World Health Organization

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

POLICY BRIEF

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Policy brief: Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection
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BACKGROUND

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. 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 from HCC and cirrhosis 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.

ABOUT THE GUIDELINES

These are the first World Health Organization (WHO) guidelines for the prevention, care and treatment of persons living with CHB infection.

The recommendations are structured along the continuum of care for persons with CHB 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 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; recommend the preferred use of the 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. Management considerations for specific populations are also highlighted, including those coinfected with HIV, HCV and hepatitis D virus (HDV); children and adolescents; and pregnant women.

Existing WHO recommendations for the prevention of HBV transmission are also highlighted, in particular the prevention of perinatal and early childhood HBV infection through infant hepatitis B vaccination.

These recommendations provide opportunities to save lives, improve clinical outcomes of persons living with CHB, reduce HBV incidence and transmission, and disease stigma, but they also pose practical challenges to policy-makers and implementers in LMICs. An additional guidelines chapter 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.

[1] 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.

SUMMARY OF RECOMMENDATIONS FOR PERSONS WITH CHRONIC HEPATITIS B INFECTION

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)*

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.

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.

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*)

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*)