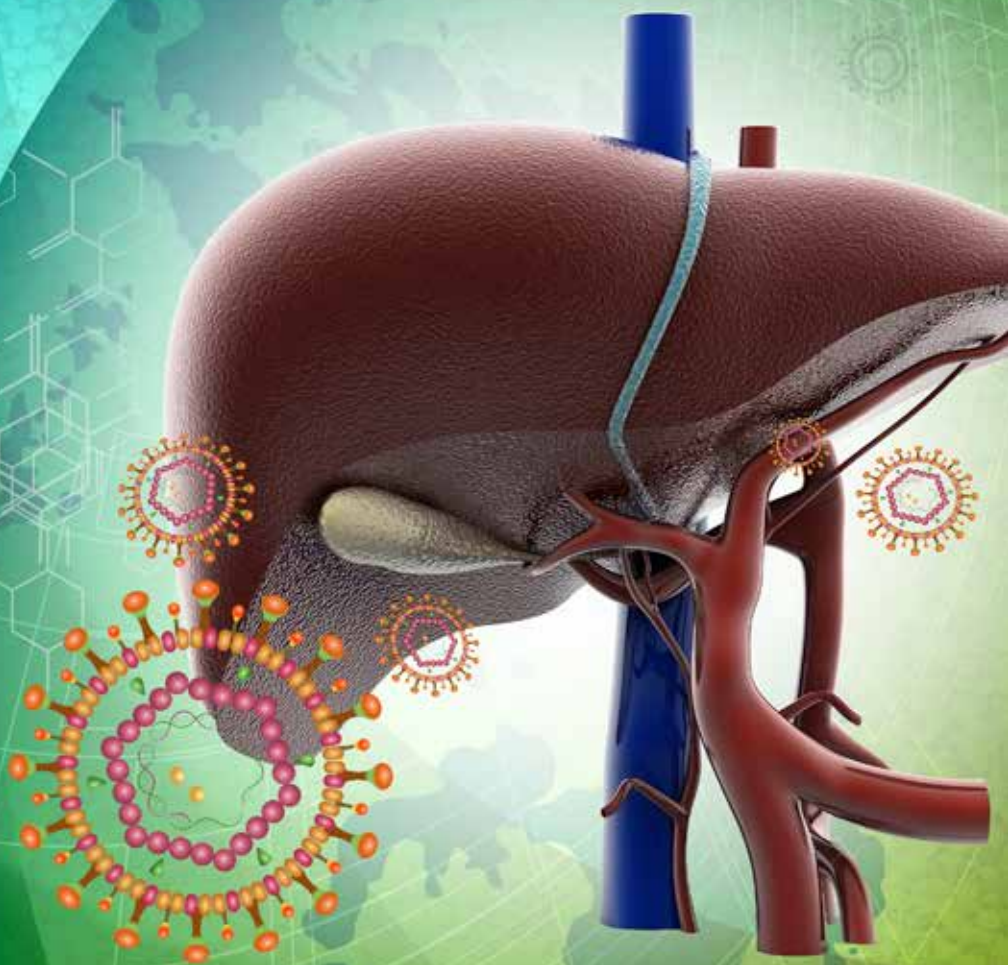


2006

Hepatology Society of the Philippines

2014 HSP Consensus Statements on the Management of Chronic Hepatitis B



FOREWORD

Chronic hepatitis B virus (CHB) infection is a serious problem that affects over 300 million people worldwide and is highly prevalent in the Asia-Pacific region. In the Philippines, an estimated 7.3 million Filipinos or 16.7% of adults are chronically infected with HBV, more than twice the average prevalence in the Western Pacific region.

In view of the above, the Hepatology Society of the Philippines (HSP) embarked on the development of consensus statements on the management of hepatitis B with the primary objectives of standardizing approach to management, empowering other physicians involved in the management of hepatitis B and to advance treatment subsidy by the Philippine Health Insurance Corporation (PhilHealth).

The local guidelines include screening and vaccination, general management, indications for assessment of fibrosis in those who did not meet treatment criteria, indications for treatment, on-treatment and post-treatment monitoring and, duration of antiviral treatment. Recommendations on the management of antiviral drug resistance, management of special populations including patients with concurrent HIV or hepatitis C infection, women of child-bearing age (pregnancy and breastfeeding), patients with decompensated liver disease, patients receiving immunosuppressive medications or chemotherapy and patients in the setting of hepatocellular carcinoma are also included. However, the guidelines did not include management for patients with liver and other solid organ transplantation, patients on renal replacement therapy, and children.

The consensus statements will be amended accordingly as new therapies become available.

