normal or abnormal (8,12). Five of the 11 other prospective cohort studies provided additional data on patient-important outcomes (16,21,23–25) and showed a consistently increased risk of liver-related outcomes with male gender, increasing age, and raised HBV DNA and ALT levels.

Outcome of cirrhosis/advanced fibrosis: HBV DNA levels not exceeding 20 000 IU/mL (i.e. 100 000 copies/mL) in persons with persistently normal serum ALT levels were associated with a low probability of advanced fibrosis in population-based prospective studies from Alaska (5,14) and Europe (44). Conversely, an HBV DNA level of >200 000 IU/mL (i.e. 1 million copies/mL) was significantly associated with histologically more advanced liver disease compared with <2000 IU/mL. The thresholds of 2000–20 000 and 20 000–200 000 IU/mL were not significantly associated with severe fibrosis (44). A cohort study from Taiwan (24) also showed that persistently normal ALT levels were associated with good long-term prognosis, and conversely, abnormal ALT levels of at least twice the ULN during follow up with an increased risk of cirrhosis.

Based on the systematic review *(see Web appendix 2: SR5b)* of persons in different phases of CHB: *Among HBeAg-positive persons*[a]*:* age above 40 years, and ALT levels above 5 times ULN (compared to less than 2 times ULN) were significant independent predictors of future reactivation (in those who had undergone seroconversion from an HBeAg-positive to anti-HBe status) in one study (17). *Among HBeAg-negative inactive carriers*[b] (18,20–23,25): HBV DNA levels above a threshold ranging from 4200 to 20 000 IU/L were significant independent predictors of future active hepatitis; and an HBV DNA level above 20 000 IU/mL was predictive of current fibrosis among HBeAg-negative persons in the "immune-escape"[c] phase (23,38–40). There was conflicting or inconsistent evidence on thresholds for ALT and age.

[a] High replicative phase of infection seen in the early stage among people infected at birth or in early childhood

[b] Low replicative phase of chronic hepatitis B characterized by HBeAg negativity, anti-HBe positivity, normal ALT and HBV DNA concentrations below 2000 IU/mL

[c] HBeAg-negative but anti-HBe-positive disease with variable levels of HBV replication and liver injury

TABLE 5.1 REVEAL-HBV cohort: incidence of hepatocellular carcinoma (HCC) at 11.4 years according to HBV DNA level, HBeAg status and ALT level at study enrolment (8)

Participant characteristic	Incidence rate of HCC (x 100 000 person-years)	Adjusted RR (95%CI)
Sex		
Female	178	Reference
Male	530	3.0 (2.0–4.5)
Age (years)		
30–39	111	Reference
40–49	399	3.6 (2.0–6.4)
50–59	566	5.1 (2.0–8.9)
>60	901	8.3 (4.6–15.0)
Baseline HBV DNA (copies/mL) [a]		
<300	108	Reference [b]
300–9999	111	NS
10 000–99 999	297	2.7 (1.3–5.6)
100 000–999 999	962	8.9 (4.6–17.5)
>1 million	1152	10.7 (5.7–20.1)
Baseline ALT (U/L)		
<45	337	Reference
>45	1342	4.1 (2.8–6.0)
HBeAg serostatus		
HBeAg-negative	264	Reference
HBeAg-positive	1130	4.3 (3.2–5.9)

RR relative risk, CI confidence interval

[a] 1 IU/mL = 5.3 copies/mL; 2000 IU/mL = 10 000 copies/mL; 20 000 IU/mL = 100 000 copies/mL; 200 000 IU/mL = 1 000 000 copies/mL

[b] Cumulative per cent incidence of HCC at 11.4 years according to HBV DNA level: <300 copies/mL (undetectable) 1.3%; 300–9999 copies/mL 1.37%; 10 000–99 999 copies/mL 3.57%;100 000–999 999 copies/mL 12.17%; >1 million copies/mL 14.89%.

Overall, the evidence from the population-based studies was rated as moderate to high quality for the outcomes of mortality and HCC, and low quality for liver cirrhosis or fibrosis (mainly due to imprecision as a result of a small number of events, and use of clinical criteria and/or ultrasound only without liver biopsy, which have a high specificity and low sensitivity for detecting cirrhosis). The quality of evidence from other studies ranged from low to moderate. There are caveats to the generalizability of the evidence. There were no data from cohorts in sub-Saharan Africa or Latin America, and the data from the REVEAL study may not apply to those with adult-acquired HBV infection, those aged <30 or >65 years, and those infected with HBV genotypes non-B or C. There were also no studies in pregnant women, children or adolescents with CHB.

HBV/HIV coinfection

There are limited outcome data on HBV/HIV-coinfected persons based on one retrospective cohort study (45), and the majority were receiving ART. A baseline CD4+ cell count below 200 cells/mm^3, an ALT elevation at baseline or during follow up, and cumulative time with detectable HIV RNA were associated with an increased risk of advanced liver disease. The evidence was rated as low quality, mainly due to the retrospective study design.

Treatment benefit in persons with advanced liver disease

A further systematic review *(see Web appendix 2:SR5c)* considered four studies that examined the impact of treatment in persons with advanced liver disease (compensated and decompensated cirrhosis and different degrees of fibrosis) (46–49). There was a 55% reduction in the incidence of hepatic decompensation and risk of HCC with continuous lamivudine therapy (46). In an observational cohort study, entecavir-treated patients had a 50–70% reduced risk of all clinical outcomes, including HCC, liver-related and all-cause mortality, when compared with an historical cohort of untreated persons with cirrhosis (48). In the open-label extension of a tenofovir trial, there was a marked increase from baseline to year 5 in both the proportion with mild or no necroinflammation (8% to 80%) and with no or mild fibrosis (39% to 63%) among those who had a biopsy at baseline and five years (47). Overall, there is moderate- to low-quality evidence of a benefit of antiviral therapy in those with compensated or decompensated cirrhosis.

5.3. Rationale for the recommendations

Balance of benefits and harms

The Guidelines Development Group assessed the overall benefits and harms of initiating antiviral therapy at different stages of hepatitis B liver disease, balancing potential benefits on clinical outcomes with the requirement for long-term adherence to NA therapy, and the potential risks for developing drug resistance and toxicities. The Guidelines Development Group prioritized urgent initiation of antiviral therapy for those with life-threatening liver disease (decompensated cirrhosis) and compensated cirrhosis, identified either clinically or using NITs (APRI score based on the single high cut-off >2 for cirrhosis in adults), regardless of ALT or HBV DNA levels. There were several reasons for this recommendation.

1. These persons are at a much higher risk of developing life-threatening complications of liver disease (death, acute liver failure, flares [i.e. ALT flare with jaundice and/or coagulopathy]/reactivation and HCC) than persons without cirrhosis, and so should be treated to prevent further clinical events and stabilize disease, even if the HBV DNA level is low or undetectable.

2. There is evidence that antiviral therapy 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. Therefore, targeting treatment to persons with cirrhosis would also be an effective use of resources.

3. NA therapy can be safely administered even to those with decompensated cirrhosis.

4. In settings where liver transplantation is an option, suppression of HBV DNA will also decrease the risk of recurrence of hepatitis B post-liver transplantation.

Selection of thresholds of HBV DNA, ALT and age: In persons who have not progressed to cirrhosis (APRI score ≤2 in adults), the Guidelines Development Group recommended targeting treatment in this group to those at highest risk of disease progression based on the detection of persistently abnormal ALT and HBV DNA levels >20 000 IU/mL, especially in those aged more than 30 years, regardless of HBeAg status. The recommended thresholds were derived from consistent evidence from large population-based cohort studies, which showed that those aged above 30 years, with persistently abnormal ALT levels[a] and evidence of ongoing HBV replication (based on HBV DNA level over 20 000 IU/mL) are at an increased risk of HCC and liver cirrhosis. However, the Guidelines Development Group recognized that there were uncertainties in the specific thresholds of age, HBV DNA and serum ALT levels for identifying significant fibrosis and/or necroinflammation. The ALT level considered abnormal or normal will also vary according to local laboratory reference ranges, but the cut-off criteria for normal serum ALT levels have been lowered (<30 U/L for males and <19 U/L for females),

[a] ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, although local laboratory normal ranges should be applied. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12– month period or predefined intervals during a 12-month period.

based on studies that showed persons with CHB and fibrosis and inflammation on liver biopsy had ALT levels within the normal range (1). The evidence for age as a predictor of disease progression was also inconsistent. The threshold of >30 years was used as this takes into account that most reported evidence (supporting a higher age threshold of >40 years) was derived from populations in Asia and Europe, and there is a risk of HCC at a younger age in sub-Saharan African where there is a significant burden of CHB. The age threshold of 30 years is not categorical, and some persons with CHB aged 30 years or less will meet the criteria for antiviral therapy with persistently abnormal ALT and HBV DNA >20 000 IU/mL. Occasionally, extrahepatic manifestations of hepatitis B, including glomerulonephritis or vasculitis, may be indications for treatment.

Treatment was not recommended in persons with minimal liver disease or fibrosis, and at low risk of progression to cirrhosis and HCC on the basis of persistently normal ALT levels and low levels of HBV replication (<2000 IU/mL), and an APRI score ≤2, as the potential harms of long-term antiviral therapy outweigh the benefits. Long-term monitoring of these persons is important and is discussed further in Chapter 9.1.

In settings where HBV DNA testing is not available: The Guidelines Development Group recognized that it is difficult to identify cirrhosis or moderate fibrosis in persons who do not have clinically obvious stigmata of chronic liver disease and its complications. The very limited access to measurement of HBV DNA levels or ability to diagnose fibrosis in LMICs means that decisions to start therapy will be based on clinical features, use of NITs and serum ALT levels alone. In these settings, treatment decisions will be imprecise and may lead to either delayed initiation in persons with advanced liver disease, with possible worsening of disease, or premature treatment initiation in others. It is recognized that NITs, including APRI and transient elastography, have a low PPV for identifying persons with cirrhosis and identify less than 50% of those with cirrhosis. The Guidelines Development Group recognized that in settings where HBV DNA is not available, there is a need for simple criteria to guide who to treat and who not to treat in those without evidence of cirrhosis (based on clinical criteria or APRI score >2 in adults).

Overall, there was a very limited evidence base to guide recommendations in the absence of HBV DNA levels, and therefore two conditional recommendations were made based mainly on expert opinion. First, treatment should be initiated in persons with persistently abnormal ALT levels (regardless of HBeAg status), but where other common causes of persistently abnormal ALT such as impaired glucose tolerance, dyslipidaemia and fatty liver have been excluded. Conversely, treatment was not recommended in HBeAg-negative persons without cirrhosis aged below 30 years with persistently normal ALT levels. It was recognized that there are several other categories of persons with CHB who do not meet the criteria for initiating or not initiating treatment, who would also require continued monitoring and observation. No specific recommendations were made for treatment indications in children, and the APRI score has not been evaluated in children.

These recommendations are consistent with existing guidance on the management of HBV/HIV-coinfected persons in the WHO 2013 consolidated ARV guidelines (50): to provide ART

to all persons with evidence of severe liver disease, regardless of CD4 cell count; and initiate ART in all those with a CD4 count less than <500 cells/mm^3 regardless of stage of liver disease. These guidelines will be updated in 2015.

Values and preferences

Antiviral therapy can be administered safely to persons with cirrhosis or advanced stages of liver disease, and is effective and generally safe. Baseline assessment and ongoing monitoring for renal dysfunction in persons on antivirals (tenofovir or entecavir) is discussed in Chapter 9.2.

Resource considerations

The targeting of antiviral therapy to persons with cirrhosis or at highest risk of developing cirrhosis is the most cost–effective use of resources. Initial evaluation should include an assessment of the stage of liver disease based on NITs such as APRI, and the degree of liver necroinflammation based on liver enzymes and measurements of HBV DNA, as well as the presence of coinfection with HDV, HCV or HIV. The ability to assess all these predictors of disease progression, and especially HBV DNA levels, is severely constrained in LMICs. The measurements that are generally available in resource-limited settings are AST and platelet count (for calculation of APRI score). HBeAg serostatus and HBV DNA levels are much less readily available. It is also recognized that NITs, including APRI and transient elastography, have a low PPV for identifying persons with cirrhosis, and do not measure important necroinflammatory changes.

In general, the annual costs of treatment with generic tenofovir are relatively low, although a range of prices exists in LMICs *(see Chapter 12: Implementation considerations for programme managers)*. Long-term treatment with tenofovir (or entecavir) also requires clinical and laboratory infrastructure for monitoring the response to treatment with ALT and, where possible, HBV DNA levels, as well as renal toxicity. Access to HBV DNA testing is currently very limited in most LMICs, and is a major impediment to the effective management of CHB in these settings. *(See also Chapters 9.1: Monitoring for disease progression and 9.2: Monitoring for tenofovir and entecavir toxicity)*

Research gaps

- Conduct longitudinal cohort studies especially in sub-Saharan Africa, but also in underresearched populations, such as children, young adults, and pregnant women with CHB to determine prognostic criteria and indications for initiating or deferring treatment.
- Conduct longitudinal studies to further evaluate different cut-offs for abnormal ALT in a range of settings and populations, as well as determine the prognostic significance of persistently normal ALT despite high HBV DNA levels in persons with CHB in sub-Saharan Africa and Asia.
- Conduct comparative trials to assess the absolute and relative benefit of antiviral therapy for persons with different baseline HBV DNA levels in cohort studies with long-term follow up.
- Assess long-term outcomes (morbidity and mortality) in HBV/HIV-coinfected persons, and impact of ART initiation at different CD4 cell count levels.

6. RECOMMENDATIONS: FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B

Recommendations

- In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)*
- NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. *(Strong recommendation, moderate quality of evidence)*

Existing recommendation for HBV/HIV coinfected persons[1]:

- In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. *(Strong recommendation, moderate quality of evidence)*

[1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.

BOX 6.1 Key points in counselling and preparing the patient prior to initiation of therapy

See also Chapter 5, Box 5.1: Key points in the initial assessment of persons with CHB prior to therapy.

Preparing to start treatment: Patients should be counselled about the indications for treatment, including the likely benefits and side-effects, willingness to commit to long-term treatment, and need to attend for 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 cost implications.

Note: HBV genotyping and resistance testing are not required to guide therapy when using nucleos(t)ide analogues (NAs) with a high barrier to resistance.

Measurement of baseline renal function[a] and assessment of baseline risk for renal dysfunction[b] should be considered in all persons prior to initiation of antiviral therapy *(see Chapter 9.2: Monitoring for tenofovir and entecavir toxicity).*

[a] Measurement of baseline renal function includes: serum creatinine levels, and calculation of 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) x (wt in kg) x 0.85 (if female) / (72 x Cr in mg%)

MDRD formula = eGFR = 175 x serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is Black) x 0.742 (if female).
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).

[b]Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, 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 (PI) for HIV, and solid organ transplantation.

6.1. Background

Over the past three decades, treatment outcomes for CHB have improved, first with IFN-alpha and now NAs (2) *(see Chapter 3.8: Antiviral therapy* and *Table 3.2)*. Currently, seven antiviral agents (six NAs – lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine, as well as standard and two formulations of PEG-IFN) are approved and widely licensed for the treatment of CHB. Although all NAs act on HBV polymerase, their mechanism of action differs, in addition to their pharmacokinetics, inhibitory capacity and resistance patterns. The widespread use of NAs with a low genetic barrier to resistance, such as lamivudine, has led to high rates of resistance in those who have received treatment for CHB.

The goal of antiviral therapy for CHB is to reduce (or reverse) necroinflammatory change and hepatic fibrosis leading to progressive liver disease, cirrhosis, decompensated cirrhosis and liver failure, HCC and death. However, there is still limited evidence from clinical trials of the effect of antiviral therapy on these clinical outcomes. Therefore, surrogate measures of long-term treatment outcomes are used to assess efficacy. These include *biochemical measures*: normalization of serum ALT as a surrogate measure for the resolution of necroinflammation in the liver; and *virological markers*: a reduction in HBV DNA to undetectable levels by PCR, and HBeAg loss or seroconversion to anti-HBe status or rarely, HBsAg loss and seroconversion to anti-HBs status.

Although NAs are potent inhibitors of HBV DNA replication, they do not result in cure, because antiviral therapy cannot eliminate the cccDNA form in the nucleus, which is the template for transcription of viral RNA. Therefore, at present, long-term (potentially lifelong) NA therapy is required in the majority of persons. Although there are some advantages of IFN therapy, such as a finite duration of therapy, and possibly a higher rate of HBsAg loss, it is less feasible for use in resource-limited settings as it requires administration by injection, is expensive, inconvenient to use, less well tolerated, and requires careful monitoring. IFN was therefore not considered a treatment option in these guidelines. IFN also cannot be used in infants less than 1 year and in pregnant women.

6.2. Summary of the evidence

Question: The purpose of the evidence review *(see Web appendix 2: SRs6a, 6b, 6c and 6d)* was to assess the effectiveness of treatment with potent NAs with a high barrier to resistance (tenofovir, entecavir) versus those with lower barriers to resistance (lamivudine, telbivudine and adefovir), among nucleoside-naive HBeAg-positive and HBeAg-negative adults with CHB. Key outcomes were rates of ALT normalization, sustained undetectable HBV DNA levels, HBeAg seroconversion, HBsAg loss, reversion of fibrosis stage, reduction in mortality and severe adverse effects, and development of antiviral resistance.

IFN and PEG-IFN were excluded from consideration in these guidelines, as they are less feasible for use in resource-limited settings. In addition, IFN cannot be used in persons with decompensated cirrhosis, pregnancy, thyroid disease, those with psychiatric conditions, those receiving immunosuppressive therapy for coexisting conditions, or in infants less than 1 year of age.

Systematic reviews and network meta-analysis

The evidence review included seven systematic reviews *(see Web appendix 2: SRs6a and 6c)* based on 47 trials and 21 cohort studies, and two additional randomized trials, which compared either: entecavir versus adefovir (3); entecavir versus lamivudine (4); entecavir versus lamivudine plus adefovir (5); and tenofovir versus adefovir (6). There were also two systematic reviews of trials in patients with decompensated cirrhosis of entecavir vs lamivudine (7) or versus lamivudine plus adefovir (8), as well as 12 studies on the long-term effectiveness and safety of either entecavir or tenofovir (9–19). There was one systematic review of 23 studies of tenofovir use in persons with HBV/HIV coinfection (20), and one published trial conducted in children and/or adolescents (21).