METHODOLOGY

The applicability and feasibility of current international guidelines formulated by the Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) on the management of hepatitis B to the existing healthcare situation in the Philippines was determined by a thorough review of the consensus statements conducted by a core working group composed of nine members (Jamias J, Bocobo J, Labio ME, Ong J, Wong S, Yu I, Co A, Macatula T, Lontok M.) The members were chosen for their expertise, academic affiliations, active clinical practice and research in hepatitis B. Literature searches were performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. Manual searches in bibliographies of key articles including those published in the *Philippine Journal of Internal Medicine (PJIM)* and *Philippine Journal of Gastroenterology* were likewise done. Local data gathering was also performed through a review of scientific papers submitted by fellows-in-training from different accredited training institutions of the Philippine Society of Gastroenterology (PSG).

A Knowledge, Attitudes and Practices (KAP) survey was also conducted among family physicians, general internists, infectious disease specialists, gastroenterologists and hepatologists during the Annual convention of the Hepatology Society of the Philippines (HSP) last January 2013. A pre-consensus development conference was held where the results of the surveys and reviews were presented and discussed. Important issues were identified by the core working group for further deliberations. Following the modified Delphi process, 17 recommendations were proposed by the core working group for votation. The consensus development conference

proper was held in July 2013 in which the Chairs and Training Officers or their representatives from all the training institutions in Gastroenterology, representatives from the Philippine College of Physicians (PCP), the Philippine Society for Microbiology and Infectious Diseases (PSMID) and the Philippine Academy of Family Physicians (PAFP) participated. During the consensus development proper, voting for each statement was done as follows: (1) Accept completely; (2) Accept with some reservation; (3) Accept with major reservation; (4) Reject with reservation; (5) Reject completely. Liberal discussion and debate was encouraged during the conference. Votation on every statement was conducted anonymously using wireless keypads. If the pre-determined agreement of 85% was not achieved, the statement is rejected and revised accordingly and subjected to up to three rounds of votation until the pre-determined agreement has been achieved. The level of evidence and the strength for each recommendation were graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Grading quality of evidence and strength of recommendation

A. Quality of Evidence and Definition

HIGH QUALITY	Further research is very unlikely to change our confidence in the estimate of effect
MODERATE QUALITY	Further research is likely to have important impact on our confidence in the estimate of effect and may change the estimate
LOW QUALITY	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
VERY LOW QUALITY	Any estimate of effect is very uncertain

B. Grade of Recommendation

STRONG	<p>When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not</p> <p>Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost</p>
CONDITIONAL (“WEAK”, “DISCRETIONARY”)	<p>When the trade-offs are less certain either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced</p> <p>Recommendation is made with less certainty; higher cost or resource consumption</p>

During the entire process of the consensus development as well as in the writing of the manuscript, no interference or representations by any third party were allowed by the consensus development group.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a serious problem that affects over 300 million people worldwide and is highly prevalent in the Asia-Pacific region.¹⁻⁵ In the Philippines, an estimated 7.3 million Filipinos or 16.7% of adults are chronically infected with HBV; more than twice the average prevalence in the Western Pacific region.^{3,6,7}

The course of chronic infection with HBV (ie, immune tolerant, immune clearance, inactive and reactivation phases) varies and is unpredictable. Chronic hepatitis B (CHB) ranges from an inactive carrier state to chronic active hepatitis that may progress to cirrhosis and hepatocellular carcinoma (HCC) in 30% and 53% of cases, respectively. CHB accounts for 5% to 10% of liver transplantations and 0.5 to 1 million deaths each year.^{1,3-5,8} The interplay of host and viral factors, superimposed co-infections (eg, hepatitis C virus [HCV], hepatitis D virus [HDV] or human immunodeficiency virus [HIV]) and the presence of risk factors (eg, alcohol abuse and obesity) alter the natural course of HBV infection and the efficacy of and response to treatment.¹

HBV is transmitted through perinatal, percutaneous, sexual or close person-to-person contact.² The risk of progression to chronic infection is around 90% in newborns of HBeAg-positive mothers, 25% to 30% in infants and children less than 5 years of age, and less than 5% in adults. Moreover, specific groups are especially at risk for HBV infection (see Table 1).²

Table 1. Groups at high risk for hepatitis B Infection who should be screened

- Household and sexual contacts of HBsAg-positive persons
- Persons who have ever injected drugs
- Persons with multiple sexual partners or have history of sexually transmitted disease
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV
- Patients undergoing renal dialysis
- All pregnant women
- Persons needing immunosuppressive therapy

Table 2. Definition of terms^{2,8}

HBV INFECTION

Chronic hepatitis B	Chronic inflammatory disease of the liver secondary to persistent infection with HBV Diagnostic criteria: HBsAg-positive >6 months; serum HBV DNA >20,000 IU/mL (105 copies/mL) in HBeAg-positive patients, or >2,000 IU/mL (>104 copies/mL) in HBeAg-negative patients; persistent or intermittent ALT/AST elevation; and liver biopsy showing chronic hepatitis with moderate to severe necroinflammation.
Immune tolerant HBV infection	HBV infection characterized by positive HBeAg, markedly elevated HBV DNA (2,000,000 IU/mL) with normal serum ALT and minimal to no evidence of hepatitis.

Inactive HBsAg carrier state	Persistent HBV infection of the liver with no significant, ongoing necroinflammation Diagnostic criteria: HBsAg-positive >6 months; HBeAg-negative; anti-HBe positive; serum HBV DNA <2,000 IU/mL; persistently normal ALT/AST levels; liver biopsy showing no significant hepatitis
Resolved hepatitis B	Previous HBV infection with no further virologic, biochemical or histological evidence of active virus infection or disease Diagnostic criteria: History of acute or chronic HBV infection or presence of anti-HBc with or without anti-HBs; HBsAg negative; undetectable serum HBV DNA or very low levels with PCR assays; normal ALT levels
Reactivation of hepatitis B	Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B

SEROLOGICAL MARKERS

Undetectable serum HBV DNA	Serum HBV DNA below detection limit of a PCR-based assay
HBeAg clearance	Loss of HBeAg in a person who was previously HBeAg positive
HBeAg seroconversion	Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative
HBeAg seroreversion	Reappearance of HBeAg in a person who was previously HBeAg negative and anti-HBe positive

ALANINE AMINOTRANSFERASE (ALT) AND LIVER FUNCTION

Low normal ALT	Serum ALT $\leq 0.5x$ ULN (upper limit of laboratory reference)
High normal ALT	Serum ALT between 0.5 and 1x ULN
Minimally raised ALT	Serum ALT between ULN and 2x ULN
Hepatitis flare	Abrupt increase in serum ALT to $\geq 5x$ ULN
Hepatic decompensation	Significant liver function abnormality as indicated by raised serum bilirubin and prolonged prothrombin time or occurrence of complications such as ascites

TREATMENT RESPONSE

Biochemical response	Normalization of serum ALT levels
Virologic response	Decrease in serum HBV DNA to undetectable levels by PCR assays AND HBeAg seroconversion in initially HBeAg-positive patients
Maintained virologic response	Virologic response is achieved and persistent while on treatment
Suboptimal virologic response	Serum HBV DNA still detectable at 24 weeks of oral antiviral therapy in a treatment-compliant patient
Sustained response	No documented clinical relapse during follow-up after stopping therapy
Complete virologic response	Maintained or sustained virologic response with HBsAg seroclearance
Primary treatment failure or non-response	Reduction of serum HBV DNA $< 1 \log$ IU/mL at 12 weeks of oral antiviral therapy in a patient with documented compliance to antiviral therapy

continue next page

RESISTANCE AND RELAPSE

Virologic breakthrough	Increase in serum HBV DNA >1 log IU/mL from nadir of initial response during treatment
Virologic relapse	Serum HBV DNA >2,000 IU/mL after stopping treatment in patients with maintained virologic response
Clinical relapse	HBV DNA >2,000 IU/mL and ALT >2 x ULN after stopping treatment in patients with maintained virologic response

References: 1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167-85. 2. Lok ASF, McMahon BJ. AASLD practice guideline update: Chronic hepatitis B: Update 2009. *Hepatology* 2009;50:1-36. 3. Wong SN, Ong JP, Labio ME, et al. Hepatitis B infection among adults in the Philippines: A national seroprevalence study. *World J Hepatol* 2013;5:214-9. 4. Hwang EW, Cheung R. Global epidemiology of hepatitis B virus (HBV) infection. *N A J Med Sci* 2011;4:7-13. 5. National Institutes of Health. NIH consensus development conference statement on management of hepatitis B. NIH Consensus and State-of-the-Science Statements. 2008;25. 6. Clements CH, Baoping Y, Crouch A, et al. Progress in the control of hepatitis B infection in the Western Pacific Region. *Vaccine* 2006;24:1975-82. 7. Goldstein ST, Zhou F, Hadler SC, et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005;34:1329-39. 8. Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61.

HEPATITIS B SCREENING AND VACCINATION

1-1 All Filipinos should be offered screening for hepatitis B. Screening tests should include HBsAg and anti-HBs. Vaccination should be given to those who are negative for both HBsAg and anti-HBs. (high quality, strong)

The prevalence of HBV infection in the Philippines is high.¹ Thus, all Filipinos should be offered HBV screening through serological testing for HBsAg and anti-HBs. Subsequently, those who are seronegative for HBV should be offered HBV vaccination.

Anti-HBc determination may also be done. Anyone with an isolated seropositivity to anti-HBc should be tested for HBV markers to reduce the likelihood of laboratory error. If the patient is persistently seropositive to anti-HBc, then the challenge is to distinguish those with a false positive test from those with previous immunity who have lost HBsAg or who have low-level occult HBV infection. For these cases, a single dose of hepatitis B vaccine should be administered and follow-up quantitative anti-HBs serology determined after 1 month. A high titer of anti-HBs (≥ 10 IU/mL) at this time indicates immunity and no need for further vaccination. However, if the titer is low (< 10 IU/mL), a full three-dose course of vaccination should be given. If post-vaccination titers are still low or undetectable, occult HBV infection may be present and the patient is not expected to respond to vaccination. Hence, serum HBV DNA testing at this point is appropriate. It is also important to note that during the acute HBV infection (during the core window), only anti-HBc is present, although such presentation is believed to account for only a small number of cases.²⁻⁵