As tenofovir and entecavir have not been compared directly in an RCT, a network meta-analysis (NMA) *(Web appendix 2: SR6b*) was also undertaken to enable a direct comparison and estimation of the relative efficacy and ranking of different antiviral therapies, based on another systematic review of all RCT and other relevant data (both indirect and direct treatment comparisons of single and combination therapy) (6,22–54) used in the development of the UK National Institute of Health and Care Excellence (NICE) chronic hepatitis B guidelines (55).

Entecavir and tenofovir comparative trials (entecavir versus adefovir, or lamivudine, or lamivudine + adefovir; tenofovir versus adefovir): A systematic review of the efficacy of entecavir versus adefovir (3) , and entecavir versus lamivudine (4) showed that a higher percentage of entecavir-treated individuals attained undetectable HBV DNA levels, improvement in liver histology (moderate quality of evidence) and normalized serum ALT levels (low quality of evidence) at 48 and 72 weeks of follow up. A further systematic review (5) comparing entecavir versus lamivudine plus adefovir showed no differences in these outcomes at 96 weeks, but entecavir increased the likelihood of HBeAg loss and seroconversion to anti-HBe (RR 2.83; 95% CI 1.27–6.33). One trial in HBeAg-positive persons (6) showed a significant effect of tenofovir (compared with adefovir) on HBV DNA suppression (<400 copies/mL) (RR 5.71; 95% CI 3.35–9.73 [73.8% vs 12.8%]) and normalization of ALT levels (RR 1.25; 95% CI 1.01–1.55) at 48 weeks. In an open-label follow up of this trial, and in those who had a biopsy at baseline and 5 years, there was regression of fibrosis in 51%, and 76% of persons with cirrhosis at baseline no longer had cirrhosis.

Network meta-analysis: For the network meta-analysis (NMA) *(see Web appendix 2:SR6c)*, a total of 21 pair-wise comparison RCTs comprising 5073 HBeAg-

positive nucleoside-naive persons, and 16 trials comprising 2604 HBeAg-negative nucleoside-naive persons were included. Based on the available RCT evidence, the NMA showed that persons treated with tenofovir monotherapy had the highest probability of achieving undetectable HBV DNA at the end of 1 year of treatment. This result was observed in both HBeAg-positive (94.1%, 95% CI: 74.7–98.9%) and HBeAg-negative (97.6%; 95% CI: 56.7–99.9%) persons. For entecavir-treated persons, it was 64.5% (95% CI: 49.1–80.5%) in HBeAg-positive and 91.9% (95% CI: 87.3–95.1%) in HBeAg-negative persons, respectively. All the other antiviral therapies were found to have a very low probability of achieving this outcome. The quality of the direct evidence was rated from high to very low, based on the NICE Technical Unit checklist for assessing NMA.

Impact in decompensated liver disease (see Web appendix 2: SR6c): The effectiveness of entecavir has also been demonstrated in adult nucleoside-naive persons with decompensated cirrhosis based on a systematic review of 13 trials of entecavir compared to lamivudine (7), and seven trials of entecavir versus lamivudine and adefovir (8). Entecavir significantly improved advanced liver disease scores in both reviews (7,8) as well as other outcomes, including undetectability of HBV DNA, HBeAg seroconversion and drug resistance (RR 0.10; 95% CI 0.04–0.24) when compared with lamivudine (7), but not when compared with lamivudine plus adefovir (8). There were no demonstrable differences in mortality. The quality of evidence for these studies ranged from low to moderate. The evidence for tenofovir is awaited.

Long-term effectiveness of entecavir and tenofovir: Evaluation of the long-term (after 3 and/or 5 years) effectiveness of entecavir and tenofovir in adult nucleoside-naive persons was based on seven studies with entecavir (10–15,56,57), and five studies with tenofovir (9,16–20), which included data from three long-term follow-up studies of an open-label extension of a trial (6) comparing tenofovir with adefovir (18,19). After 3 and 5 years of treatment with entecavir or tenofovir, there were low cumulative rates of mortality (entecavir: 3% and 3.8%; tenofovir: 0.7% and 1.4%, respectively), HCC (entecavir: 3.9% and 6.6%; tenofovir: 1.4% and 2.4%, respectively), and genotypic resistance to entecavir at 5 years of treatment (0.8–1.2%) (11–13,15). Results from three prospective studies on tenofovir were similar, but the majority of participants in these studies did not have cirrhosis. Long-term follow-up data of entecavir-treated patients found a reduced risk of all clinical outcomes (HCC, liver-related and all cause mortality) when compared with untreated persons, but especially in those with cirrhosis (57,58). The quality of evidence for all outcomes was generally rated as low.

Other populations

Tenofovir in HBV/HIV-coinfected persons: A systematic review of 23 prospective and retrospective studies (including six RCTs) of tenofovir in persons with HBV and HIV coinfection (20) showed an increase in the proportion with suppressed HBV DNA over time (1 year, 57.4% [95% CI: 53.0–61.7%]; 3 years, 85.6% [95% CI: 79.2–90.7%]), which was higher in HBeAg-negative compared to HBeAg-positive persons (20). This review was also supplemented with existing reviews conducted for the 2013 WHO consolidated ARV guidelines (59) *(see Chapter 7.2: What ART regimen to start with*, which showed that a once-daily combination of tenofovir + lamivudine (or emtricitabine) + efavirenz had a better virological and treatment response compared with five other once- or twice-daily regimens.

Studies in children and adolescents: A smaller body of evidence is available from two trials. This includes a placebo-controlled RCT of tenofovir in adolescents, which showed a high virological response (89%) and normalization of serum ALT at 72 weeks of treatment, and no observed resistance (21). Another placebo-controlled trial of entecavir in children is still ongoing (AI463189 trial), but based on data submitted for a new drug application to the US FDA, entecavir is superior to placebo at reducing HBV DNA levels to <50 IU/mL, inducing HBeAg seroconversion (24% vs 2%) and normalizing serum ALT levels (67% vs 27%) at week 48.

6.3. Rationale for the recommendations

Balance of benefits and harms for use of tenofovir or entecavir

The goal of antiviral therapy for CHB is to reduce morbidity and mortality due to progressive liver disease. The Guidelines Development Group strongly recommended the use of antiviral drugs with a high barrier to resistance (either tenofovir or entecavir) as the preferred first-line treatments to avoid the deleterious effects of drug resistance (Table 6.1a) for several reasons:

1. Tenofovir and entecavir are both potent inhibitors of HBV replication, and based on data from both the systematic reviews and NMA, are the most effective antiviral therapies to achieve undetectable HBV DNA levels and normalization of ALT levels in nucleos(t)ide-naive HBeAg-positive and HBeAg-negative persons with CHB (and in HBV/HIV-coinfected persons) (when compared to lamivudine or adefovir).

2. Histological improvement in hepatic fibrosis has also been documented. Although these short-term outcomes have not yet translated into differences in mortality in clinical trials, the Guidelines Development Group considered that effective and durable suppression of HBV DNA replication can be regarded as a primary end-point and surrogate marker of treatment response *(see Chapter 8: When to stop treatment)*. In addition, although HBeAg seroconversion (in HBeAg-positive

persons) occurs in the minority (10–15% per year), and HBsAg loss is infrequent even with potent inhibitors of HBV replication, prolonged HBV DNA suppression may reduce disease progression, although the magnitude of this effect remains uncertain. NAs may also improve clinical outcomes in persons with decompensated liver disease.

3. These drugs have a high genetic barrier to resistance, and very low observed rates of drug resistance over long-term (5-year) follow up (in contrast to high rates with lamivudine and other drugs with a low barrier to resistance). However, resistance to entecavir occurs frequently in persons with lamivudine resistance.

4. The major concern of long-term NA therapy is the selection of drug-resistant mutations, particularly with lamivudine, adefovir and telbivudine – NAs that have a low genetic barrier to resistance. The accumulation of several mutations reduces drug efficacy leading to cross-resistance, which limits future options for treatment. Lamivudine results in the highest rate of drug-resistant mutations of up to 70–80%, with an annual incidence of approximately 20% (44,60,61). Multidrug-resistant hepatitis B may follow sequential monotherapy, i.e. the sequential use of lamivudine, adefovir and entecavir. Amino acid substitutions in the HBV DNA polymerase associated with resistance have not yet been definitively reported for tenofovir, and breakthroughs have been attributed to non-adherence. As a result, very low rates of resistance have been reported with tenofovir and entecavir use. However, resistance to entecavir occurs frequently in persons with lamivudine resistance, which will limit its use in Asian settings where lamivudine use has been widespread.

5. The convenience of administration (once-daily oral), low rates of side-effects and minimal requirement for toxicity monitoring of tenofovir and entecavir favour their acceptability in LMICs *(see also Chapter 9.2: Monitoring for tenfovir and entecavir toxicity)*. HBV resistance testing is not required to guide therapy when using NAs with a high barrier to resistance.

6. Both tenofovir and entecavir have been shown to be effective in children, although antiviral treatment will be indicated in only a small proportion of children. Tenofovir is licensed for use in children aged 12 years or older and entecavir in children older than 2 years *(see Table 6.1b)*.

7. The use of tenofovir also offers good potential for harmonizing treatment across different populations, as tenofovir + lamivudine (or emtricitabine) is the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for persons coinfected with HIV and HBV, and can also be used among persons with TB, and pregnant women.

   Among HBV/HIV-infected persons (see also Chapter 11.2: Management considerations for specific populations): In the 2013 WHO ARV consolidated guidelines (59), the simplified regimen of tenofovir + lamivudine (or emtricitabine) + efavirenz was recommended as the preferred regimen in all HIV-infected adults, including pregnant women and adults with tuberculosis (TB) and HBV coinfection, for the following reasons.

- It has a better virological response compared with other once- or twice-daily regimens.
- There is no increased risk of birth defects with efavirenz compared with other ARV drugs used during the first trimester of pregnancy.
- It can be taken as a simple one pill once a day as a fixed-dose combination.
- The regimen also offers good potential for harmonizing treatment across different populations, as tenofovir + lamivudine (or emtricitabine) are the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for persons coinfected with HIV and HBV, and can also be used among persons with TB, and pregnant women. Efavirenz is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) with HBV/ HIV coinfection as it has less risk of hepatic toxicity compared to nevirapine.

Balance of benefits and harms for the use of NAs versus IFN

The main advantages of NAs over IFN (which has not been considered in these guidelines) are the convenience of dosage (once-daily oral administration), tolerability and affordability. The disadvantages of NAs are that they require lifelong therapy in the majority, which is associated with high cumulative costs *(see also Chapter 12: Implementation considerations for programme managers)* and a risk of drug resistance.

The Guidelines Development Group recognized that there may be very specific circumstances when the use of IFN may be considered, for example, when HBV DNA viral load and genotyping are available, IFN is available and affordable, or coinfection with HDV is present, as this offers the opportunity for a finite, short course of treatment. However, this needs to take account of several absolute and relative contraindications to IFN, which include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant disease, pregnancy, seizures and psychiatric illness, concomitant use of certain drugs, retinopathy, thrombocytopenia or leucopenia. IFN also cannot be used in infants less than 1 year of age.

Values and preferences

The side-effect profile, convenience (once-daily oral administration) and minimal requirement for toxicity monitoring of tenofovir and entecavir favour their widespread acceptability to individuals and health-care workers in most countries, particularly in LMICs. The requirement for prolonged (lifelong) treatment in the majority of persons *(see Chapter 8: Second-line regimens for the management of treatment failure;* and *Chapter 9.2: Monitoring for tenofovir and entecavir toxicity)* represents a challenge to long-term adherence among patients and for ongoing monitoring to health-care providers, especially in the absence of a clear benefit on clinical outcomes and survival. However, tenofovir effectively suppresses HBV replication to <15 IU/mL in the majority of HBeAg-positive and HBeAg-negative persons, including those with high HBV DNA viral loads, which minimizes the need for regular HBV DNA monitoring in resource-limited settings.

Resource considerations

In general, generic tenofovir is widely available at low cost in many LMICs, particularly as part of national ART programmes, although the annual cost per person may range from US$ 50 to US$ 350 per annum, and as much as US$ 500 in some parts of Asia. The costs are currently higher for entecavir, but it has the potential to be manufactured at a much lower cost, as it is both off-patent and the daily dose is low *(see Chapter 12: Implementation considerations for programme managers)*. The higher cost of tenofovir and entecavir in many settings is the reason that other drugs such as lamivudine continue to be widely used, despite the additional costs incurred due to the development of drug resistance. The Guidelines Development Group also expressed concern regarding the more limited access to tenofovir of persons without HIV coinfection outside of ART programmes in many countries. Tenofovir has the potential to be more widely available and affordable in LMICs through access to reduced prices via a range of mechanisms, including license agreements negotiated with the Medicines Patent Pool for use in HIV (but also available for HBV).

In persons on potent NAs with a high barrier to resistance, few side-effects and which are administered as a single tablet a day, the requirements for monitoring and input of caregivers can be minimized. However, measuring HBV DNA viral load is costly (between US$ 100 and US$ 400) and, even in countries where HBV DNA testing is not routine, there is uncertainty as to the minimal monitoring requirements for treatment response and renal toxicity.

TABLE 6.1.a Recommended drugs for the treatment of CHB and their doses in adults *(see also Table 9.1: Recommended dosage in adults with renal impairment)*

Drug	Dose
Tenofovir	300 mg[a] once daily
Tenofovir plus emtricitabine	Tenofovir 245 mg; emtricitabine 200 mg
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease)	1 mg once daily

[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir with reduced renal and bone toxicities compared to tenofovir.

TABLE 6.1.b Recommended drugs for the treatment of CHB and their doses in children *(see also Table 9.1: Recommended dosage in adults with renal impairment)*

Drug	Dose	
Tenofovir (in children 12 years of age and older, and weighing at least 35 kg)	300 mg once daily	
Entecavir (in children 2 years of age or older and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg)	Recommended once-daily dose of oral solution (mL)	
	Body weight (kg)	Treatment-naive persons[a]
	10 to 11	3
	>11 to 14	4
	>14 to 17	5
	>17 to 20	6
	>20 to 23	7
	>23 to 26	8
	>26 to 30	9
	>30	10

[a] Children with body weight more than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

TABLE 6.2 Other drugs used for the treatment of CHB and their doses in adults

Drug	Dose
Telbivudine	600 mg once daily
Lamivudine	300 mg once daily
Adefovir	10 mg once daily
Pegylated interferon alpha-2a [b]	180 µg once per week[a]
Pegylated interferon alpha-2b [b]	0.5 or 1.0 µg per kg per week

[a] Reduced to 135 µg if creatinine clearance is less than 30 mL/min

[b] A number of relative and absolute contraindications to IFN also exist, which include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant disease, pregnancy, seizures and psychiatric illness, concomitant use of some drugs, retinopathy, thrombocytopenia or leucopenia. IFN also cannot be used in infants less than 1 year.

BOX 6.2 Assessment prior to initiation of antiviral therapy

A thorough assessment and counselling of the patient is crucial for successful antiviral therapy. Box 5.1, Chapter 5 summarizes the key points in counselling and preparation prior to initiation of antiviral therapy. These include: assessment of severity of liver disease; level of viral replication; presence of comorbidities; preventive measures to reduce HBV transmission to others; counselling on lifestyle; specific counselling and preparation for starting treatment; assessment of risk factors for renal dysfunction and measurement of baseline renal function.

BOX 6.3 Monitoring adherence to antiviral therapy

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.

Self-report: Asking people or their caregivers how many doses of medication they have missed within a specified number of days in the past, or since their last visit can help to estimate non-adherence. However, although this method is commonly used, people may not remember missed doses accurately or may not report missed doses. Regular counselling on the importance of remembering and/or documenting doses of antiviral medicines as well as creating a clinic environment that promotes honest reporting of non-adherence are critical for effective routine monitoring of adherence.

Viral load monitoring: Although access to HBV DNA viral load monitoring is the optimal way to diagnose and confirm treatment failure, treatment failure is often caused by lapses in adherence to antiviral therapy, as well as from other factors (such as drug stock-outs or malabsorption). Viral load monitoring provides an opportunity for care providers to monitor non-adherence in real time, and therefore needs to be complemented with other approaches.

Pharmacy refill records: Pharmacy refill records provide information on when people on antiviral therapy collected their drugs. When people obtain pharmacy refills at irregular intervals, this may indicate non-adherence; however, in many routine care settings, people may pick up their medications when receiving care, irrespective of their adherence level. Health-care providers may therefore overestimate adherence on the sole basis of pharmacy refill records, and so should combine this with other tools.

Patients on long-term tenofovir and entecavir therapy will require ongoing monitoring for treatment response and renal toxicity. *See Chapter 9.2: Monitoring for tenofovir and entecavir toxicity.*

Research gaps

- Assess the impact of antiviral therapy on CHB liver-associated and all-cause morbidity and mortality, especially in LMICs.
- Conduct treatment and cost–effectiveness studies on the use of tenofovir and entecavir in persons with CHB, especially in sub-Saharan Africa, and also among children in whom antiviral treatment is indicated.
- Develop and evaluate broadly curative antiviral strategies to achieve persistent clearance (cure) of HBV infection and allow discontinuation of 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.

7. RECOMMENDATIONS: SECOND-LINE ANTIVIRAL THERAPIES FOR MANAGEMENT OF TREATMENT FAILURE

Recommendations

- In persons with confirmed or suspected antiviral resistance[a,b,c] (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir[d] or telbivudine, a switch to tenofovir[e] is recommended. *(Strong recommendation, low quality of evidence)*

[a] Treatment failure: May be primary or secondary.

In settings with access to HBV DNA testing: Primary antiviral therapy failure may be defined as failure of a drug to reduce HBV DNA levels by ≥1 x $\log_{10}$ IU/mL within 3 months following initiation of therapy. Secondary antiviral treatment failure may be defined as a rebound of HBV DNA levels of ≥1 x $\log_{10}$ IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x $\log_{10}$ IU/mL decrease in serum HBV DNA).

In settings without access to HBV DNA testing: 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, laboratory measures such as an increase in serum aminotransferases, and/or evidence of progressive liver disease. *Note:* Elevation in ALT level 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.

[b] Treatment adherence should be reinforced in all persons with confirmed or suspected antiviral resistance. *See also Chapter 6, Box 6.2, Monitoring adherence to antiviral therapy.*

[c] Some countries and health-care providers may consider switching persons to tenofovir from existing antiviral regimens with a low barrier to resistance before evidence of treatment failure, but no formal recommendation has been made in these guidelines.

[d] For adefovir resistance, a switch to either tenofovir or entecavir can be considered.

[e] To date, there has been no reported resistance with tenofovir. 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.

7.1. Background

A major concern with long-term NA therapy is the selection of drug-resistance mutations. HBV has a high rate of replication with up to $10^{10–12}$ mutations generated every day. Higher rates of resistance are observed in persons with high baseline HBV DNA levels, longer duration of treatment, and a slower treatment-related decline in HBV DNA levels (1,2). Several drug-resistance mutations in the HBV polymerase reduce efficacy to more than one NA, resulting in cross-resistance to several agents, which limits future options for treatment. This is a particular risk in persons treated sequentially with NAs with a low barrier to resistance (lamivudine, adefovir and telbivudine) as monotherapy (3–8). Once drug-resistance mutations have developed, they are archived within the virus population and are rapidly selected if the same, or a cross-reacting antiviral agent, is reintroduced. 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 (6). In general, the management of such persons previously treated with lamivudine, adefovir or telbivudine is based on the established in vitro and in vivo efficacy of the potent NAs tenofovir and entecavir, and knowledge of the patterns of cross-resistance across different NAs (1,7,8).

Of the six approved NAs (lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine), lamivudine is associated with the highest rate of drug resistance, entecavir with very low rates of resistance (except in persons previously exposed to lamivudine and adefovir), and currently none with tenofovir. The widespread use of lamivudine for persons with CHB and high HBV DNA levels in some countries has led to a high burden of lamivudine-resistant hepatitis B. Lamivudine resistance is of particular importance in the Asia–Pacific region where the prevalence of HBV infection is high, the infection is mainly acquired perinatally or in early childhood, and lamivudine and adefovir have been widely used without access to appropriate second-line regimens (1,2,9–15).

7.2. Summary of the evidence

Question: The purpose of the evidence review was to assess the most effective treatment regimen for the management of treatment failure due to resistance in persons previously treated with single agents with a low barrier to resistance (lamivudine, telbivudine or adefovir) *(see Web appendix 2:SRs7, 6b and 6d).* The interventions analysed include switching to treatment with agents with a high barrier to resistance (tenofovir or entecavir) compared to adding in a second agent (combination therapy), or continuing regimens with a low barrier to resistance (lamivudine, telbivudine or adefovir). Key outcomes were rates of ALT normalization, undetectable HBV DNA, HBeAg seroconversion, HBsAg loss, reversion of fibrosis stage, mortality, severe adverse effects and antiviral resistance.

Systematic review and network meta-analysis

The systematic review *(see Web appendix 2: SR7)* was based on data from one existing systematic review (16), comprising five RCTs and three non-randomized studies in China and South Korea, together with several randomized trials in persons with lamivudine resistance or a partial response to lamivudine (17–23). Included studies compared the effects of entecavir with either continuation of lamivudine, or a combination of lamivudine plus adefovir, or use of lamivudine plus adefovir versus continuation of lamivudine plus adefovir.

A switch to entecavir (compared with continuation of lamivudine) significantly improved virological and biochemical outcomes over 96 weeks (17–20). However,

high rates of entecavir resistance were observed at 5 years. The quality of evidence for these outcomes was moderate due to imprecision. In the systematic review comparing entecavir with lamivudine plus adefovir, there were no differences in any of the assessed outcomes (undetectable HBV DNA, ALT normalization, and HBeAg seroconversion) after 48 weeks (16). The quality of evidence for these outcomes was low or very low.

Network meta-analysis: As tenofovir and entecavir have not been compared directly in an RCT, an NMA *(see Web appendix 2: SR6b)* was also undertaken to enable a direct comparison and estimation of the relative efficacy and ranking of different antiviral therapies, based on another systematic review of all the relevant RCT data (both indirect and direct treatment comparisons of single, combination and sequential therapy) (18,24–32) used in the development of the UK NICE CHB guidelines (33). The treatments evaluated were a switch to an NA with a high barrier to resistance or continuation with or add-on therapy, and included the following agents: tenofovir, entecavir, adefovir, lamivudine, telbivudine and emtricitabine (in combination with tenofovir).

Seven RCTs of pair-wise comparisons based on 919 HBeAg-positive, lamivudine-resistant persons were included for the outcome of undetectable HBV DNA (<300 copies/mL [i.e. 60 IU/mL]), and six studies based on 771 persons for the outcome of HBeAg seroconversion (33). Tenofovir followed by entecavir plus adefovir combination therapy had the highest probability of achieving undetectable HBV DNA (66.2% and 33.8%, respectively) and HBeAg seroconversion (39.8% and 31.2%, respectively) at the end of 1 year of treatment among all the evaluated treatments. After 1 year of tenofovir treatment, 89% (95% CI: 51.8–98.2%) of lamivudine-resistant persons would be expected to achieve undetectable HBV DNA and 17.6% (95% CI: 1.4–74.9%) HBeAg seroconversion. No NMA was conducted for lamivudine-resistant, HBeAg-negative persons. The quality of the direct evidence (pair-wise comparisons) was rated as moderate to very low.

7.3. Rationale for the recommendations

Balance of benefits and harms

The Guidelines Development Group recognized that, in some countries, the widespread use of lamivudine and other NAs with a low barrier to resistance as first-line therapy for CHB has led to a high burden of resistant CHB. Overall, the Guidelines Development Group endorsed the principle that the most potent agent, and one which does not share cross-resistance, should be used to treat resistant CHB.

The Guidelines Development Group therefore recommended switching to tenofovir monotherapy as the most effective antiviral therapy for persons with confirmed or suspected lamivudine resistance for several reasons, which are listed below.

1. Despite the lack of direct evidence from RCTs on evaluation of tenofovir in persons with HBV drug resistance, evidence from the NMA showed that of all the antivirals considered, tenofovir is associated with the highest probability at 1 year of achieving low or undetectable HBV DNA levels in persons with lamivudine-resistant HBV. The Guidelines Development Group considered that the same tenofovir switch strategy would also apply to HBeAg-negative persons, although no NMA was available for this group. This would have a beneficial effect on disease progression and also reduce possible transmission of resistance.

2. There are deleterious consequences of continuing treatment with an ineffective antiviral agent, and ongoing HBV replication confers an increased risk of disease progression to cirrhosis, end-stage liver disease and HCC.

3. The use of tenofovir, 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 lamivudine (L180M + M204V/I) confers cross-resistance to telbivudine and entecavir, but not tenofovir. In addition, although treatment failure and development of resistance occurs rarely in naive persons treated with entecavir, resistance to entecavir is more common in persons with lamivudine resistance. The Guidelines Development Group therefore recommended that entecavir not be used as salvage therapy in persons with known or suspected lamivudine resistance (34).

4. Primary non-response (defined as less than 1 log decrease in HBV DNA level after 3 months of treatment, in settings where HBV DNA testing is available) is rare in persons initiating and adherent to entecavir or tenofovir treatment, but can occur in persons treated with lamivudine, adefovir or telbivudine. Sequential treatment of persons with lamivudine-resistant CHB with adefovir or telbivudine or entecavir can lead to the selection of multidrug-resistant hepatitis B and should be avoided.

5. A switch to tenofovir monotherapy in persons who have developed resistance to lamivudine, adefovir, telbivudine or entecavir simplifies clinical management and drug procurement.

6. There was little evidence from the systematic review for an advantage of adding NAs or combined use of NAs conferring a benefit in cases of lamivudine resistance.

7. Tenofovir has the potential to be more widely available and affordable in LMICs through access to reduced prices via a range of mechanisms including license agreements negotiated with the Medicines Patent Pool for use in HIV infection (but also available for HBV infection).

8. The Guidelines Development Group also recognized that the most common reason for virological breakthrough is poor adherence, and therefore regular counselling should be offered on the importance of treatment adherence, especially in persons with evidence of virological breakthrough.

The Group also recognized that the most effective strategy to minimize the future burden of lamivudine resistance was the wider use of NAs with a high barrier to resistance in first-line therapy. The Guidelines Development Group considered that some countries and physicians may consider switching persons to tenofovir from existing antiviral regimens with a low barrier to resistance before evidence of treatment failure, but no formal recommendation was made.

Resource considerations

Drug costs: see Chapter 6: First-line antiviral therapies: resource considerations.

Diagnosis of treatment failure: Measurement of HBV DNA levels and testing for drug resistance are fundamental to confirming treatment failure and genotypic HBV resistance, but there is extremely limited access to these in LMICs. In these settings, ascertainment of the development of resistance will largely be based on clinical suspicion and, in some instances, by an increase in serum aminotransferases. However, elevation in ALT tends to occur late and has been shown to be a relatively poor predictive marker of resistance (35). In countries where resistance testing is not available, a change to tenofovir would not incur added costs, although this may not be applicable in Asia.

BOX 7.1 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 in all persons with confirmed or suspected antiviral resistance. *See also Chapter 6, Box 6.2, Monitoring adherence to antiviral therapy.*

Definition of treatment failure

In settings where HBV DNA testing is available: Primary antiviral treatment failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by ≥1 x $\log_{10}$ IU/mL within 3 months. Secondary antiviral treatment failure may be defined as a rebound of HBV DNA levels of ≥1 x $\log_{10}$ IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x $\log_{10}$ 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 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: Elevation in ALT level 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.

Research gaps

- Evaluate further the utility and predictive value of monitoring ALT levels and other markers to identify the development of genotypic or phenotypic resistance.
- Evaluate the impact of treatment with NAs with a high genetic barrier to resistance in persons with treatment failure, and on other important outcomes, such as histological improvement, development of further drug resistance and adverse events.

8. RECOMMENDATIONS: WHEN TO STOP TREATMENT

See also Chapter 9: Monitoring and Chapter 6: Box 6.2. Monitoring adherence to antiviral therapy

Recommendations

Lifelong NA therapy

- All persons **with cirrhosis**[a] based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analogues (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. *(Strong recommendation, low quality of evidence)*

Discontinuation

- Discontinuation of NA therapy may be considered exceptionally in:
  - persons without clinical evidence of cirrhosis[a] (or based on APRI score ≤2 in adults);
  - **and** who can be followed carefully long term for reactivation;
  - **and** if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons 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 *(where testing is available)*.

    › *Where HBV DNA testing is not available:* Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. *(Conditional recommendation, low quality of evidence)*

Retreatment

- Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) *(where HBV DNA testing is available[c]) (Strong recommendation, low quality of 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/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

[b] ALT levels fluctuate in persons with CHB and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women (based on greater sensitivity observed in hepatitis C for histological disease in the liver), though local laboratory normal ranges should be applied (1). Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.

[c] *See Chapter 9.1: Monitoring in persons prior to, during and post-treatment.* Although the evidence base is limited, ALT and HBV DNA can be measured monthly for the first 3 months, then every three months during the first year to detect severe exacerbations.

8.1. 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 is considered to be the optimal goal of antiviral therapy, and a marker of sustained treatment response in both HBeAg-positive and HBeAg-negative persons, but is achieved in only a minority of HBeAg-positive persons (10–15% after 5 years), and rarely in those who are HBeAg negative. HBeAg seroconversion in HBeAg-positive persons may also be considered as a potential stopping point to guide treatment cessation, but again is infrequent even with potent NAs.

Although NAs are potent inhibitors of HBV DNA replication, they do not result in cure, because NA therapy does not eliminate the replicative template cccDNA in the nucleus or integrated viral genome. Therefore, although there are considerable advantages of finite NA therapy, both for patients and policy-makers particularly in LMICs, long-term maintenance suppressive therapy is generally required. A finite duration of treatment may be possible in some HBeAg-positive persons who achieve anti-HBe seroconversion and a sustained undetectable HBV DNA viral load. However, in resource-limited settings where there is limited access to HBV DNA monitoring, it remains unclear how long therapy should continue, and when and under what conditions NA therapy may be stopped,

8.2. Summary of the evidence

Question: The purpose of the evidence review was to assess what criteria should be used to stop treatment *(see Web appendix 2: SRs8a and 8b)*. The review examined evidence for the durability of treatment response after cessation of antiviral therapy in both HBeAg-positive and HBeAg-negative persons, 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, HCC), progression of liver disease, reversion of fibrosis stage and mortality, severe adverse effects and antiviral resistance.

There were no systematic reviews or RCTs that directly compared the durations of different antiviral therapies (i.e. treatment cessation at defined time points versus treatment continuation). Instead, the search identified 26 prospective and retrospective observational studies and one RCT, which reported relapse rates after cessation of different antiviral agents – lamivudine (2–19), adefovir (20–22), entecavir (23,24), and multiple different antivirals (25–28), following varying treatment durations and responses. The heterogeneity of treatment duration, and varying follow up after treatment cessation, criteria for treatment discontinuation and assessment of relapse precluded pooled analyses of outcomes.

In general, virological responses were not durable, and relapse rates after treatment discontinuation (with different definitions) at 1 year ranged from 40% to 95% (2–20,25–27) if the duration of consolidated treatment was less than 1 year. After discontinuation of lamivudine, relapse rates increased with the duration of follow up (1 year: 16–66%; 3 years: 26–52%; 5 years: 30–56%) and appeared to stabilize from 12 to 24 months onward. In a further study of discontinuation after HBeAg seroconversion, 90% had recurrent viraemia and 38% had ALT flares compared to those who continued therapy (28). Relapse rates also appear to be high based on the few studies that have examined relapse rates after cessation of NAs with a higher barrier to resistance (three with entecavir but none with tenofovir). Only 3% of HBeAg-negative virological responders treated with entecavir for approximately 1 year had a sustained response (HBV DNA level <300 copies/mL) 6 months after cessation (24). In a further prospective study, the 1-year relapse rate (rise in HBV DNA and ALT levels) was 53% and 29%, respectively (23). Most relapses occurred more than 6 months after treatment cessation.

Independent factors associated with an increased probability of relapse after treatment cessation included the presence of cirrhosis, older age, shorter NA therapy duration, and higher pretreatment HBV DNA levels (29–32). The overall quality of evidence on relapse rates and risk factors after stopping antiviral therapy from these studies was rated as very low.

8.3. Rationale for the recommendations

Balance of benefits and harms

The Guidelines Development Group considered the overall benefits and risks of discontinuation of antiviral therapy. The advantages of stopping NA therapy are a finite duration of treatment, with improved adherence and retention in care, reduced costs, and minimization of renal and bone toxicity. The disadvantages are the risk of reactivation of suppressed disease with discontinuation of therapy, resulting in an unpredictable worsening of disease and possible development of fulminant hepatitis and acute-on-chronic liver failure, as well as the risk of developing resistance with "stop–start" therapy. Persons who discontinue therapy will also require careful long-term follow up for early detection of relapse. The Guidelines Development Group noted that the evidence base for stopping rules was limited. *(See also Chapter 9.1: Monitoring in persons prior to, during and post-treatment.)*

The Guidelines Development Group strongly recommended that persons with cirrhosis should never discontinue antiviral therapy. They are at high risk for reactivation and also as they have much less hepatic reserve, for life-threatening hepatic decompensation after an exacerbation. In this group of persons, the Guidelines Development Group considered that the risks of stopping therapy (and benefits of continued therapy) outweighed any advantage of finite therapy. HBV/HIV-coinfected persons initiated on therapy should also remain on long-term HBV suppressive therapy.

The Guidelines Development Group considered whether there were any criteria or patient subgroup in whom therapy may exceptionally be stopped, in particular, HBeAg-positive persons who achieve HBeAg seroconversion or HBsAg loss, which are the optimal goals of treatment and surrogate markers of sustained antiviral response. Overall, the evidence shows that treatment even with potent NAs (entecavir or tenofovir) infrequently leads to HBeAg seroconversion and loss of HBsAg in HBeAg-positive persons, and (even more rarely) HBsAg loss or anti-HBs seroconversion in HBeAg-negative persons. In addition, relapse occurs in a substantial proportion after discontinuation of treatment, even with the potent NAs, and following HBeAg seroconversion. There is also no clear evidence that relapse rates after discontinuation are lower with tenofovir compared to entecavir.

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 considered that long-term antiviral suppressive therapy will be necessary for the majority, and recommended a very conservative approach to stopping therapy – only in a small proportion of carefully selected HBeAg-positive or HBeAg-negative persons without cirrhosis. Discontinuation of therapy can be considered exceptionally in those persons with evidence of sustained HBsAg loss, or in HBeAg-positive persons who seroconvert to anti-HBe after at least 1 year of treatment consolidation, and have undetectable HBV DNA levels (where testing is available) and normal ALT levels. An additional requirement was that these persons should be closely monitored with serum ALT and preferably HBV DNA levels immediately after and for 1 year after stopping therapy 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. The Guidelines Development Group recognized that uncontrolled HBV replication could be detrimental to patients, and stopping therapy could prove a poor alternative to uninterrupted treatment. Chapter 9.1 summarizes the recommendations and rationale for a minimum frequency of monitoring after stopping treatment. Although there is a limited evidence base, ALT and HBV DNA could be measured monthly for the first 3 months then every 3 months during the first year to avoid severe exacerbations.

Values and preferences

Finite treatment is preferable to indefinite or long-term treatment for patients, health-care workers, and national policy-makers. However, initial treatment success may be reversed in persons who have reactivation of disease and relapse after cessation of treatment. Given the more limited access to monitoring in LMICs, both patients and caregivers require a durable off-treatment response to minimize the risk of further progression after treatment cessation. Patients 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 9.1: Monitoring in persons prior to, during and post-treatment.)*

Resource considerations

The ability to monitor for resumption of HBV replication in all persons after stopping therapy requires HBV DNA monitoring. HBV DNA testing is relatively costly and is not available in most

LMICs. The evidence base for monitoring with liver enzymes alone, which is less expensive, is limited, and cannot be recommended currently for disease relapse. HBV resistance testing is not required to guide therapy when using NAs with a high barrier to resistance.