References: 1. Wong SN, Ong JP, Labio ME, et al. Hepatitis B infection among adults in the Philippines: A national seroprevalence study. *World J Hepatol* 2013;5:214-9. 2. McMahon BJ, Parkinson AJ, Helminiak C, et al. Response to hepatitis B vaccine of persons positive for antibody to hepatitis B core antigen. *Gastroenterology* 1992;103:590-4. 3. Al-Mekhaizeem KA, Miriello M, Sherker AH. The frequency and significance of isolated hepatitis B core antibody and the suggested management of patients. *CMAJ* 2001;165:1063-4. 4. Almedia Neto C, Strauss E, Sabino EC, et al. Significance of isolated hepatitis B core antibody in blood from Sao Paulo. *Rev Inst Med Trop Sao Paulo* 2001;43:203-8. 5. Reiss G, Keeffe EB. Review article: hepatitis vaccination in patients with chronic liver disease. *Aliment Pharmacol Ther* 2004;19:715-27.

EVALUATION OF PATIENTS WITH CHRONIC HEPATITIS B

2-1 A comprehensive evaluation, patient education and counseling should be done in all patients with chronic hepatitis B infection [high quality, strong].

2-2 Initial evaluation should include the following: HBeAg, anti-HBe, HBV DNA, ALT and liver ultrasound [high quality, strong]. HBsAg quantification is recommended [moderate quality, strong].

2-3 For those with risk factors, testing for HCV (anti-HCV), HIV (EIA) and screening and surveillance for HCC (AFP and ultrasound every 6 months) should be done [high quality, strong].

2-4 Immunity to hepatitis A (anti-HAV IgG) should be determined. If negative, vaccination is strongly recommended [high quality, strong].

Counseling of patients with HBV should be provided during initial evaluation and on every consultation. Details on the disease, treatment options and need for long-term follow up and monitoring should be emphasized. Avoidance of high-risk behavior and prevention of HBV transmission should be discussed with patients, their sexual partners and household members. Heavy alcohol intake (>20 g/day in women and >30 g/day in men) also increases the risk of liver disease and patients should be advised to abstain or limit alcohol consumption.^{1,2}

An assessment of patients with CHB should include the evaluation of HBV risk factors and related co-infections, alcohol intake, any family history of HBV infection or HCC, and a complete physical examination.^{1,2} Serological markers for HBV, particularly HBeAg, anti-HBe and HBV DNA, in conjunction with biochemical (by serum alanine aminotransferase [ALT]) and other clinical evidence of liver disease (by liver ultrasound) are necessary for identifying the status of HBV infection and assessing the need for and response to treatment.¹⁻³ Because low HBsAg levels may distinguish true inactive carriers from CHB when HBV DNA and ALT levels are low, HBsAg quantification is also recommended.⁴ HBsAg loss before the onset of cirrhosis has also been associated with improved outcomes with less risk of progression to hepatic decompensation or HCC.³

Laboratory examinations (eg, complete blood counts [CBC] with platelets, hepatic panel, prothrombin time [PT]) and liver ultrasound are used to assess liver status. Liver cirrhosis is suspected in patients who have a reversal in the ALT to aspartate aminotransferase (AST) ratio (<1), a progressive decline in serum albumin concentrations and/or an increase in γ -globulins, and a prolongation in the PT (often with a decline in platelet counts).³ Histopathological confirmation, including the grading and staging of liver disease by a liver biopsy, should also be performed if suspected. Furthermore, HCC screening and surveillance through serum α -feto-protein (AFP) and liver ultrasound every 6 months is indicated for HBV subgroups considered at higher risk for HCC (see Table 3).¹⁻⁶

Table 3. HBV subgroups at risk for HCC who require surveillance

- Asian male hepatitis B carriers over age 40^{5,6}
- Asian female hepatitis B carriers over age 50⁵
- Hepatitis B carrier with a family history of HCC^{5,7}
- Cirrhotic hepatitis B carriers^{5,6}
- HCV co-infection^{5,7}
- Persistent HBV DNA >2,000 IU/mL^{5,8}
- HBV genotype C⁸

Screening for HCV (via anti-HCV) or HIV (via enzyme immunoassay [EIA]) co-infections in at-risk patients should also be performed.^{1-3,5,6,9} HCV co-infection increases the risk for severe hepatitis, cirrhosis and HCC. Similarly, those with HIV co-infection have higher levels of HBV DNA, lower rates of spontaneous HBeAg seroconversion, more severe liver disease and increased rates of liver-related deaths. Patients with CHB should also be screened for hepatitis A virus antibodies (anti-HAV IgG) and vaccination is strongly recommended in hepatitis A virus (HAV) seronegative patients.^{1,3} Although HBV does not increase the risk of HAV infection, patients with chronic liver disease from HBV infection are susceptible to developing fulminant hepatitis A.¹⁰⁻¹⁴