There are also cost implications to long-term tenofovir or entecavir therapy. Although generic tenfovir is widely available at low cost in many LMICs, particularly as part of national ART programmes, the annual cost per person may range from US$ 50 for generic tenfovir to US$ 350, and as high as US$ 500 in parts of Asia. The costs are currently higher for entecavir, but it has the potential to be manufactured at a much lower cost, as it is both off-patent and the daily dose is low. *(See Chapter 12: Implementation considerations for programme managers.)*

Research gaps

- Conduct randomized comparative trials of different treatment continuation/discontinuation strategies with tenofovir and entecavir following HBeAg serconversion, to inform stopping rules and monitoring requirements. These should include studies in adolescents and children.
- Conduct longitudinal studies to identify subgroups of HBeAg-positive and HBeAg-negative persons at low (and high) risk of ongoing reactivation, seroreversion or conversion to anti-HBe-positive active disease after treatment with tenofovir or entecavir, to better identify candidates for earlier discontinuation of NA therapy.
- Evaluate lower cost and point-of-care assays for HBV DNA and HBsAg quantification as potential markers to determine stopping rules for therapy, and to monitor for relapse.

9. RECOMMENDATIONS: MONITORING

9.1. Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment

Recommendations

- It is recommended that the following be monitored at least annually:
  - ALT levels (and AST for APRI), HBsAg[a], HBeAg[b], and HBV DNA levels *(where HBV DNA testing is available)*
  - Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline;
  - If on treatment, adherence should be monitored regularly and at each visit[c]. *(Strong recommendation, moderate quality of evidence)*

More frequent monitoring

- ***In persons who do not yet meet the criteria for antiviral therapy:*** More frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels[d] or HBV DNA levels that fluctuate between 2000 IU/mL and 20 000 IU/mL[e] *(where HBV DNA testing is available)* and in HIV-coinfected persons[f]. *(Conditional recommendation, low quality of evidence)*
- ***In persons on treatment or following treatment discontinuation:*** More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis[g]); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected persons[f]; and in persons after discontinuation of treatment. *(Conditional recommendation, very low quality of evidence)*

[a] In persons on treatment, monitor for HBsAg loss (although this occurs rarely), and for seroreversion to HBsAg positivity after discontinuation of treatment.

[b] Monitoring of HBeAg/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 serorevert.

[c] *See Chapter 6: Box 6.2. Monitoring adherence to antiviral therapy.*

[d] ALT levels fluctuate in persons with CHB and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied (1). Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12- month period or predefined intervals during a 12-month period.

[e] *See Chapter 5: Who to treat and who not to treat.*

[f] Monitoring response to ART and the diagnosis of treatment failure (Chapter 7.3). In: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

[g] 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/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

BOX 9.1 Goals of monitoring

In persons who do not yet meet the criteria for antiviral therapy: The aim of monitoring is to identify a change in clinical status (i.e. development of clinical features of cirrhosis) or APRI score >2 in adults, development of HCC, or a rise in ALT or HBV DNA levels, which may indicate progression to active disease requiring treatment.

In persons on treatment or following treatment discontinuation: The aim of monitoring during and after treatment is to evaluate the effectiveness of treatment response, treatment adherence, adverse effects of treatment, progression of liver disease and development of HCC, the potential for treatment discontinuation, and to identify reactivation early on after treatment discontinuation.
(See also Chapter 6: Box 6.2. Monitoring adherence to antiviral therapy.)

9.1.1. Background

Chronic hepatitis B is a dynamic disease, and persons with CHB need follow up and monitoring before, during and after discontinuation of antiviral therapy for disease progression and development of HCC, treatment response and toxicities. Prior to treatment, the goal of monitoring is to identify the changing patterns and progression of disease and when to initiate therapy. This can be ascertained by longitudinal monitoring of ALT and, where available, HBeAg and HBV DNA levels. Fluctuations or persistently abnormal serum ALT and HBV DNA levels >20 000 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. This confers a good prognosis and does not require treatment. Similarly, persons with inactive disease, who are HBeAg-negative with normal ALT levels and low HBV DNA levels (previously called inactive HBsAg carriers), require regular monitoring of HBV DNA and ALT levels to ensure that they remain inactive carriers or, to determine the timing of treatment, any increase in ALT or HBV DNA levels, or evidence of progression to cirrhosis. Continued monitoring during treatment and after treatment discontinuation is required to evaluate the effectiveness of treatment response, treatment adherence and potential adverse effects, identify potential stopping points, and reactivation early on after treatment discontinuation (2). Persons with CHB also require monitoring for the development of HCC *(see Chapter 9.3: Monitoring for HCC)*.

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 prior to treatment, as well as assess treatment response are not well established, as the evidence base is limited (2).The tests that need to be used and the frequency of testing will depend on the patient's serological profile (HBeAg-positive or -negative), and HBV DNA viral levels.

9.1.2. Summary of the evidence

Question: The purpose of the evidence review was to determine the optimal timing and frequency of monitoring for disease progression in persons not yet on antiviral therapy; for treatment response in those on treatment; and to detect relapse following treatment discontinuation *(see Web appendix 2: SRs5a and 9a)*. No studies were identified that had directly compared different monitoring approaches and frequency of monitoring to assess for 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 persons not yet on treatment, or the different phases of CHB (3,4). In addition, four systematic reviews (5–8), two clinical trials (9,10), and three retrospective observational studies (11–13) assessed outcomes at different time points before or during the course of antiviral therapy. A full review of baseline prognostic factors for key liver-related outcomes is available in Chapter 6: Who to treat and who not to treat.

Monitoring prior to treatment (see Web appendix 2: SR5a and chapter 5.2: Summary of evidence – Identifying individuals at highest and very low risk of progression)

Persistently normal serum ALT and HBV DNA levels that never exceed 20 000 IU/mL are associated with lower levels of hepatic necroinflammation and fibrosis in large population-based prospective cohorts (14–16), while a threshold of HBV DNA of 200 000 IU/mL was significantly associated with histologically significant liver disease compared with a level of less than 2000 IU/mL. The thresholds of 2000–20 000, and 20 000–200 000 IU/mL were not significantly associated with severe fibrosis. A cohort study from Taiwan also showed that, among HBeAg-negative persons, persistently normal ALT was associated with good long-term prognosis, whereas an ALT level of at least twice the ULN during follow up was associated with a higher risk of cirrhosis (17).

Inactive carriers (HBeAg-negative and normal ALT): Studies to investigate monitoring of ALT levels to predict future ALT flares or elevation (18) suggest that a minimum period of monitoring of 3 months would identify about 90% of people with flares, but the evidence did not take into account persons lost to follow up. Less than 3% of those with an HBV DNA level of 2000 IU/mL had elevated ALT at 6 months or 1 year. The observational studies provided very limited evidence on the frequency of monitoring for reactivation, and so evidence was rated as low or very low quality because of both indirectness (no study directly investigated different frequencies of monitoring) and imprecision due to few events or risk of bias.

Monitoring during treatment (see Web appendix 2: SR9a): Four systematic reviews (5–8), two clinical trials (9,10), and three retrospective observational

studies (11–13) assessed outcomes at different time points during the course of antiviral therapy. These data showed that the majority (around 80%) of HBeAg-positive persons (and 50–70% of HBeAg-negative persons) achieved a treatment response (both undetectable levels of HBV DNA and normalized ALT levels) with potent NAs (entecavir and tenofovir) by week 48 of treatment (5–8), even in patients with decompensated cirrhosis (8). It was noted that the findings were based on monitoring regimens during phase 3 trials, and may not reflect clinical practice or feasibility in LMICs.

9.1.3. Rationale for the recommendations

Balance of benefits and harms

Monitoring prior to treatment: In persons who do not yet meet the criteria for antiviral therapy according to these guidelines[a] *(see Chapter 5: Recommendations on who to treat and not to treat among persons with chronic hepatitis B)*, the aim of periodic monitoring is to allow ongoing assessment of disease stability, or to identify progression to active disease requiring treatment. Lack of monitoring may result in undetected progression to end-stage liver disease and associated complications that might have been preventable 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 rate of progression), and often enough to detect evidence of significant progression and any transient flares in ALT requiring treatment, and avoid loss to follow up, but not result in overinterpretation of fluctuations in serum ALT, especially in the absence of concomitant measurement of HBV DNA levels, which may be rising or falling. Monitoring of HBeAg is helpful for several reasons: it indicates the presence of active HBV replication and high infectivity, and spontaneous improvement may occur following HBeAg-positive seroconversion (anti-HBe), with a decline in HBV replication, and normalization of ALT levels, which confers a good prognosis and does not require treatment.

The Guidelines Development Group therefore recommended at least annual monitoring of HBeAg and serum ALT and HBV DNA levels to determine any persistent abnormality in ALT or in HBV DNA levels (based on the thresholds of raised HBV DNA and ALT levels for subsequent risk of disease progression), as well as for progression to cirrhosis, based on clinical features or on NITs (APRI >2 in adults), which would be an indication for antiviral therapy *(see Chapter 5: Who to treat and who not to treat among persons with chronic hepatitis B)*. Repeat NITs can also be performed to assess for progressive

[a] *See Chapter 5: Who to treat and who not to treat among persons with chronic hepatitis B.* Antiviral therapy is **not** recommended and can be deferred in persons without clinical or other evidence of cirrhosis (or based on APRI score ≤2), **and** with persistently normal ALT levels **and** low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age. *(Strong recommendation, low quality of evidence)*

Where HBV DNA testing is not available: Treatment can be deferred in HBeAg-positive persons aged 30 years or less **and** persistently normal ALT levels). *(Conditional recommendation, low quality of evidence)*

changes in APRI and FibroScan scores that could indicate progression to cirrhosis – an indication for treatment, regardless of the HBV DNA or ALT levels.

More frequent monitoring was recommended conditionally based on limited evidence in those who already have fluctuating elevated ALT or HBV DNA levels (between 2000 IU/mL and 20 000 IU/mL) as they are at higher risk of progression to active hepatitis and require treatment. Monitoring for persons with HBV/HIV coinfection should be done every 6 to 12 months in accordance with the WHO ARV guidelines (19). These guidelines will be updated in 2015.

Monitoring on treatment and after treatment discontinuation: Monitoring while on treatment is required to assess adherence, evaluate whether viral suppression is sustained (where HBV DNA can be measured), check for evidence of progression of liver disease, indications for stopping treatment and need to restart. Data from multiple clinical trials show that potent NAs with a high barrier to resistance (i.e. tenofovir and entecavir) suppress HBV DNA replication to low or undetectable levels in the majority of persons by 24–48 weeks of treatment, with low rates of resistance (but with limited success in achieving durable end-points, particularly loss of HBeAg in HBeAg-positive persons 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 HBV DNA levels (where testing is available), and also NITs such as APRI to assess for progression to cirrhosis. HBV genotyping and resistance testing are not required to guide therapy.

More frequent and careful monitoring was recommended conditionally based on limited evidence in the following groups: those with more advanced disease (compensated or decompensated cirrhosis) because the risk of HCC is reduced but not eliminated with treatment, and their higher risk of adverse events; during the first year of treatment to assess treatment response; where adherence to therapy is a concern; and after stopping therapy. The Guidelines Development Group noted that if monitoring is too infrequent, there is a risk of loss to follow up, treatment interruption or, in some persons, unnecessary prolongation of treatment. Monitoring of adherence is particularly important in resource-limited settings, where HBV DNA levels cannot be measured during treatment *(see Chapter 6: Box 6.2. Monitoring adherence to antiviral therapy)*. Approaches to monitoring side-effects during treatment are summarized in Chapter 9.2.

After stopping treatment, long-term monitoring is required *(see Chapter 8: When to stop treatment)*. Although the evidence base is very limited, ALT and HBV DNA can be measured monthly for the first 3 months, 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).

Resource considerations

There are cost implications to regular ALT and DNA monitoring. Where there is limited access to HBV DNA assays, such as in LMICs (particularly rural areas), monitoring will require, at a minimum, serum ALT levels to establish the risk of progression. However, interpretation of disease stage and exacerbations of disease in HBeAg-positive and HBeAg-negative persons requires not only serum ALT testing but also concomitant measurement of HBV DNA concentrations. NITs (such as APRI) can also be used for ongoing assessment of liver disease stage and evidence of progression, but should be used alongside clinical criteria and other laboratory criteria (ALT and HBV DNA levels) to identify those in need of treatment, as their PPV for identifying those with cirrhosis is low. Additional benefits of integrating routine monitoring for HCC alongside routine monitoring for disease progression are that it provides a further opportunity to detect the development of cirrhosis and initiate antiviral therapy to prevent progression to HCC or liver failure *(see Chapter 9.3: Monitoring for hepatocellular carcinoma)*.

There is the potential for community care and nurse-led clinics for persons with inactive disease and stable persons on treatment, with specialist care reserved for persons with advanced disease, cirrhosis, uncertain progression or in those in whom indications for treatment are uncertain. Additional training of health-care workers will be required for interpreting the laboratory results if care and follow up are provided by non-physicians.

9.2. Monitoring for tenofovir and entecavir toxicity

Recommendations

- Measurement of baseline renal function[a] and assessment of baseline risk for renal dysfunction[b] should be considered in all persons prior to initiation of antiviral therapy.
- Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children. *(Conditional recommendation, very low quality of evidence)*

[a] Measurement of baseline renal function includes: serum creatinine levels, and calculation of creatinine clearance (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) x (wt in kg) x 0.85 (if female) / (72xCr in mg%)

MDRD formula: eGFR = 175 x serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is Black) x 0.742 (if female).
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).

[b] Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, 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 (PI) for HIV, and solid organ transplantation.

BOX 9.2 Assessment and monitoring of renal function

1. At *baseline*, consider either avoidance of tenofovir and use of entecavir instead, or dose reduction of tenofovir (guided by Table 9.1), if the estimated glomerular filtration rate (eGFR) is <50 mL/min, or in those with risk factors for renal dysfunction, including long-term diabetes, uncontrolled hypertension or severe osteopenia/osteoporosis. The use of tenofovir is not recommended in children aged 2–12 years, or in any child with renal impairment.

2. Use of tenofovir should be avoided with concurrent/recent use of adefovir or other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, vancomycin, cidofovir) due to the increased risk of renal adverse reactions.

3. During *treatment*, consider adjusting the dosing interval of tenofovir or interrupting therapy (guided by Table 9.1) and closely monitoring renal function if the creatinine clearance (CrCl) falls below 50 mL/min, or in case of progressive decline of renal function when no other cause has been identified.

4. If therapy is discontinued, liver function should be monitored closely, as severe acute exacerbations of hepatitis have been reported on discontinuation of therapy, and resumption of antiviral therapy may be required.

5. *Monitoring during NA therapy may include:* urine dipsticks for proteinuria and glycosuria (in the absence of diabetes or where 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 in children on tenofovir. For individuals with normal renal function, a minimum monitoring package could include annual urine dipstick testing and creatinine measurement for eGFR where possible.

6. *Frequency of monitoring* during NA therapy depends on the presence of risk factors for renal dysfunction and should be more frequent in persons at higher risk.

    a. *Persons at high risk of renal toxicity:* every 6 months, unless there is evidence of worsening. Closer renal monitoring is required in persons with CrCl <50 mL/min.
    b. *Persons at low risk of renal toxicity:* either no routine monitoring of renal function, or every 12 months unless there is evidence of worsening.

7. If low bone mineral density is detected or suspected because of a fracture, then appropriate consultation should be obtained.

TABLE 9.1. Recommended dosage in adults with renal impairment

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

CAPD continuous ambulatory peritoneal dialysis CrCl creatinine clearance

[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

[b] Tenofovir is also available in a granule formulation (33 mg/g in 60 g pack) for ease of swallowing. Dosing is the same for oral granules and tablets.

[c] Calculated using lean body weight

[d] For doses less than 0.5 mg, oral solution is recommended. Entecavir is not recommended for those with lamivudine resistance.

9.2.1. Background

Tenofovir is principally 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 (1–4). Small decreases in bone mineral density with osteopenia or osteoporosis during the early phases of treatment have also been reported (5–8) and, more rarely, lactic acidosis or severe hepatomegaly with steatosis, which may be fatal. Known risk factors for the development of tenofovir-induced nephrotoxicity include underlying renal dysfunction, low CD4 count and low body weight (9–11). The mechanisms underlying the renal toxicities are not fully understood, although tubular dysfunction is known to occur. Genetic variability within the *MRP7* gene may influence renal tubular transport of tenofovir and contribute to the development of toxicity (12). Although tubular dysfunction is reversible in most cases after withdrawal of tenofovir, persistent renal dysfunction has been reported (13). Entecavir is also principally eliminated via the kidney, but proximal tubular dysfunction is less common. In addition to the effects of antiviral therapy, HBV infection may also impact on renal function (14,15).

9.2.2. Summary of the evidence

Question: The purpose of the evidence review *(see Web appendix 2: SR9b)* was to assess the optimal type and frequency of monitoring for toxicity in adults, adolescents and children on tenofovir or entecavir treatment for CHB. An initial search of the literature did not identify any trials or other studies that directly compared the outcomes of different toxicity monitoring strategies, and the review therefore focused on the long-term renal adverse effects related to tenofovir and entecavir in both nucleoside-naive and -experienced patients. This included eight studies of adults who had received tenofovir treatment, of which two were in HBV/HIV-coinfected patients; and four studies in those who had received entecavir (9,16–22,24,26–32). No studies were identified in children. As the data came from non-controlled observational studies, the quality of evidence was rated very low.

No studies have compared monitoring strategies for people receiving tenofovir, such as routine toxicity monitoring versus no monitoring or targeted monitoring in case of perceived clinical need. The Development of AntiRetroviral Therapy in Africa (DART) clinical trial in HIV-infected adults compared laboratory with clinical monitoring, and showed that individuals receiving tenofovir had an increased risk of reduced eGFR but no increased risk of renal failure over a median 5 years of follow up (low-quality evidence) (23).

Several prospective studies have reported renal function at between 2 and 5 years of tenofovir treatment (16–19,24). Overall, a higher percentage (8.9%) of

patients 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 5 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 (19). In patients with decompensated liver disease, 9% of those treated with tenofovir for 48 weeks had an increase in serum creatinine concentrations, but treatment discontinuation was rare (20). Of the long-term (3–5 years) effectiveness studies of entecavir, there was limited reporting of adverse outcomes (25–31). In one RCT, 1.6% of patients receiving entecavir monotherapy had an increase in serum creatinine through 96 weeks (32).

In HBV/HIV coinfection: The incidence of tenofovir-related kidney dysfunction among HIV-infected persons is also low in the short- to medium term (9–11,14,22). This is despite a high burden of chronic kidney disease (up to 25% of those starting ART have decreased eGFRs), including HIV-associated nephropathy (33). Prospective cohort studies over 5 years of follow up show that around 3% of patients experienced an increase in serum creatinine levels, with a modest reduction in renal function (eGFR change of –9.8 mL/min/1.73 m^2 at 4.5 years) as well as bone mineral density, but the clinical significance of these side-effects, especially with prolonged therapy, has not yet been established (9,20).

Independent risk factors significantly associated with a decrease in GFR in HBV-monoinfected and HBV/HIV-coinfected patients include increased age, non-African origin, lower baseline eGFR, duration of tenofovir therapy, and HBV DNA level >2000 IU/mL (8–10).

In children and adolescents: Tenofovir-related decreases in bone mineral density have been observed in children, although it is unclear how reduced bone mineral density might impact future growth patterns or the risk of bone fracture. In an RCT of tenofovir among adolescents (12 to <18 years), no patient met the safety end-point of a 6% decrease in spine bone mineral density at week 72 (34). There is uncertainty as to how best to measure and monitor tenofovir-related bone toxicity among children. 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 tenofovir. The safety profile of entecavir in children was consistent with that observed in adults, with no reported renal adverse events over 48 weeks in an ongoing entecavir trial reported in an FDA application (AI463289 trial).

Assays to monitor nephrotoxicity: There are limited data on the optimal assay to monitor for tenofovir-related renal toxicity. Data suggest that some persons may have normal serum creatinine levels but impaired renal function, so overreliance on absolute serum creatinine values may lead to tenofovir administration in

persons with pre-existing kidney disease. A high frequency of glycosuria has also been found in people without diabetes who underwent a biopsy for tenofovir nephrotoxicity, with increased serum creatinine compared with tenofovir-treated people with a normal GFR, suggesting that dipstick testing for glycosuria may be a cost-effective screening test for serious tenofovir-induced kidney injury (35).

9.2.3. Rationale for the recommendations

Balance of benefits and harms

Although tenofovir is associated with a risk of nephrotoxicity, hypophosphataemia, bone mineral loss and osteopenia, the evidence review showed a low risk of these adverse effects (ranging from 0.3% to 2% for nephrotoxicity) with long-term tenofovir or entecavir, even among HIV-infected persons, but particularly in the absence of risk factors. The Guidelines Development Group made a conditional recommendation for both baseline assessment of renal function and categorization of baseline risk of renal dysfunction in persons with HBV monoinfection; and for annual monitoring of renal function and growth monitoring in children, based on limited evidence.

Baseline assessment: The baseline assessment of renal function and categorization of baseline risk of renal dysfunction allows for both dose adjustment of tenofovir or use of the alternative entecavir in case of eGFR decrease, as well as better targeting of follow-up monitoring to those at higher risk of renal impairment (i.e. with decompensated cirrhosis, underlying renal disease [CrCl <50 mL/min], low BMI and older age). The evidence for the differential renal toxicity of entecavir versus tenofovir was not considered in detail, but entecavir was considered the preferred option in persons with an eGFR <50 mL/min. Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir that may have less renal and bone toxicity. It was noted that in the 2013 WHO ARV consolidated guidelines (36), a baseline measurement of creatinine is not a requirement for initiating ART with the preferred tenofovir-based regimen in HIV-infected persons. These guidelines will be updated in 2015.

Monitoring: The incidence of progression to moderate or severe kidney dysfunction was low among tenofovir users, and there was limited comparative evidence of the benefits and cost–effectiveness of routine monitoring versus no or incidental monitoring in persons with hepatitis B. However, the Guidelines Development Group considered that monitoring of renal function to detect changes in eGFR after initiation of tenofovir therapy was important to prevent development or progression of kidney disease. This is particularly the case in LMICs where there is limited access to dialysis for those who progress to end-stage renal disease. In persons at low risk of renal toxicity, periodic monitoring of renal function every 12 months was recommended. More frequent monitoring (approximately every 6 months) was recommended in persons with impaired eGFR at baseline (<50 mL/min) and other groups at higher risk of renal toxicity (i.e. those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension, or who are receiving concomitant therapy with boosted PIs

or nephrotoxic drugs), or in those with evidence of worsening of renal function during treatment. Most cases of tubular dysfunction are reversible, and so the risk of renal impairment can also be reduced if appropriate dose adjustments are made based on renal function monitoring.

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 tenofovir is usually directed at the tubules; glomerular function tests do not adequately measure tubular dysfunction, and there are currently no other simple tests to detect renal tubular toxicity. In addition, some persons may have normal serum creatinine levels but impaired renal function, and reliance on absolute serum creatinine values may lead to tenofovir administration in persons 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. Growth should be monitored in children and adolescents using tenofovir.

Resource considerations

Measurement and long-term monitoring of serum creatinine and serum phosphate levels, and bone mineral density scanning increases 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 LMICs. There are also challenges in provision of appropriate laboratory infrastructure and human resources for lifelong therapy and follow up *(see Chapter 12: Implementation considerations for national programmes)*.

Research gaps

- Evaluate the relative impact and cost–effectiveness of routine laboratory screening and monitoring of renal function in all persons on long-term tenofovir and entecavir or only in high-risk populations, such as those with hypertension or diabetes, or those using boosted PIs.
- 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 persons at greatest risk of tenofovir-related toxicity.
- Establish the long-term safety, efficacy and toxicity of tenofovir alafenamide versus tenofovir disoproxil fumarate in HBV-monoinfected and HBV/HIV-coinfected populations.

9.3. Monitoring for hepatocellular carcinoma (HCC)

Recommendations

- Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:
  - persons with cirrhosis, regardless of age or other risk factors *(Strong recommendation, low quality of evidence)*
  - persons with a family history of HCC *(Strong recommendation, low quality of evidence)*
  - persons aged over 40 years (lower age may apply according to regional incidence of HCC[a]), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL *(where HBV DNA testing is available). (Conditional recommendation, low quality of evidence)*

[a] The GLOBOCAN project of the International Agency on Cancer (IARC) (http://globocan.iarc.fr/ia/World/atlas.html) provides contemporary estimates of the incidence of, mortality and prevalence of major types of cancer, including HCC, at national level, for 184 countries of the world. The GLOBOCAN estimates are presented for 2012, separately for each sex. One-, three- and five-year prevalence data are available for the adult population only (ages 15 years and over).

9.3.1. Background

Chronic HBV infection leads to an increased risk of death from liver cirrhosis and liver cancer, with an estimated 650 000 annual deaths from HCC (1). In resource-limited and high HBV-burden settings, persons are often diagnosed with HBV only when they present for the first time with HCC. While the majority of these (80–90%) have cirrhosis at the time of diagnosis of HCC, it may sometimes occur without the presence of cirrhosis; this is especially true for HCC due to HBV. A further major challenge with HCC is that it is rapidly progressive, and may be asymptomatic until it presents clinically at an advanced stage. 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 the underlying liver function, and is improved if treatment can be commenced at an early stage of the disease, when the tumour is small. Surveillance is therefore required to detect HCC at an early stage (tumour size <3 cm in diameter) and increase the chances of effective treatment. Effective surveillance programmes require a means for implementing such treatment for small HCC in LMICs, recognizing that access to liver transplantation or resection remains limited, even in high-income settings. These treatments would include alcohol injection or radiofrequency ablation of small tumours. Current surveillance tools include ultrasound and/or alpha-fetoprotein (AFP) measurement, but there is no consensus on the best strategy or frequency of monitoring for HCC in persons with CHB, although existing evidence suggests that semi-annual surveillance detects HCC at an earlier stage and improves survival.

9.3.2. Summary of the evidence

Question: The purpose of the evidence review *(see Web appendix 2: SR9c)* was to identify the most effective surveillance strategy among those with CHB for early

detection of small HCC. The interventions included the following methods or combinations of methods at different monitoring intervals: abdominal ultrasound scan and (USS) serum AFP, and were compared with either no intervention or one of these screening interventions. Outcomes included disease-specific or all-cause mortality; diagnosis of HCC; size and stage of HCC detected (<3 cm or ≥3 cm in diameter); and cost–effectiveness. Studies were included only if ≥50% of persons met the definition for CHB.

Eight studies were included in the review, of which five were clinical studies (two RCTs conducted in China (2,3) but reported in several different publications (2,4–7); two in Korea (8,9); and one in Canada (10), and three economic evaluations (one each from the USA (11), Colombia (12), and the UK (13)), with a Cochrane review conducted in 2012 (14). Each of the clinical studies examined a different screening comparison: AFP 6-monthly versus no intervention (3); USS and AFP 6-monthly versus AFP 6-monthly (10); USS and AFP 6-monthly versus no intervention (2); or USS and AFP ≤6-monthly versus USS and AFP >6-monthly (8). Overall, there were a limited number of studies for each screening comparison, and none that included children, pregnant women or HBV/HIV-coinfected individuals. The majority of study participants were male. The overall quality of evidence was rated as low or very low.

Approaches to screening for HCC: Overall, the data showed an impact on disease-specific mortality of 6-monthly USS and AFP compared to no intervention (odds ratio [OR] 0.57, 95% CI: 0.37–0.89) or ≤6-monthly USS and AFP versus >6-monthly (OR 0.63, 95% CI: 0.40–0.98), but not for 6-monthly AFP alone versus no intervention. In addition, 5-year survival favoured 6-monthly screening versus no intervention (31.4% vs 23.3%; *P*=0.026). Although there was no statistically significant difference in the number of new cases of HCC detected, there was significantly earlier detection of HCC in terms of stage and smaller lesion size (<3 cm or <5 cm in diameter) with either 6-monthly USS and AFP screening (OR 11.2, 95% CI: 6.73–18.72) or >6-monthly screening (OR 2.13, 95% CI: 1.42–3.18), as well as with 6-monthly AFP alone, compared with no intervention. An observational study also found that 6-monthly AFP screening was effective in detecting most HCC tumours at a resectable stage and significantly prolonged survival rates (15) versus no intervention. A systematic review published after completion of this review (16) identified two additional relevant observational studies (17,18) – one that compared USS plus AFP versus no screening (17), and the other USS versus no screening (18). Both showed an overall survival benefit of screening when compared with no screening, consistent with the findings of the main review. Of the three economic evaluation studies (11–13), two found screening every 6 months using both AFP level and USS to be the most cost–effective strategy (12,13). The third study conducted in rural Alaska reported that restricting USS to persons with raised AFP levels was less costly and more cost–effective compared to USS alone every 6 months in all persons (11).

Who should be screened for HCC? The key evidence for risk factors (or combinations of factors) specific for the development of HCC *(see Chapter 5: Who to treat and who not to treat; Table 5.1)* was derived from the large population-based REVEAL-HBV cohort from Taiwan (19–23), as well as several other prospective (24–28) and retrospective cohort studies (29–31), studies in HBV/HIV-coinfected patients (32) and one systematic review (33). These longitudinal cohorts show that the most important risk factors for the development of 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, compared to those aged <40 years, the RR for HCC was 3.6 (2.0–6.4) for those aged 40–49 years, 5.1 (2.0–8.9) for those 50–59 years, and 8.3 (4.6–15.0) for those >60 years; and for HBeAg positivity it was 4.3 (3.2–5.9) *(see Chapter 5, Table 5.1)* (22). In addition, there is a consistent and linear increase in the incidence of HCC with baseline HBV DNA over 10 000 copies/mL (2000 IU/mL) irrespective of the presence of cirrhosis. Those with a family history of HCC have a threefold higher risk, and this was greatest among those who were also HBeAg-positive (HR= 45.52; 95% CI: 22.9–90.6) (Table 9.1) (22). Other factors associated with an increased risk of developing HCC are ethnicity (risk of HCC is greater in people of African or Asian family origin), duration of infection (risk higher in those with neonatal/perinatal and childhood infection), those with genotype C and core promoter mutants, and those with a history of smoking, high alcohol intake and diabetes.

Risk calculators have been developed, which provide an easy-to-use formula to predict the risk of HCC from models (34–36) that include age, sex, levels of albumin, bilirubin and ALT, HBeAg status, HBV DNA levels and presence of cirrhosis. These models were derived largely from longitudinal cohort data of Asian patients and have not been extensively validated in non-Asians. The evidence was rated as being of high-to-moderate quality (due to imprecision or limitations in the outcome assessment). More limited data were available in HBV/HIV-coinfected patients, but low CD4+ cell count and longer cumulated time with detectable HIV RNA were associated with an increased risk of developing HCC.

TABLE 9.4. Cumulative incidence of hepatocellular carcinoma (HCC) according to family history of HCC, baseline HBV DNA level and HBeAg status (22)

	Cumulative incidence (%)	Adjusted HR (95%CI)
NO family history	7.5	Reference
Family history of HCC	15.8	2.46 (1.63–3.72)
NO family history **HBV DNA <10 000 copies/mL**	2.5	Reference
HBeAg positive **Family history of HCC**	40	45.52 (22.86–90.63)
HBeAg positive **NO family history**	19.1	13.91 (9.31–20.77)
HBeAg negative **Family history of HCC** **HBV DNA >10 000 copies/mL**	17.6	9.90 (4.52–21.37)
HBeAg negative **NO family history** **HBV DNA >10 000 copies/mL**	10.3	4.43 (3.02–6.50)
HBeAg negative **Family history of HCC** **HBV DNA <10 000 copies/mL**	5.4	NS

All data among HBsAg-positive persons with CHB

HR hazard ratio, CI confidence interval

9.3.3. Rationale for the recommendations

Balance of benefits and harms

Screening approaches: Overall, the RCT and economic evaluation evidence favoured the combination of ultrasound and AFP monitoring at approximately 6-monthly intervals compared to no surveillance to detect HCC in the early stages and improve overall survival through earlier potentially effective therapies. The Guidelines Development Group also considered that the overall benefits of screening high-risk persons with CHB outweighed the potential harms. Affected individuals develop HCC in mid-to-late adulthood, and deaths from HCC drain health-care resources and productive capacity in LMICs where HBV infection is prevalent. HCC is generally silent until symptomatic (typically when large, i.e. >10 cm in size), and the prognosis is extremely poor in persons with advanced-stage symptomatic tumours and underlying hepatic dysfunction. Additional benefits of integrating routine monitoring for HCC alongside routine monitoring for disease progression are that it provides a further opportunity to detect the development of cirrhosis and initiate antiviral therapy to prevent progression to HCC or liver failure (*see Chapter 9.1: Monitoring in persons prior to, during and post-treatment).* However, the Guidelines Development

Group recognized that surveillance would be effective in improving survival only if LMICs also plan for how to treat small HCC through, for example, ablation, alcohol injection, chemoembolization or resection, as well as the use of antiviral therapy, and manage complications of advanced liver disease. At present, there is very limited access to such interventions in these settings. Antiviral therapy reduces the risk of HCC (37), and has benefits even in persons with HCC, including decreased risk of recurrence following HCC treatment, decreased necroinflammation and reduced risk of hepatic decompensation.

Potential harms of screening include false-positive AFP and ultrasound detection of small lesions other than tumours, such as regenerative nodules in cirrhotic livers, which may not develop into malignant HCC, resulting in unnecessary and costly interventions, as well as the inconvenience of attending for screening visits. There is also a trade-off in duration of intervals between screenings. If the intervals are too long, this may delay the detection of HCC, particularly in non-cirrhotic persons. vIn contrast, if HCC surveillance is more frequently performed, there will be an associated increase in cost per diagnosis.

Who to screen? Evidence from longitudinal studies shows that the most important risk factors for development of HCC (associated with an approximately fourfold increased risk) are the presence of cirrhosis, HBeAg positivity and a family history of HCC. The majority of persons (80–90%) also have cirrhosis at the time of diagnosis of HCC and therefore the Guidelines Development Group recommended that those with cirrhosis as well as 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 considered that the optimal age at which surveillance for HCC should commence cannot yet be established with certainty, as the incidence of HCC varies with age according to region, and occurs at a younger mean age in Africans compared to Asians (see http://globocan.iarc.fr/ia/World/atlas.html, IARC GLOBOCAN). Therefore, no specific age threshold for screening was recommended.

Resource use and implementation considerations

For surveillance to be effective in improving survival, there must be a means to treat small HCC. This includes access to expertise in ablation, chemoembolization or resection (and transplantation), as well as management of advanced liver disease, and provision of antiviral therapy to prevent the development of HCC or tumour recurrence following resection. Surveillance for HCC will need to be integrated into existing monitoring for disease progression, treatment response and toxicity in those on antiviral therapy. There will also be a need for additional training in the use and expert interpretation of ultrasound imaging for small HCC.

Research gaps

- Determine risk factors (including age) and thresholds for HCC and natural history in African populations through longitudinal cohort studies in sub-Saharan Africa.
- Conduct further RCTs of head-to-head comparisons between different HCC surveillance strategies, especially in sub-Saharan Africa.
- Evaluate low-cost treatment strategies, including alcohol injection for small HCC, in LMICs.
- Evaluate the impact of NA therapy on tumour-free survival after resection or ablation of small HCCs.

10. RECOMMENDATIONS FROM EXISTING WHO GUIDANCE: PREVENTION

10.1. Infant and neonatal hepatitis B vaccination

Recommendations

Existing recommendations in infants and neonates[1]

- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours[a], followed by two or three doses.

[1] WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.

[a] In countries where there is high disease endemicity and where HBV is mainly spread from mother to infant at birth or from child to child during early childhood, providing the first dose at birth is particularly important, but even in countries where there is intermediate or low endemicity, a substantial proportion of chronic infections are acquired through early transmission.

Primary hepatitis B vaccination *(source: Existing WHO position on hepatitis B vaccine [2009])*(1)

The primary hepatitis B immunization series conventionally consists of three doses of vaccine (i.e. one monovalent birth dose followed by two monovalent or combined vaccine doses). However, four doses may be given for programmatic reasons (for example, one monovalent birth dose followed by three monovalent or combined vaccine doses), administered according to the schedules of national routine immunization programmes. For older children and adults, the primary series of three doses with appropriate intervals applies.