References: 1. Lok ASF, McMahon BJ. AASLD practice guideline update: Chronic hepatitis B: Update 2009. *Hepatology* 2009;50:1-36. 2. Liaw YF, Kao J-H, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61. 3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167-85. 4. Chan H, Thompson A, Martinot-Peignoux M, et al. Hepatitis B surface antigen quantification: why and how to use it in 2011 – a core group report. *J Hepatol* 2011;55:1121-31. 5. Bruix J, Sherman M; American Association for the Study of Liver Diseases. AASLD Practice Guideline. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-2. 6. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010;4:439-74. 7. Belongia EA, Costa J, Gareen IF, et al. NIH Consensus development statement on management of hepatitis B. *NIH Consens State Sci Statements* 2008;25:1-29. 8. Wu CF, Yu MW, Lin CL, et al. Long-term tracking of hepatitis B viral load and the relationship with risk for hepatocellular carcinoma in men. *Carcinogenesis* 2008;29:106-12. 9. Nguyen VT, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Viral Hepat* 2009;16:453-63. 10. Keeffe EB. Hepatitis A and B superimposed on chronic liver disease: vaccine-preventable diseases. *Trans Am Clin Climatol Assoc* 2006;117:227-37. 11. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol* 1995;90:201-5. 12. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2006;55:1-23. 13. Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. *Ann Intern Med* 1989;110:838-9. 14. Williams I, Bell B, Kaluba J, Shapiro C. Association between chronic liver disease and death from hepatitis A, United States, 1989-92 [Abstract no. A39]. IX Triennial International Symposium on Viral Hepatitis and Liver Disease. Rome, Italy, April 21-25, 1996.

WHEN TO DO LIVER BIOPSY OR ASSESS FOR LIVER FIBROSIS

3-1 For patients who do not meet the treatment criteria (Statement 4), assessment for liver fibrosis is recommended in patients who aged 40 years and older OR those with a strong family history of HCC to evaluate the need for treatment [high quality, strong].

3-2 Liver biopsy still remains the gold standard for assessing liver fibrosis [high quality, strong]. However, transient elastography is an alternative for those who have contraindications to liver biopsy and those who desire a non-invasive method [high quality, conditional].

Assessment of liver fibrosis is important in managing patients with CHB. It serves to determine the extent of liver damage, rule out other causes of liver disease, help recognize patients who may benefit from antiviral therapy, evaluate response to treatment, establish the best time to start surveillance and stratify the risk of HCC and hepatic decompensation.^{1,3}

Liver biopsy is the gold standard in evaluating liver fibrosis.³ It is recommended in patients not considered for treatment with high normal or slightly elevated ALT levels and in patients >40 years of age.^{2,3} A study showed that the risk of complications was higher when ALT levels were elevated (>0.5x ULN to 2x ULN) due to subtle but chronic, progressive and permanent immune-mediated liver damage.⁴ Another study in Europe revealed that there was no difference in the stage of liver fibrosis and the incidence of cirrhosis between patients with normal and elevated transaminases and that advanced age (≥40 years) is the most important risk factor for cirrhosis.⁵

Although relatively safe, liver biopsy may be associated with serious complications and is subject to sampling error and interobserver variability. Hence, it is impractical to be done regularly to monitor patients on antiviral treatment.^{1,3} Alternatively, liver stiffness measurement (LSM) by transient elastography (TE) is a non-invasive method that may be used. It can accurately assess the severity of liver fibrosis and predict the development of HCC.^{1,3,6-8} However, interpretation of TE results may be difficult in the presence of severe inflammation associated with high ALT levels and standardization of LSM optimal cut-offs points have yet to be determined.^{1,3}

References: 1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167-85. 2. Lok ASF, McMahon BJ. AASLD practice guideline update: Chronic hepatitis B: Update 2009. *Hepatology* 2009;50:1-36. 3. Liaw YF, Kao J-H, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61. 4. Yuen MF, Yuan HJ, Wong DKH, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005;54:1610-4. 5. Göbel T, Erhardt A, Hewig M, et al. High prevalence of significant liver fibrosis and cirrhosis in chronic hepatitis B patients with normal ALT in central Europe. *J Med Virol* 2011;83:968-73. 6. Sporea I, Sirli R, Deleanu A, et al. Liver stiffness measurement by transient elastography in clinical practice. *J Gastrointest Liver Dis* 2008;17:395-9. 7. Jung KS, Kims SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology* 2011;53:885-94. 8. Cardoso AC, Carvalho-Filho RJ, Stern C, et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. *Liver Int* 2012;32:612-21.

INDICATIONS FOR TREATMENT

4-1 Treatment should be considered for those with (1) persistently elevated ALT levels $\geq 2x$ ULN [high quality, strong] over 3 to 6 months [moderate quality, strong] AND (2) HBV DNA level $\geq 20,000$ IU/mL if HBeAg-positive and $\geq 2,000$ IU/mL if HBeAg-negative [high quality, strong].

4-2 Patients with advanced fibrosis or at least moderate inflammation on biopsy should be treated even if the ALT is normal [high quality, strong].

4-3 Treatment should be initiated in cirrhotic patients with detectable HBV DNA regardless of the level of serum ALT [high quality, strong].

4-4 For patients who do not meet treatment criteria, monitoring of ALT every 3 to 6 months is recommended [high quality, strong].

The decision to start treatment depends on the risk of disease progression and the likelihood of treatment response. Those with high levels of viral replication (as reflected by the serum HBV DNA level and HBeAg status) and necroinflammatory activity in the liver (as reflected by the serum ALT levels) are at increased risk of developing cirrhosis and HCC.^{1,2} Other host factors such as older age, duration of infection, family history of HCC, heavy alcohol consumption and co-infection with hepatitis C, hepatitis delta and HIV are also associated with an increased risk for complications.³

Starting treatment is also influenced by the likelihood of achieving treatment endpoints. An elevated serum ALT at baseline is an important predictor of response compared to those with normal ALT.⁴ In those with normal ALT, HBeAg seroconversion occurs in less than 10% of patients.⁴ In a trial of Asian patients with normal ALT, response to treatment was poor.⁴

The urgency of initiating treatment is largely dictated by the severity of liver disease. This is determined using clinical and laboratory parameters. Urgent treatment is recommended for those with life-threatening conditions such as acute liver failure, protracted severe acute hepatitis, decompensated cirrhosis and those with

severe hepatitis flares. In those with compensated cirrhosis or significant fibrosis on biopsy or non-invasive testing, treatment is recommended if HBV DNA is detectable regardless of the serum ALT level.

Threshold values considered as triggers for treatment are constantly being revised. Whether a serum HBV DNA level greater than 2,000 IU/mL (European Association for the Study of the Liver [EASL]) or 20,000 IU/mL for HBeAg positive (American Association for the Study of Liver Diseases [AASLD]) is associated with better outcomes remains controversial. Similarly, the cut-off used for the serum ALT whether greater than ULN (EASL) or twice the ULN (AASLD) as well as what constitutes a normal ALT is a topic of debate.

References: 1. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73. 2. Liaw YF, Kao JH, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61. 3. Degertekin B, Lok AS. Indications for therapy in hepatitis B. *Hepatology* 2009;49:S129-37. 4. Lok ASF, McMahon BJ. AASLD practice guideline. Chronic hepatitis B: Update 2009. *Hepatology* 2009;50:1-36.

OPTIONS FOR TREATMENT

5-1 Options for antiviral agents for treatment-naïve HBeAg-positive and HBeAg-negative individuals are: Peg-IFN alpha 2a at a dose of 180 µg/wk OR peg-IFN alpha 2b at a dose of 1-1.5 µg/kg/wk [high quality, strong], conventional IFN 5-10 MU 3x/wk [high quality, conditional], entecavir (ETV) 0.5 mg/day, tenofovir (TDF) 300 mg/day [high quality, strong], lamivudine (LAM) 100mg/day, adefovir (ADV) 10mg/day, telbivudine (LdT) 600mg/day [high quality, conditional], clevudine (CLV) 30mg/day [moderate quality, conditional].

5-2 Peg-IFN, ETV and TDF are preferred first-line agents [high quality, strong].

The ultimate goal of antiviral treatment for CHB is to reduce the risk of HCC, liver failure, liver cirrhosis and improve survival. With the availability of increasing options for treatment and a better understanding of the natural history of CHB, the optimal choice depends on efficacy, safety, resistance profile and durability of response.

Immunomodulatory agents (eg, interferon [IFN], pegylated [peg]-IFN) and nucleos(t)ide analogues (NAs) (eg, lamivudine [LAM], adefovir [ADV], entecavir [ETV], telbivudine [LdT], tenofovir [TDF], clevudine [CLV]) are the two main classes of antiviral agents approved for the treatment of CHB. International guidelines recommend peg-IFN, ETV or TDF as first-line therapies. However, there are no specific recommendations on which to choose from among these options. The main advantages of peg-IFN are its finite duration of treatment and higher rates of sustained response off-therapy. However, side effects and the need for more intensive monitoring remain a concern.

NAs, on the other hand, have an excellent safety profile making it the agent of choice in patients with decompensated cirrhosis, under immunosuppression and in the setting of liver transplantation. In addition, NAs are the most potent drugs currently available for suppressing viral replication. Serum HBV DNA levels less than 60-80 IU/mL are achieved in 94% and 98% to 99% of patients treated with long-term ETV and TDF, respectively.^{1,2} The first generation NAs such as LAM, ADV and LdT are no longer preferred as first-line agents because it often leads to incomplete viral suppression due to the development of resistance in 20% to 75% of patients with long-term use.³⁻⁶ The choice of treatment should be individualized and should take into account socio-demographic factors such as affordability, patient and health provider preference, occupational requirements and the possibility of pregnancy.