In countries where there is high disease endemicity and where HBV is mainly spread from mother to infant at birth or from child to child during early childhood, providing the first dose at birth is critical. In settings where a high proportion of HBsAg-positive mothers are also HBeAg positive, exclusion of the birth dose in the hepatitis B immunization schedule may result in a large proportion (up to 90%) of infants born from these mothers already being chronically infected with HBV before the first scheduled dose of vaccination at 4–8 weeks of age. The birth dose should be followed by two or three doses to complete the primary series. In most cases, one of the following two options is considered appropriate: (i) a three-dose schedule of hepatitis B vaccine, with the first dose (monovalent) being given at birth, and the second and third (monovalent or combined vaccine) given at the same time as the first and third doses of diphtheria–tetanus–pertussis (DTP)

vaccine; or (ii) four doses, where a monovalent birth dose is followed by three monovalent or combined vaccine doses, usually given with other routine infant vaccines. Combination vaccine products that include HBV are widely used in Expanded Programme on Immunization/national immunization programmes, but only monovalent HBV vaccine can be used at birth.

BOX 10.1 Programmatic measures to improve implementation of hepatitis B birth dose vaccination (within 24 hours of birth) (2,3)

1. Increasing the number of infants born in facilities or attended by trained health staff to improve birth dose coverage;
2. Ensuring that there is coordination between immunization services and maternal health services so that the vaccine is available at the place of delivery or immediately after birth;
3. Expanding vaccine management systems and innovative outreach to provide vaccine for home births so that hepatitis vaccine is available in settings where births take place;
4. Development of new heat-stable and freeze-stable hepatitis B vaccine;
5. Health promotion efforts aimed at parents, and training aimed at providers to increase awareness about the importance of administering hepatitis B vaccine within 24 hours of birth;
6. Availability of hepatitis B vaccine not combined with other childhood immunizations so that HBV vaccines can be administered alone as a birth dose;
7. 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.

Passive immunization against hepatitis B with HBIG: Temporary immunity is conferred by administering HBIG for post-exposure prophylaxis. HBIG prophylaxis, in conjunction with HBV vaccination, may be of additional benefit for the following: newborn infants whose mothers are HBsAg-positive, particularly if they are also HBeAg-positive. In fullterm neonates born to mothers who are HBsAg-positive but HBeAg-negative, protection against perinatally acquired infection achieved by immediate vaccination against HBV (given within 24 hours) may not be significantly improved by the addition of HBIG.

Catch-up hepatitis B vaccination strategies *(source: Existing WHO position on hepatitis B vaccine [2009])*(1)

In countries with intermediate or low endemicity, there may be a substantial disease burden from acute and chronic infection acquired by older children, adolescents and adults, many of whom may have been born prior to universal vaccination. In these countries, implementation of routine infant immunization will produce broad population-based immunity to HBV infection and eventually prevent transmission among all age groups. However, time-limited catch-up strategies targeted at unvaccinated people in the older age groups may be needed to hasten the development of population-based immunity and to decrease more rapidly the incidence of acute hepatitis B.

Possible target groups for catch-up immunization include age-specific cohorts (for example, young adolescents) and persons with risk factors for acquiring HBV infection. The establishment of surveillance for acute hepatitis B and the performance of HBsAg seroprevalence studies for CHB can assist in determining the groups at highest risk of acquiring infection (for example, health workers, travellers to areas where HBV infection is prevalent, PWID, men who have sex with men, and persons with multiple sex partners). Vaccination and other prevention efforts may be targeted at these groups.

10.2. Prevention of mother-to-child HBV transmission using antiviral therapy

See also Chapter 5: Who to treat and not to treat; Chapter 6: First-line antiviral therapies; and Chapter 11: Management considerations in special populations, including pregnant women.

Antiviral therapy

- In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults[a], and tenofovir[b] is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.

Existing recommendations in HIV-infected pregnant and breastfeeding women[2]

- In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped. *(Strong recommendation, low to moderate quality of evidence)*

[2] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

[a] *See also Chapter 5: Who to treat and who not to treat.*

[b] *See also Chapter 6: First-line antiviral therapies for chronic hepatitis B.*

10.2.1. Background

In highly endemic areas, HBV is most commonly spread from mother to child at birth from exposure to maternal blood and secretions at delivery, or from person to person in early childhood (5). In areas of low endemicity, perinatal or early childhood transmission of HBV may be responsible for over a third of chronic infections (6). Transmission early in life is also associated with a higher risk of (lifelong) chronic infection (7). It is therefore important that the most effective interventions to prevent mother-to-child transmission of HBV are identified and utilized. The currently recommended practice to reduce mother-to-child perinatal transmission or horizontal transmission relies on the administration of HBV vaccine and, in some countries, concurrent administration of hepatitis B immune globulin (HBIG), although screening practices and the resultant prophylaxis that infants receive vary from country to country (8) *(see also Chapter 10.1: Infant and neonatal hepatitis B vaccination)*. Hepatitis B vaccination is considered safe and effective and prevents transmission in 80–95% of cases (9,10). In-utero transmission is relatively rare and is not the major means of transmission of HBV from mothers to infants, although it may occur if intrauterine placental leakage arises as a result of threatened preterm labour (11). A proportion of infants born to HBsAg-positive mothers acquire hepatitis B despite both HBV vaccination and/or HBIG prophylaxis. Estimates of the risk of transmission, despite HBV vaccination and HBIG, vary, but are related to levels of maternal HBV viraemia. Very high maternal concentrations of HBV DNA, typically observed in HBeAg-positive women, confer a 10% or more risk of transmission, despite HBIG and vaccine prophylaxis (11–14).

In HIV-infected pregnant women, the risk of mother-to-child transmission of HIV can be substantially reduced during pregnancy, labour and delivery, and breastfeeding to as little as 1–2% through the use of ART initiated during pregnancy (15). The WHO-recommended tenofovir-containing regimens are also highly effective against HBV infection. A small but growing body of data suggests that maternal treatment with NA therapy in the third trimester of pregnancy in addition to vaccine and HBIG for the infant may also reduce HBV transmission to the infant. This may help address the imperfect adherence to the neonatal vaccination schedule, and particularly to the administration of the initial birth dose of vaccine (with or without HBIG) in neonates born to highly viraemic mothers. However, although several countries have adopted a policy of treating highly viraemic pregnant mothers, especially in Asia, with lamivudine, telbivudine or tenofovir, the efficacy of adjuvant maternal treatment with antivirals in the third trimester of pregnancy is unclear. Such treatment would be for a limited period for the purpose of reducing the risk of infection to the baby. If a woman requires treatment based on her own clinical condition then that treatment would be continued through the pregnancy. Lamivudine is the most widely studied agent of those that are active against HIV and HBV; there is also a sizeable body of data in women who have received tenofovir as part of an ART regimen.

10.2.2. Summary of the evidence

Question: The purpose of the evidence review *(see Web appendix 2: SR10)* was to assess the clinical and economic evidence for the effectiveness of antiviral therapy during the third trimester of pregnancy (defined as 27–40 weeks of gestation) to reduce maternal transmission of HBV infection, and to identify the most effective therapies (tenofovir, lamivudine, telbivudine, emtricitabine plus tenofovir/tenofovir plus emtricitabine, entecavir, adefovir) compared to each other (either as monotherapy or combination therapy), placebo or no intervention (with or without use of the birth dose vaccine). Key outcomes were transmission of HBsAg, newborn and infant HBsAg- and HBeAg seropositivity (0–9 months and 9–15 months); HBV DNA positivity; congenital abnormalities; adverse events (maternal or infant); antiviral resistance; cost–effectiveness.

A total of 35 studies were identified (12,16–54). There were 12 RCTs, 19 observational studies, and two systematic reviews (53,54); which evaluated either telbivudine or lamivudine versus no treatment, in addition to four economic evaluations (47–50). There were no studies specific to persons with HIV coinfection. The majority of studies included the administration of both hepatitis B vaccine and HBIG to the infants.

Overall, the results suggest that maternal treatment with either lamivudine or telbivudine during the third trimester of pregnancy may be clinically effective and cost–effective in reducing the vertical transmission of hepatitis B infection when compared with no treatment or placebo. However, there was only one outcome – newborn HBV DNA positivity (a less reliable measure of mother-to-child transmission than HBsAg seropositivity), where the GRADE quality score from analysis of the RCTs of lamivudine was rated as high to support this conclusion, with a statistically significant benefit in favour of treatment with lamivudine versus no intervention or placebo (OR 0.25, 95% CI: 0.16–0.37). The non-RCTs also supported this finding (OR 0.03, 95% CI: 0.00–0.46), based on a moderate GRADE score. Similar statistically significant findings were observed for telbivudine versus no intervention or placebo based on seven non-RCTs. Other outcomes associated with statistically significant differences in favour of lamivudine and telbivudine, but with low GRADE scores were: infant DNA positivity, and newborn and infant HBsAg positivity. Since the review, a further large trial has reported reduced HBV transmission and HBsAg-positivity in infants born to telbivudine or lamivudine-treated HBsAg-positive mothers (2.2% (95% CI: 0.6–3.8%) vs 7.6% (95% CI: 4.9–10.3%) in the untreated group at week 52 (55).

Cost–effectiveness: A total of four economic evaluations (three from the USA and one from Taiwan) evaluated lamivudine against no antiviral therapy, HBIG, and two other antiviral therapies (47–50). All the studies showed that a combination of maternal and neonatal prophylaxis is neither cost-saving nor cost–effective when

compared to neonatal prophylaxis alone in preventing vertical transmission of hepatitis B.

Safety in pregnancy: Among the potential concerns about the safety of antivirals, including tenofovir, are adverse birth outcomes. A systematic review (56) assessed the toxicity of fetal exposure to tenofovir in pregnancy. A review of data from the Antiretroviral Pregnancy Registry shows that the prevalence of overall birth defects with exposure to tenofovir in the first trimester was 2.4% of 1612 live births and did not differ from the background rate in the United States of America (57). A limited number of studies showed no difference in fetal growth between infants exposed or not exposed to tenofovir (58,59). Tenofovir has limited penetration in breast milk, which would limit potential toxicity for the breastfeeding infant.

10.2.3. Rationale for conclusions

Balance of benefits and harms

The Guidelines Development Group recognized that the most important strategy to prevent mother-to-child HBV transmission is to deliver the first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, in accordance with the existing recommendations of the WHO Strategic Advisory Group of Experts (SAGE) (1). Hepatitis B vaccination is considered safe and effective, and prevents transmission in 80–95% of cases (1). National strategies to prevent perinatal transmission should include providing hepatitis B vaccine at birth and ensuring high coverage of the birth dose through a combination of strengthened maternal and infant care at birth with skilled health-care workers present to administer the vaccine, and innovative outreach to provide vaccine for children born at home *(see also Box 10.1)*. In addition, making available HBV vaccine that is not combined with other infant vaccines in all countries is crucial to the strategy of administering the birth dose. HBIG prophylaxis in conjunction with HBV vaccination may be of additional benefit for newborn infants whose mothers are HBsAg-positive, particularly if they are also HBeAg-positive, but may not be feasible in most settings, due to concerns related to supply, safety and cost.

The Guidelines Development Group also recognized that a proportion of infants born to mothers with very high maternal concentrations of HBV DNA acquire hepatitis B, despite both HBV vaccination and/or HBIG prophylaxis, and considered the current evidence base for the additional benefit of antiviral therapy. The Guidelines Development Group did not make a formal recommendation as a result of the current limited and low-quality evidence base with three ongoing (and one completed but unpublished) trials due to report in 2015–2016, limited evaluation of the potential harms of antiviral use in pregnancy, and the lack of consensus as to the programmatic implications of a policy of more widespread antiviral use in pregnancy, given the very limited access to HBV viral load assays. Overall, data were limited for comparisons of the different antivirals, and suitable data were identified only for three different antivirals: lamivudine, telbivudine

and tenofovir. The review showed that maternal treatment with either lamivudine or telbivudine during the third trimester of pregnancy may be clinically effective and cost–effective in helping to further reduce the vertical transmission of hepatitis B infection when compared with no treatment or placebo, in addition to HBV vaccine and HBIG for the newborn. However, for lamivudine, there was only one outcome – newborn HBV DNA positivity with a high GRADE quality score, and all findings on the relative efficacy of telbivudine versus lamivudine were rated as low. In addition, although tenofovir would be considered the preferred antiviral because of its high potency, higher barrier to resistance, and evidence of safety in pregnancy (lower teratogenic risk), efficacy data were limited to one observational study, and the quality of the evidence was rated as very low. Studies are in progress and will be reported in 2015.

Several potential harms of antiviral use in pregnancy need to be more fully evaluated. These include the risk of development of HIV and HBV drug resistance if less potent drugs, such as lamivudine, telbivudine or adefovir, are used in mothers with a high HBV DNA viral load, especially if the duration of therapy is insufficient to reduce viraemia to low levels, and risks of toxicity to the baby, including through breastfeeding. HBsAg can be detected in breast milk. No differences in the rates of HBV infection have been reported between breastfed versus formula-fed infants (60) and breastfeeding is not contraindicated in HBV-positive mothers. However, little is known regarding the effects on the infant of exposure to NAs during breastfeeding (61,62). There is also a risk of exacerbation or postpartum flare in the mother after cessation of antiviral therapy. Cirrhosis is relatively uncommon in the younger age group of pregnant women with good liver function, but there is a small increased risk of flares in serum ALT during pregnancy and post partum. Fatal cases are fortunately rare (63,64). The Guidelines Development Group concluded that the principal indication to treat mothers throughout pregnancy should be the necessity for treatment of CHB in the mother *(see Chapter 5: Who to treat and who not to treat among persons with CHB)*. For women already on therapy who become pregnant, treatment may not need to be discontinued.

Research gaps

- Conduct high-quality, direct, head-to-head RCTs in pregnant women to establish the relative efficacy of different antiviral regimens together with HBIG to reduce mother-to-child HBV transmission, and the optimal threshold of HBV DNA for antiviral therapy.
- Determine the risk of exacerbation or post-partum flare in the mother after cessation of antiviral therapy, as well as establish the optimal duration of continuation of therapy post partum (4 weeks or 12 weeks).
- Establish the safety of exposure to different NA therapies during pregnancy and breastfeeding through additional surveillance programmes, especially in LMICs.

10.3. Prevention of transmission of hepatitis B and measures to reduce disease progression in persons with chronic hepatitis B

BOX 10.2 Prevention of transmission of hepatitis B and measures to reduce disease progression in persons with chronic hepatitis B

See also Chapter 5, Box 5.1: Key points for initial assessment of persons with CHB prior to therapy

Persons with CHB should receive counselling regarding cofactors likely to accelerate disease progression (such as alcohol), the risk and modes of onward transmission, and the need for long-term follow up.

1. **General measures to reduce HBV transmission**
   Individuals who are HBsAg positive should: adopt correct and consistent condom use during sexual intercourse if the partner is neither HBV immune nor has been vaccinated; not share razors, toothbrushes, or other personal care items; not donate blood, organs or sperm; and follow standard universal precautions with open cuts or bleeding.

2. **HBV vaccination of household and sexual contacts *(source: Existing WHO position on hepatitis B vaccine [2009])*(1)**
   Household members and sexual partners of persons with CHB are at increased risk of HBV infection and should be vaccinated if they are negative for HBsAg, anti-HBs and IgG anti-HBc. Dosing schedules depend on the type of vaccine, age at administration, need for rapid immunization and previous non-response to HBV vaccination. Combined hepatitis A and B vaccines are also available. Though approximately 10% of healthy adults do not mount an anti-HBs response (≥10 mIU/mL) to the primary immunization schedule, post-vaccination testing for anti-HBs is not recommended in any guideline. However, in some groups, such as health-care workers or sexual contacts of HBsAg-positive persons, post-immunization testing for anti-HBs is desirable and non-responders should receive a repeat three-dose (1 month apart) course of vaccination. This gives rise to protective antibody levels in 44–100% of individuals. Individuals who do not develop protective HBs antibody levels 1–2 months after revaccination can be considered for repeat vaccination (0, 1 and 2 months with a 6-month booster) with double the standard dosage of vaccine (1).

3. **Alcohol reduction to reduce disease progression *(source: Existing WHO guidelines on care and treatment of persons with HCV infection [2014]* (65)**
   Significant alcohol intake (>20 g/day in women and >30 g/day in men) can accelerate the progression of HBV- and HCV-related cirrhosis. In the 2014 WHO guidelines for the screening, care and treatment of persons with hepatitis C infection (65), it was recommended that a brief alcohol intake assessment should be conducted in all persons with HCV infection, followed by the offer of a behavioural alcohol reduction intervention in persons with moderate-to-high alcohol intake. This was based on a systematic review of persons with hepatitis C but also included studies among those with CHB. Therefore, a similar approach would be applicable to those with CHB.

   The WHO ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) package was considered an appropriate framework to design alcohol screening and reduction interventions, because it is evidence based, proposes a standardized approach, and is aimed at the primary health-care level (66). The ASSIST package includes tools for carrying out an assessment of the level of intake of alcohol and other substances, and instructions on implementing a brief counselling intervention.

10.4. Prevention of hepatitis B and C transmission in health-care settings *(source: Existing WHO guidelines (67–69))*

TABLE 10.1. WHO recommendations on prevention of HBV infection in health-care settings[a]

Recommendations
• hand hygiene: including surgical hand preparation, hand washing and use of gloves
• safe handling and disposal of sharps and waste
• safe cleaning of equipment
• testing of donated blood
• improved access to safe blood
• training of health personnel

[a] Additional general guidance on post-exposure prophylaxis following needlestick injury/sexual exposure/mucosal or percutaneous (bite) HBV exposure

- Wounds should be washed with soap and water, and mucous membranes flushed with water.
- The source individual should be screened for HBsAg, HIV and HCV antibody.
- HBsAg, anti-HBs and IgG anti-HBc should be checked in the exposed individual, to assess whether the individual is infected, immune or non-immune to hepatitis B.
- If the source individual is HBsAg positive or status is unknown, HBIG (0.06 mL/kg or 500 IU) is given intramuscularly and active vaccination commenced (0, 1 and 2 months) if the exposed individual is non-immune. HBIG and vaccine should be given at different injection sites. HBIG is repeated at 1 month if the contact is HBeAg positive, has high HBV DNA levels or if this information is not known. If the exposed individual is a known non-responder to HBV vaccination, then two doses of HBIG should be given 1 month apart.
- Anti-HBs titres should be measured 1–2 months after vaccination.