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MONITORING DURING TREATMENT

6-1 During treatment, serum ALT and HBV DNA levels should be monitored every 3 to 6 months [high quality, strong].

6-2 For HBeAg-positive patients, seroconversion should be monitored every 3 to 6 months. For HBeAg-negative patients, HBsAg should be checked every 6 to 12 months when HBV DNA level is undetectable. Renal function should be monitored if ADV or TDF is used [high quality, strong].

6-3 For patients on IFN-based treatment, CBC should be monitored every month and TSH every 3 months. Monitoring for other adverse events should be done [high quality, strong].

*see Table 4 on suggested monitoring during and after treatment

Recent evidence suggests that long-term suppression of viral replication is important in reducing HBV complications. Monitoring sustained virological response during and after treatment is essential because of limited success in achieving durable endpoints for currently available agents and possible antiviral resistance with long-term therapy.¹ Parameters used to assess treatment response include decrease in serum HBV DNA level, loss of HBeAg with or without detection of anti-HBe, normalization of serum ALT and improvement in liver histology.^{1,2} Virological suppression and loss of HBeAg or HBsAg with or without seroconversion play a major role in monitoring treatment success and determining the duration of antiviral therapy (Table 4).¹

Early viral response may predict the possibility of sustained response or antiviral resistance.¹ Virological response in patients on IFN-based treatments should be evaluated at 6 months. Patients on NAs should be evaluated every 3 to 6 months during therapy, depending on the severity of hepatic disease and the type of NAs used.^{2,3} In cirrhotic patients who may have exacerbations of hepatitis B, HBV DNA levels should be monitored every 3 months at least during the first year of treatment and until HBV DNA is undetectable.²

The absolute HBV DNA level after 24 weeks of therapy has been identified as the best predictor of long-term efficacy in multiple analyses of various baseline factors and on-treatment responses. Lower 24-week serum HBV DNA levels after LAM, LdT, or ETV were associated with higher rates of HBV DNA suppression to undetectable levels, ALT normalization, HBeAg seroconversion and lack of resistance.⁴

In HBeAg-positive patients, HBeAg and anti-HBe should be monitored every 3 to 6 months. Consideration of treatment cessation is considered 6 to 12 months after anti-HBe seroconversion. In HBeAg-negative patients, HBsAg is monitored every 6 to 12 months.^{5,6} HBV DNA should be measured at 3 and 6 months during treatment with NAs. Once virologic suppression is achieved, HBV DNA can be monitored every 6 months thereafter.^{5,6}

Serum HBsAg appears to correlate with covalently closed circular DNA (cccDNA) and is considered a surrogate marker of infected cells. Using recently available commercial quantitative assays, qHBsAg has been shown to be helpful in the understanding and management of CHB.^{7,8} Early HBsAg monitoring can be used to develop a response-guided algorithm in patients on peg-interferon treatment: (1) to stop or switch therapy at week 12 in poor responders, (2) to continue standard 48-week treatment in most patients with a favorable response and (3) to extend therapy for intermediate on-treatment responders to improve the chances of response. The role of HBsAg monitoring during NA therapy must be clarified.^{2,7,8}

The most likely pathway leading to the development of complications for Asian patients with CHB is prolonged low-level viremia causing insidious and continual liver damage as reflected by a relatively mild elevation in ALT levels.⁹ Regular monitoring should thus be done.

NAs are excreted in the kidneys and dosing adjustments are necessary in patients with a creatinine clearance <50 mL/min.^{2,7} Some decline in renal function has been reported with all nucleotide analogues except LdT.² Monitoring serum creatinine and serum phosphate levels is recommended during ADV and TDF therapy. Serum creatinine levels should also be monitored in all patients on nucleoside analogue therapy with a high risk for renal impairment (ie, decompensated cirrhosis, creatinine clearance <60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs, solid organ transplantation).² Patients at high risk for renal impairment should be monitored monthly during the first 3 months, every 3 months until the end of first year and every 6 months thereafter.^{2,3} Monitoring renal function in low-risk patients should be done every 3 months during the first year and every 6 months thereafter. More frequent monitoring is advised if creatinine clearance is <60 mL/min or serum phosphate level is <2 mg/dL.²

Myelosuppression and hyper- or hypothyroidism may occur with IFN-based therapies. Thus, full blood counts should be monitored monthly and thyroid stimulating hormone (TSH) every 3 months.^{2,3} Because of the risk of myopathy with long-term CLV treatment, serum creatinine kinase and lactate levels should also be monitored in patients on CLV for >32 weeks.¹⁰