Injection safety in health-care settings

Injection practices worldwide and especially in LMICs include multiple, avoidable unsafe practices that ultimately lead to large-scale transmission of bloodborne viruses among patients, health-care providers and the community at large. Unsafe practices include, but are not limited to, the following prevalent and high-risk practices:

1. Reuse of injection equipment to administer injections to more than one person, including reintroduction of injection equipment into multidose vials, reuse of syringe barrels or of the whole syringe, informal cleaning and other practices;
2. Accidental needlestick injuries in health-care workers, which occur while giving an injection or after the injection, including recapping contaminated needles, and handling infected sharps before and after disposal;
3. Overuse of injections for health conditions where oral formulations are available and recommended as the first-line treatment;

4. Unsafe sharps waste management, putting health-care workers, waste management workers and the community at large at risk. Unsafe management of sharps waste includes incomplete incineration, disposal in open pits or dumping sites, leaving used injection equipment in hospital laundry, and other practices that fail to secure infected sharps waste.

WHO guidelines in 2015 will provide recommendations on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous therapeutic injections in health-care settings (www.who.int/injection_safety/en). This guidance will help prevent the reuse of syringes on patients and decrease the rate of needle-stick injuries in health-care workers related to injection procedures. It will complement existing WHO best practices and the toolkit for injections and related procedures, published by WHO in 2010 (69), which notes the importance of a sufficient supply of quality-assured syringes and matching quantities of safety boxes.

10.5 Prevention of hepatitis B and C and sexual transmission in persons who inject drugs *(source: Existing WHO guidelines (66,70,71)*

Transmission of HBV through the sharing of contaminated injecting equipment among PWID is an important route of HBV and HCV transmission in some countries. Therefore, reducing this risk of transmission is an essential component of care. Existing WHO guidance recommends a comprehensive package of harm reduction interventions, which comprise nine activities specifically for PWID (70) *(see Tables 10.2 and 10.3)*. Screening and testing for comorbidities among people who use drugs is crucial for informing treatment plans (drug–drug interactions, potential hepatotoxicity, among others).

Table 10.4 summarizes WHO recommendations for preventing the sexual transmission of HBV infection.

TABLE 10.2. WHO/UNODC/UNAIDS comprehensive package of interventions for HIV prevention, treatment and care in people who inject drugs (70)

Recommendations
1. Needle and syringe programmes
2. Opioid substitution therapy and other drug dependence treatment
3. HIV testing and counselling
4. Antiretroviral therapy
5. Prevention and treatment of sexually transmitted infections
6. Condom programmes for people who inject drugs and their sexual partners
7. Targeted information, education and communication for people who inject drugs and their sexual partners
8. Vaccination, diagnosis and treatment of viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis.

TABLE 10.3. WHO recommendations for prevention of HBV and HCV infection among people who inject drugs (71)

Recommendations
• Offer people who inject drugs the rapid hepatitis B vaccination regimen.
• Offer people who inject drugs incentives to increase uptake and complete the hepatitis B vaccination schedule.
• Implement sterile needle and syringe programmes that also provide low dead-space syringes for distribution to people who inject drugs.
• Offer peer interventions to people who inject drugs to reduce the incidence of viral hepatitis.
• Offer opioid substitution therapy to treat opioid dependence; reduce HCV risk behaviour and transmission through injecting drug use; and increase adherence to HCV treatment.
• Integrate treatment of opioid dependence with medical services for hepatitis.

TABLE 10.4. WHO recommendations on prevention of sexual transmission of HBV infection (72,73)

Recommendations
• Promotion of correct and consistent condom use
• Routine screening of sex workers in high-prevalence settings
• Targeting sex workers for catch-up HBV immunization strategies in settings where infant immunization has not reached full coverage
• Integrated action to eliminate discrimination and gender violence, and to increase access to medical and social services for vulnerable persons.

11. MANAGEMENT CONSIDERATIONS FOR SPECIFIC POPULATIONS

See also Chapter 5: Who to treat and who not to treat; and Chapter 6: First-line antiviral therapies

A comprehensive approach to management includes measures to prevent onward transmission of hepatitis B, screening for HIV, hepatitis C and D, provision of hepatitis B vaccination, and general care and treatment. Management also needs to address the additional needs of special populations with CHB, including persons coinfected with HIV, HDV or HCV; those with advanced or decompensated liver disease as well as extrahepatic manifestations, those with acute hepatitis B, and children and adolescents, pregnant women, and PWID. The following chapter provides a summary of key considerations in the treatment and care of these populations for implementing the recommendations covered in Chapters 4 to 10.

11.1 Coinfections

HBV, HIV, HCV and HDV share similar transmission routes. Concurrent infection with these viruses usually results in more severe and progressive liver disease, and a higher incidence of cirrhosis, HCC and mortality. Coinfected persons are therefore more likely to need treatment. In general, the dominant virus responsible for liver disease should be identified and initial treatment targeted toward this virus. For example, if HCV is dominant, treatment should first be given to achieve HCV clearance and cure, followed by determination of whether treatment for hepatitis B is warranted based on ALT and HBV DNA levels.

11.1.1. HBV/HIV coinfection

See also: Chapter 3.9: Background – Special populations
Chapter 5.2: Who to treat and not to treat among persons with CHB – Summary of the evidence – HBV/HIV coinfection
Chapter 6.2: First-line antiviral therapies for CHB – Summary of the evidence – Other populations
Chapter 9.2.2: Monitoring for tenofovir and entecavir toxicity – Summary of the evidence and
Chapter 10.2: Prevention of mother-to-child HBV transmission using antiviral therapy – Background

HIV coinfection has been shown to have a profound impact on almost every

aspect of the natural history of HBV infection and includes more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection (1–7). Other challenges with coinfection include cross-resistance between HIV and HBV drugs (8,9) increased liver injury, either due to direct hepatotoxicity (10,11) or ART-related immune-reconstitution hepatitis, with elevation of ALT and even fulminant hepatitis if ART does not cover both HIV and HBV infections adequately (12–14).

HBV screening and vaccination: (see also Chapter 10.1: Catch-up hepatitis B vaccination strategies) The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and anti-HBs to identify those with CHB, and vaccinated if non-immune (i.e. no marker of resolved HBV infection – HBsAg and anti-HBs positivity). Response to HBV vaccine is lower in persons with HIV or with a low CD4 count, and 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 schedule (15). In 2015, there will be new WHO recommendations on screening strategies for hepatitis B and C, and updated HBV vaccination recommendations from SAGE.

When to initiate ART in HBV/HIV-coinfected persons: In the 2013 WHO ARV guidelines (16), the recommendations were for initiation of ART in all HIV-infected adults with a CD4 cell count less than 500 cells/mm^3 (regardless of stage of liver disease); in all pregnant or breastfeeding women regardless of CD4 count; and in all children less than 5 years of age regardless of CD4 count. In persons with evidence of severe chronic liver disease who are at greatest risk of progression and mortality from liver disease, initiation of ART is recommended regardless of CD4 count. ART initiation in persons with cirrhosis may improve overall survival and is therefore strongly recommended.

There was insufficient evidence and/or favourable benefit–risk profile to support initiating ART in everyone coinfected with HIV and HBV with a CD4 count >500 cells/mm^3 or regardless of CD4 count or WHO clinical stage. Therefore, for those without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults (i.e. provide ART at a CD4 count <500 cells/mm^3). The use of dual anti-HIV and anti-HBV therapy has simplified the recommendations for widening the use of tenofovir with emtricitabine or lamivudine in HBV/HIV-coinfected persons, regardless of immunological, virological or histological considerations.

Other considerations: An increase in ALT level in HIV-coinfected persons may be the result of HIV-related opportunistic infections, hepatotoxicity from ART or TB drugs, alcohol use, HBV clearance, immune reconstitution, emergence of

drug resistance, reactivation after withdrawal of therapy, or superinfection with HDV, HAV, HCV, or even HEV in endemic regions. With advanced liver disease, increased drug levels of efavirenz may occur, which increases the risk for central nervous system toxicity. In addition, certain ARVs such as tipranavir or nevirapine have an increased risk for hepatotoxicity, and should be avoided in persons with advanced liver disease.

TABLE 11.1. Summary of existing recommendations for when to initiate ART in adults and adolescents, including persons with HBV/HIV coinfection (16)

Recommendations
• As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 counts ≤350 cells/mm^3. *(Strong recommendation, moderate-quality evidence)*
• ART should be initiated in all individuals with HIV with a CD4 count ≤500 cells/mm^3 regardless of WHO clinical stage. *(Strong recommendation, moderate-quality evidence)*[a]
• ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 count in the following situations: - Individuals with HIV and active TB disease *(Strong recommendation, low-quality evidence)* - Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease[a] *(Strong recommendation, low-quality evidence)* - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners *(Strong recommendation, high-quality evidence)* - Pregnant and breastfeeding women with HIV[b].
• All children infected with HIV below 5 years of age, regardless of CD4 count or WHO clinical stage: - Infants diagnosed in the first year of life *(Strong recommendation, moderate-quality evidence)* - Children infected with HIV between 1 and <5 years of age *(Conditional recommendation, very low-quality evidence)*; severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 count. *(Strong recommendation, moderate-quality evidence)*

[a] Severe chronic liver disease includes cirrhosis and end-stage liver disease, and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal haemorrhage and hepatic encephalopathy), sepsis or liver insufficiency (jaundice).

[b] All pregnant and breastfeeding women infected with HIV should initiate a triple ARV regimen, which should be maintained at least for the duration of risk of mother-to-child transmission. Women meeting treatment eligibility criteria should continue lifelong ART *(Strong recommendation, moderate-quality evidence).*

For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment *(Conditional recommendation, low-quality evidence).*

In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of risk for mother-to-child transmission has ceased *(Conditional recommendation, low-quality evidence).*

Choice of ART regimen: In 2013, WHO updated its recommendations on the use of ART in adults, adolescents, pregnant women and children (16), including those with HIV/HBV coinfection. These guidelines, which will be updated in 2015, recommend that HIV/HBV-coinfected persons should be simultaneously treated for both HIV and HBV infection, and receive ART that is active against both viruses to reduce the risk of resistance. A tenofovir-based regimen is the recommended therapy, which should include tenofovir/lamivudine, or tenofovir/emtricitabine (provided there is no contraindication to tenofovir), together with a third drug efavirenz, to prevent the selection of HIV-resistant mutants. Tenofovir is available co-formulated with lamivudine or emtricitabine and efavirenz. This treatment strategy has achieved high rates of HBV DNA suppression (90%), HBeAg loss (46%) and HBsAg loss (12%) in HBeAg-positive patients after 5 years of treatment, without evidence of resistance, and reduced progression to cirrhosis (17), with no significant differences in response in those with or without HIV coinfection (18). To date, no viral resistance to tenofovir in vivo has been described, although resistant strains have been identified in vitro. Although the risk of developing cirrhosis is negligible in HBV/HIV-coinfected persons on long-term tenofovir combined with emtricitabine or lamivudine therapy, the risk of HCC persists, but is low.

Renal function (and possibly bone function) should be monitored at least annually because of the impact on renal and bone metabolism *(see Chapter 9.2: Monitoring for tenofovir and entecavir toxicity, and Table 9.1: Recommended doses in adults with renal impairment)*. If tenofovir-associated renal toxicity occurs, the dose of tenofovir should be adjusted according to the renal clearance. If tenofovir is absolutely contraindicated, there are little data on the best alternative treatment. Entecavir may be an option, as part of an active ART regimen (and not alone because of its weak antiviral activity against HIV), in persons in whom tenofovir is contraindicated, and who have never been exposed to lamivudine (or do not have lamivudine-associated HBV polymerase resistance).

Treatment of HIV without the use of tenofovir in the regimen may lead to flares of hepatitis B due to ART-associated immune reconstitution. Similarly, treatment discontinuation, especially of lamivudine, has been associated with HBV reactivation, ALT flares and, in rare cases, hepatic decompensation. If ARVs need to be changed because of HIV drug resistance or drug toxicity, then tenofovir and lamivudine or tenofovir/emtricitabine should be continued together with the new ARV drugs (16).

Children: Additional management challenges in HBV/HIV-coinfected children include choice of ART regimen in children initiating ART for their HIV infection, but who do not require treatment for their HBV infection. In children under the age of 12 years, tenofovir cannot be used, and it would be logistically challenging to

use a lamivudine-free regimen. In these children, use of a standard ART regimen (that may include the use of lamivudine) may be advisable with subsequent modification to a tenofovir-based regimen when the child is 12 years of age.

TABLE 11.2. Summary of recommended first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children, including persons with HBV/HIV coinfection (16)

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults and adolescents (including pregnant and breastfeeding women and adults with TB coinfection and HBV coinfection)	TDF + 3TC (or FTC) + EFV as a fixed-dose combination (*Strong recommendation, moderate-quality evidence*)	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP (*Strong recommendation, moderate-quality evidence*)
Children ≥3 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC (or AZT) + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

3TC lamivudine; ABC abacavir; ATV atazanavir; AZT zidovudine; d4T stavudine; DRV darunavir; EFV efavirenz; FTC emtricitabine; LPV lopinavir; NVP nevirapine; r ritonavir; TDF tenofovir

[a] ABC or boosted PIs (ATV/r, DRV/r , LPV/r) can be used in special circumstances.

[b] Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities *(Strong recommendation, moderate-quality evidence)*. For adults, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.

11.1.2. HBV/HDV coinfection *(see also Chapter 3.9: Background: Special populations)*

Two major types of HDV infection occur: *acute coinfection* (persons are infected simultaneously with both HBV and HDV, which can lead to a mild-to-severe or even fulminant hepatitis (19,20), but recovery is usually complete and development of chronic delta hepatitis is rare (21). In contrast, *superinfection* with HDV (in a person already chronically infected with HBV), accelerates the course of chronic disease in all age groups, which develops in 70–90% of persons with HDV superinfection (22–25). Active coinfection or chronic infection with HDV is diagnosed by high titres of IgG and IgM anti-HDV, and confirmed by detection of HDV RNA in serum (26,27). However, HDV diagnostics are not widely available, and there has also been limited standardization of HDV RNA assays (26,28), which may also be used for monitoring response to antiviral therapy. Prevention and control of HDV requires prevention of

HBV infection through hepatitis B immunization (29), although there is no protection against HDV for those already HBV infected.

There are limited data to inform definitive guidance on the management of persons with HDV infection. Persistent HDV replication is the most important predictor of mortality and the need for antiviral therapy. PEG-IFN is the only drug effective against HDV (29–33); antiviral NAs have no or limited effect on HDV replication (33,34). The optimal duration of therapy is not well defined, nor how long patients need to be HDV RNA negative after the end of therapy to achieve a sustained virological response, but more than 1 year of therapy may be necessary. The overall rate of sustained virological response remains low, including in children (31,32), and most patients relapse after discontinuation of therapy (33). New therapeutic agents and strategies are needed, and novel drugs, such as prenylation or HBV entry inhibitors, have shown early promise.

11.1.3. HBV/HCV coinfection *(see also Chapter 3.9: Background: Special populations)*

In HBV-infected persons, HCV coinfection accelerates progression of liver disease and increases the risk of HCC (35–37). HBV DNA levels are usually low or undetectable and as HCV is responsible for the activity of chronic hepatitis in most persons, they should generally receive initial treatment for HCV infection. If there is no access to HCV and HBV viral load measurements, it may be difficult to determine which virus is responsible for abnormal aminotransferases, and treatment of both infections may be required. The optimal regimens are uncertain, and more treatment studies are required in coinfected persons. PEG-IFN and ribavirin can be effective (38–41), but the treatment of hepatitis B and C is now largely based on treatment with direct-acting antivirals, and follow current WHO guidelines (42). HBV DNA monitoring is necessary as there is a potential risk of HBV reactivation during treatment or after clearance of HCV, which can be treated with NAs (37).

11.1.4. HBV/Tuberculosis *(see also Chapter 3.9: Background: Special populations)*

Groups at increased risk of infection with HBV 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 extra clinical vigilance (43). PWID and prisoners have a high risk of acquiring HBV and HCV, and are also at increased risk of coinfection with TB (43,44). Screening of HIV-positive patients is recommended using a four-symptom screening algorithm to rule out active TB. In the absence of a cough, weight loss, fever and night sweats, active TB can be confidently ruled out. Otherwise, further investigations for TB and other disease would be recommended (45–47). Drug-induced liver injury with elevation of aminotransferases is three- to sixfold higher in persons coinfected with HBV, HCV or HIV who are receiving antituberculosis drugs, due to hepatotoxicity with isoniazid, rifampicin and pyrazinamide (48).

11.2. Decompensated cirrhosis and advanced liver disease

Consolidated hepatitis guidelines are planned for 2016, which will include recommendations on more detailed management of complications in advanced liver disease, including ascites, bacterial peritonitis, upper gastrointestinal haemorrhage from oesophageal varices, and encephalopathy (*see Chapters 6 and 7: First-line antiviral therapies for CHB and Second-line antiviral regimens for management of treatment failure)*. Older persons in particular may present with cirrhosis and complications of chronic liver disease and HCC. Liver failure and HCC are rarely seen less than 20 years after infection. Compensated cirrhosis may progress over time to decompensated cirrhosis with associated weight loss, weakness, wasting, oedema, dark urine, and 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:ALT; a low platelet count (suggesting the development of portal hypertension); an increase in ALP and gGT, a fall 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. The exacerbations associated with either a decline in viral replication or reactivation of viral replication and recurrence of disease can be severe and life threatening. Indeed, the pattern of recurrent reactivation with multiple remissions and recurrences is a particularly severe form of CHB, frequently leading to cirrhosis and ultimately hepatic failure.

Regular clinical examination and monitoring (every 6–12 months) of serum bilirubin, albumin, international normalized ratio (INR) and liver ultrasound before and during treatment is an essential part of the ongoing care of persons with HBV-related cirrhosis in order to detect further disease progression, including decompensation and evidence of HCC. All persons with decompensated cirrhosis should be considered for urgent antiviral therapy with tenofovir or entecavir, even if the HBV DNA level is low or undetectable, in order to improve clinical outcomes, and to prevent flares/reactivation *(see Chapters 6 and 7: First-line antiviral therapies for CHB* and *Second-line antiviral regimens for management of treatment failure)*. Suppression of HBV DNA will also decrease the risk of recurrence of hepatitis B post-liver transplantation. In unstable persons with deteriorating renal function, entecavir can be used at a recommended dosage of 1 mg daily and persons should be monitored for lactic acidosis. NA therapy should usually be continued indefinitely in persons with cirrhosis. The risk of developing HCC is high in these persons, even with effective NA therapy and therefore long-term HCC surveillance is mandatory. IFN therapy is generally contraindicated because of significant adverse effects due to serious bacterial infections and possible exacerbation of

liver disease even with low doses. Management of persons with complications of cirrhosis and advanced liver disease, such as assessment and management of oesophageal varices, and prophylaxis to prevent variceal bleeding and spontaneous bacterial peritonitis will also require care by appropriately trained personnel.

11.3. Extrahepatic manifestations

HBsAg-positive persons with HBV-related extrahepatic manifestations (skin manifestations, polyarteritis nodosa and glomerulonephritis) and active HBV replication may respond to NA antiviral therapy. Comparative trials of antiviral therapy are lacking, and the efficacy reported in case reports is variable. Lamivudine has been the most widely used, and entecavir and tenofovir would be expected to have enhanced efficacy in this group. PEG-IFN may worsen some immune-mediated extrahepatic manifestations and it is advisable to avoid its use.

11.4. Acute hepatitis B

Antiviral therapy is not necessary for uncomplicated symptomatic acute hepatitis B, as >95% of immunocompetent adults will spontaneously clear HBV infection (49). Persons with fulminant or severe acute hepatitis may benefit from NA therapy with entecavir or tenofovir, to improve survival and reduce the risk of recurrent hepatitis B (50–52). The duration of treatment is not established, but continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is generally advised.

11.5. Children and adolescents *(see also Chapter 3.9: Background: Special populations)*

CHB is usually benign and asymptomatic in children, as they are generally in the immune-tolerant phase. In addition, there are low curative response rates with both NAs (necessitating long-term therapy) and IFN treatment, and concerns over long-term safety and risks of drug resistance. For these reasons, a conservative approach to treatment is generally indicated, unless there are other criteria for treatment, such as cirrhosis or evidence of severe ongoing necroinflammatory disease on liver biopsy. Although the majority of children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease guided by liver histology and a family history of HCC remains important. The use of NITs and identification of appropriate cut-offs have not yet been defined in children. Only conventional IFN, lamivudine and adefovir have been evaluated for safety and efficacy, but children generally have a similar response as adults (53–56). IFN cannot be used in infants aged less than 1 year. The FDA has approved tenofovir for use in adolescents and children above the age of 12 years for HBV treatment (and 3 years or older for HIV treatment). In March 2014, the

FDA approved entecavir for children with CHB above 2 years of age. Therefore, treatment options for children below 12 years, and especially below 2 years, remain limited. Studies with NAs are ongoing to better define treatment strategies.

11.6. Pregnant women *(see also Chapter 5: Who to treat and who not to treat among persons with CHB, Chapter 6: First-line antiviral therapies for CHB* and *Chapter 10.2: Prevention of mother-to-child HBV transmission using antiviral therapy)*

Indications for treatment in adults with CHB also apply to pregnant women. Based on safety data from the Antiretroviral Pregnancy Registry in pregnant HIV-positive women who have received tenofovir and/or lamivudine or emtricitabine (16), tenofovir is the preferred antiviral, because it has a better resistance profile and more extensive safety data in pregnant HBV-positive women. The safety of entecavir in pregnancy is not known, and IFN-based therapy is contraindicated.

For prevention of mother-to-child HBV transmission, the most important strategy is to deliver the first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours followed by at least two timely subsequent doses, in accordance with existing recommendation by the WHO Strategic Advisory Group of Experts (SAGE) (57). The Guidelines Development Group did not make a formal recommendation on the use of antiviral therapy to prevent mother-to-child transmission, as key trials are still ongoing, and there is a lack of consensus as to the programmatic implications of a policy of more widespread antiviral use in pregnancy. If a pregnant woman remains untreated or anti-HBV therapy is discontinued during pregnancy or early after delivery for any reason, close monitoring is necessary, as there is a risk of hepatic flares, especially after delivery.

11.7. Persons who inject drugs (PWID) *(See also Chapter 10.5: Prevention of hepatitis transmission in persons who inject drugs)*

Injecting drug use is prevalent in many countries around the world, affecting people in low-, middle- and high-income countries. PWID are at increased risk of acute and chronic HBV infection (in addition to HIV and HCV infection) and liver-related disease, as well as all-cause morbidity and mortality, and therefore require additional care. When caring for PWID, the central tenets of respect and non-discrimination should be followed, and additional adherence and psychological support provided as required.

11.8. Dialysis and renal transplant patients *(see Table 9.1: Recommended dosages in adults with renal impairment)*

HBV is prevalent in persons with end-stage renal disease, including renal transplant recipients, who should be screened for HBV infection, and HBV-seronegative

persons vaccinated. All NAs (lamivudine, tenofovir and entecavir) require dose adjustment and should be used with caution in persons with renal impairment or in 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 in renal transplant recipients because of the risk of graft rejection. All HBsAg-positive persons undergoing renal transplantation should receive prophylactic NA therapy to prevent HBV reactivation.

11.9. Health-care workers *(See also Chapter 10.4: Prevention of hepatitis B and C transmission in health-care settings)*

Health-care workers need special consideration for HBV screening and HBV vaccination; however, this is not widely implemented in LMICs. Those who are HBsAg positive and undertake exposure-prone procedures, such as surgeons, gynaecologists, nurses, phlebotomists, personal care attendants and dentists, should be considered for antiviral therapy to reduce direct transmission to persons. In accordance with 2013 ARV recommendations (16), they should receive a potent antiviral agent with a high barrier to resistance (i.e. entecavir or tenofovir) to reduce 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 needlestick or other occupational exposures.

11.10. Indigenous peoples

Indigenous peoples are a special population group consisting of persons who are native to a region, but who retain social, cultural, economic and political characteristics that are distinct from those of the dominant societies in which they live. Spread across the world from the Arctic to the South Pacific, they are the descendants – according to a common definition – of those who inhabited a country or a geographical region at the time when people of different cultures or ethnic origins arrived. They are also a group with a high prevalence of HBV infection in many parts of the world. This group includes peoples of the Arctic and the Americas, and Maori and aboriginal peoples of New Zealand and Australia (58–61). These populations also often are or feel excluded from health-care services and, as they may live in remote communities far from hospitals and well-equipped clinics, have poor access to care medical care. The needs of these communities must be considered as countries plan for hepatitis treatment programmes, and implement the management recommendations.

12. IMPLEMENTATION CONSIDERATIONS FOR NATIONAL PROGRAMMES

12.1. Introduction

Successful implementation of the recommendations in these guidelines and establishment of affordable screening, treatment and care programmes in the public and private sectors for persons with chronic hepatitis B (and C) infections in LMICs will depend on a well-planned process of adaptation and integration into relevant regional and national strategies and guidelines. There are several key considerations for national stakeholders and decision-makers, and this chapter provides an assessment framework for use by planners at the national level in order to identify which inputs and systems are currently available, and which areas require additional investment. The six building blocks for health systems identified by WHO provides a useful foundation (1). Many of the same challenges have been addressed by TB and ART programmes, and similar approaches are likely to be relevant for hepatitis programmes.

12.2. Key principles

Key principles to enhance the effectiveness and sustainability of hepatitis programmes include the following:

1. Considering national responses for hepatitis care and treatment within the broader health and development contexts, which include strengthening linkages with other health and non-health programmes (2);

2. Ensuring that human rights and ethical principles of fairness, equity and urgency guide the development of national treatment policies so that barriers in access to testing, prevention and treatment services, particularly among certain populations, are addressed;

3. Defining programme needs based on a broad, inclusive and transparent consultative process;

4. Securing the necessary financial resources and political support required to implement these recommendations.

12.3. Key considerations to support country planning and decision-making

Decisions on how to adapt and implement these guidelines at country level should be based on a careful assessment of the country epidemiological situation, estimated costs, human resource and infrastructure requirements, including how these should be addressed. In addition, consideration should be given to affordable access at the patient level, supported through public funding from the national government, insurance schemes, or other sources, and existing services or infrastructure for HBV care and treatment. Decisions regarding national adaptation of these guidelines should also be made through a transparent, open and informed process, with broad stakeholder engagement to ensure that national programmes are effective, acceptable and equitable, and address community needs. It is recognized that at present, many low-income countries, especially in sub-Saharan Africa, lack access to basic infrastructure, diagnostics and drugs to implement care and treatment for both chronic hepatitis B and C. Checklist 12.1 provides a list of key issues across the health system to help plan and estimate the resources needed for implementation of HBV management recommendations.

The key programmatic components of service delivery for CHB care and treatment are adequate clinic infrastructure, human resources (doctors, nurses, trained persons to provide testing and counselling), a referral system, laboratory and diagnostic services, reliable drug supply, monitoring and evaluation, and civil society participation.

Infrastructure, service delivery and human resources

The setting, infrastructure and operational implications of providing long-term antiviral therapy to all eligible adults, adolescents and children with CHB need to be first considered. Countries need to ensure that systems are in place so that those with the most advanced liver disease are given priority. For this, a phased approach with an early learning phase before full scale up of testing and treatment may be appropriate. Building on and integrating with other health programmes or existing testing and treatment services, such as those already established for HIV and TB, or for difficult-to-access populations such as PWID, is strongly encouraged to both improve treatment access and optimize resources.

A high-income setting model of specialist hepatitis care with a high physician-to-patient ratio and availability of laboratory monitoring of HBV DNA is not currently feasible in LMICs. Service delivery plans need to be adapted accordingly, including the adoption of a simplified public health approach to care that enabled successful expansion of care and treatment in persons infected with TB and HIV in many LMICs.

Many health-care workers have had limited training and experience in assessing persons with chronic liver disease or in providing antiviral therapy for CHB. Nationally standardized training, mentoring and supervision for all health-care workers involved in HBV care will be needed to allow sites to successfully take on the responsibility of providing lifelong antiviral therapy for CHB. Strategies are also needed to monitor and support adherence and retention, and re-engagement in care for those lost to follow up to optimize long-term treatment outcomes.

Laboratory and diagnostic services

These guideline recommendations will require increased access to laboratory and diagnostic services. The following laboratory infrastructure and diagnostic capacity will be required: (i) training of staff in laboratory assays and good laboratory practices in handling clinical specimens and biohazardous waste; (ii) institution of national policies for the use of licensed in-vitro diagnostic devices (IVD) for all laboratory tests; (iii) participation in quality assurance programmes and inter-laboratory comparisons to ensure that testing services are accurate and reliable, with national accreditation, even if in-house assays are in use because of resource constraints.

Available assays: In addition to HBsAg testing, laboratories should have the capacity to test for HBeAg and anti-HBe. HBV DNA quantification is important for decisions on initiating antiviral therapy and monitoring individuals on antiviral therapy. However, HBV DNA viral load assays (and also antiviral drug resistance testing) may not be widely available in LMICs. Access could be facilitated by utilizing the same platforms in current wide use for HIV viral load monitoring and through access to point-of-care assays for HBV DNA. In those settings where HBV DNA viral load measurements are possible, reporting should be standardized to IU/mL (I IU/mL ≈ 5.3 copies/mL).

Staging of liver disease: Capacity to accurately estimate AST and ALT levels and platelet counts is essential to calculate an APRI score, which is the recommended NIT in LMICs for identifying individuals at greatest risk of progression of chronic liver disease who will benefit most from antiviral therapy. These are easy to perform and their interpretation is simple. AST and ALT estimations will facilitate the estimation of FIB-4, an additional NIT. In settings where cost and resources are not constraints, the recommended NIT is transient elastography (FibroScan), but this requires regular service/recalibration of the equipment and trained operators.

In order to monitor potential renal toxicities following the use of tenofovir or entecavir, laboratories need to have the capacity to estimate serum creatinine levels and calculate GFR. Urine dipsticks for testing for proteinuria and glycosuria can be used as point-of-care tests, and serum phosphate levels and bone mineral density scans are additional monitoring tools where cost is not a constraint. In order to facilitate surveillance for early detection of HCC lesions in CHB, alpha-fetoprotein measurements in combination with ultrasound imaging, must be available.

Drug supply and pharmacy issues

Robust procurement and supply management systems are needed to ensure the continued availability of the required diagnostics, medicines (tenofovir or entecavir) and other commodities across the various levels of the health system. Pooled or joint procurement can be used to secure lower costs through economies of scale, and careful demand forecasting is key to minimizing waste. WHO and collaborating organizations have developed a variety of tools to assist with ARV drug quantification and supply management, which can be adapted for use for antiviral drugs for CHB. Integrated supply systems should be promoted when planning for decentralization, building on what exists and strengthening capacity where required. Appropriate pharmacy and drug storage facilities should also be considered during planning.

Costing and planning

A key barrier to HBV treatment in resource-limited settings is the cost of medicines (including taxes, import charges), as well as costs of diagnostic and monitoring facilities, and staff. Although generic tenofovir in combination with other ARVs (for HIV) is now widely available and affordable as first-line therapy in persons who are HBV/HIV coinfected through national ART programmes, there is currently no international public sector procurement programme for those with HBV infection alone. Several generic products based on tenofovir and lamivudine have been approved through the WHO quality assurance prequalification programme. The cost of generic tenofovir alone may range widely from around US$ 50 per year of treatment to US$ 350 (and as high as US$ 500 in some parts of Asia), and for generic lamivudine US$ 25 per year. Entecavir is off-patent, but availability and costs vary widely (these are generally higher than for tenofovir), ranging from US$ 30 to US$ 70 per month in India to up to US$ 450 per month in South Africa. However, at a low daily dose at 0.5 mg with inexpensive raw material, there is the potential for much lower manufacturing and therefore treatment costs. The higher costs of tenofovir and entecavir in many settings is the reason that other drugs such as lamivudine continue to be widely used, despite the additional costs incurred due to the development of drug resistance. Tenofovir has the potential to be more widely available and affordable in LMICs through access to reduced prices via a range of mechanisms, including license agreements negotiated with the Medicines Patent Pool for use in HIV (but also available for HBV).

HBV DNA testing also remains costly (US$ 100–400 per test), and therefore inaccessible for resource-limited settings. There is a critical need for these diagnostics and drugs to be available at more affordable prices in LMICs through national government price negotiation and pooled procurement.

BOX 12.1 Implementation checklist of key health system issues

1. Communication, leadership and advocacy

- Who will be responsible for developing or updating national guidelines or protocols for patient management and monitoring, and health-care worker training materials?
- How will recommendations be communicated to (1) health-care facilities, including public, not-for-profit and private institutions; (2) health-care workers; and (3) other relevant stakeholders, such as people living with CHB?
- Who will take overall responsibility for advocacy with stakeholders such as political leaders, health personnel and the mass media?

2. Staffing and human resources

- How many additional health-care workers are needed to implement the recommendations? Which cadres of health-care workers (physicians, health officers, nurses, midwifes, community health workers and laboratory assistants) are needed and how can they be recruited?
- How can task-shifting/sharing be employed to optimize available human resources and expand service delivery?
- What training, capacity-building and skills-building are needed and for whom? How will it be delivered and paid for?
- What strategies will be put in place to monitor and support lifelong adherence to therapy and retention in care, and re-engage those lost to follow up?

3. Drugs and supplies

- What systems are required for forecasting treatment needs and procuring recommended drugs (tenofovir and/or entecavir) and other commodities at the best possible prices?
- Has a transition plan been developed to phase out suboptimal medicines (such as lamivudine, telbivudine or adefovir) and introduce tenofovir and entecavir?
- Do supply management systems need to be strengthened to manage the increased demand for diagnostics and medicines?
- Is a regulatory process in place to approve and register these medicines and diagnostics in a timely manner? Who is responsible for managing it?
- Are laboratory quality control and external quality assurance systems in place and fully functional?
- Do national laws allow for the purchase and importation of all necessary commodities? Are there patent issues?

4. System organization

- Are linkages and referrals systems between testing and treatment services adequate?
- Do services need to be integrated and/or decentralized to support implementation of the recommendations?
- Have treatment access plans been developed in consultation with managers of other relevant programmes (ARV, TB, maternal and child health, and drug dependence services)?
- What strategies will be put in place at the policy and service delivery levels to ensure that possible disparities in access to care and treatment will be addressed?
- What systems will be in place to ensure that the sickest people are adequately given priority?
- What interventions will be implemented to promote and reinforce adherence and retention in care?

BOX 12.1 Implementation checklist of key health system issues (continued)

5. Infrastructure

- What additional infrastructure (such as clinic space, laboratories, pharmacies, administration areas and equipment) is needed to support implementation? Is it available from existing ARV programmes or other health programmes, or does it require new investment?
- What additional transport infrastructure (such as vehicles) is needed?
- What additional communication infrastructure is needed, including that between health facilities, health-care workers, laboratories and patients?
- What training programmes and toolkits are needed to support HBV management programmes?

6. Costs

- What is the estimated total annual investment of implementing new recommendations?
- What are the unit costs for
  - antiviral drugs
  - neonatal and infant HBV vaccination
  - hepatitis testing, staging and counselling
  - general hepatitis care, including management of advanced liver disease
  - clinical and laboratory monitoring
  - training, mentoring, quality assurance and monitoring
  - community-level services?

7. Funding

- Where will the funds come from, such as government budget, social security or health insurance, out-of-pocket expenditure, or private foundations?
- What will be done to mobilize additional resources to meet estimated investment needs?
- What potential cost savings can be achieved through economies of scale or synergy with other interventions and programmes?

8. Monitoring and evaluation

- What indicators are needed at the facility and programme levels to adequately monitor coverage and assess the impact of antiviral therapy and other interventions? What are the human resources, equipment and infrastructure requirements?
- Are monitoring and evaluation systems interoperable (between the local and national levels) to avoid duplication and ensure consistency?
- What quality control, quality assurance and quality improvement systems are in place to optimize service delivery?

9. Implementation plan

- Does the plan have time-bound targets or objectives?
- Does the plan contain specific outcomes?
- Does the plan clearly identify the roles and responsibilities of the various stakeholders (such as government at the central, provincial and local levels, nongovernmental organizations, technical partners, communities and persons with CHB) involved in the process of treatment expansion?

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CHAPTER 5

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CHAPTER 12

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978 92 4 154905 9