Table 4. Parameters for monitoring treatment success^{2,8}

Serum marker	On treatment	After treatment
HBV DNA	Every 3 to 6 months (every 6 months after 1 year)	Every 3 to 6 months (every 3 to 6 months for cirrhotics and 6 to 12 months after one year for treatment responders)
HBeAg, anti-HBe	Every 3 to 6 months (for HBeAg-positive patients)	Every 3 months (every 6 to 12 months after one year)
HBsAg	Every 6 to 12 months (for HBeAg-negative and once HBV DNA is undetectable)	Every 12 months
ALT	Every 3 months	Every 3 months (every 3 to 6 months for cirrhotics and 6 to 12 months after one year for treatment responders)

Serum marker	On treatment	After treatment
Creatinine/Phosphate (ADV/TDF)	Monthly for 3 months, then every 3 months for 1 year, then every 6 months thereafter	Not required
CBC (IFN)	Every month	Not required
TSH (IFN)	Every 3 months	Not required

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MONITORING AFTER TREATMENT

7-1 After completion of treatment, monitoring for relapse should be done using serum ALT and HBV DNA level every 3 to 6 months in the first year, and every 6 to 12 months thereafter. For cirrhotic patients, monitoring every 3 to 6 months is recommended [moderate quality, conditional].

7-2 For partial or non-responders to IFN and peg-IFN, monitoring of HBV DNA every 3 to 6 months should be done to identify a delayed response [high quality, strong] or plan re-treatment with a nucleos(t)ide analogue when indicated [moderate quality, conditional].

*see Table 4 on suggested monitoring during and after treatment

Serial monitoring of HBV DNA and ALT after completion of treatment should be performed to detect relapses and plan re-treatment, if indicated.¹ ALT activity changes over time and ALT determinations at least every 3 months within the first year post-treatment are recommended to ensure sustained off-treatment biochemical response.²

Post-treatment recurrent viremia, biochemical flares and HBeAg seroreversion have been documented despite previously documented HBeAg seroconversion and complete viral suppression with NAs and at least 12 months of consolidation therapy.³⁻⁵ Similarly, studies suggest that the effectiveness of antiviral therapy is non-durable in a substantial proportion of HBeAg-negative patients, with virological relapse rates between 31% to 53%.⁵⁻⁸ Nonetheless, resuming treatment after biochemical and virological relapses has been shown to be safe and effective.^{5,7}

Partial or non-responders to IFN therapy should continue to be monitored and NA therapy started when treatment criteria are met. IFN induces a continued immune modulatory effect with a delayed response occurring in some patients after completion of IFN therapy.⁹ Delayed HBeAg seroconversion in HBeAg-positive CHB occurs in 10% to 15% of patients 1 to 2 years after conventional IFN treatment.^{10,11} HBeAg seroconversion in non-responders to peg-IFN therapy range from 14% after 1 year and 27% after 3 years of completing

treatment.¹² However, patients who achieve anti-HBe seroconversion should continue to be monitored because HBeAg seroreversion or progression to HBeAg-negative CHB may occur. Similarly, regular monitoring of HBeAg-negative patients after IFN therapy should be done to detect possible disease reactivation.^{2,9}

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DURATION OF TREATMENT: IFN

8-1 For conventional IFN, the recommended duration of therapy is 24 weeks for HBeAg-positive patients and 48 weeks for HBeAg-negative patients [high quality, conditional]. For peg-IFN, the recommended duration of therapy is 48 weeks for both HBeAg-positive and HBeAg-negative [high quality, strong].

IFN is given for a finite duration regardless of treatment response.^{1,2} A meta-analysis of controlled trials on HBeAg-positive patients showed that substantial response rates are achieved after 16 to 24 weeks of conventional IFN treatment. In contrast, based on available data, the preferred duration for conventional IFN treatment in HBeAg-negative CHB is 48 weeks.²

For peg-IFN, weekly administration of 180 µg peg-IFN-α2a over 48 weeks in HBeAg-positive CHB yielded higher HBeAg seroconversion rates (36.2%) at 6 months post-treatment compared with shorter treatment durations.³ Forty-eight weeks is also the standard treatment duration with peg-IFN-α2a in HBeAg-negative patients and has been associated with biochemical response rates of 40% to 59% and sustained virological response rates between 19% to 43%.^{4,5} Extending peg-IFN treatment for 60 to 96 weeks may further improve sustained virological response rates in HBeAg-negative patients.⁶⁻⁸ However, larger and more exhaustive studies are needed before longer peg-IFN treatment durations can be recommended.

Finally, recent studies suggest that on-treatment HBsAg levels in conjunction with HBV DNA may predict non-responders to IFN treatment.⁹ Specifically, there is a low probability of anti-HBe seroconversion in HBeAg-positive patients who fail to achieve HBsAg levels <20,000 IU/mL or any decline in serum HBsAg levels after 3 months on peg-IFN.^{1,9,11} Likewise, in predominantly genotype D HBeAg-negative CHB, failure to achieve both a decline in HBsAg levels and a ≥2 log₁₀ IU/mL reduction in serum HBV DNA after 3 months of peg-IFN is predictive of poor treatment response.^{1,9,12,13} In such cases, early discontinuation of peg-IFN therapy may be considered.^{1,9}

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DURATION OF TREATMENT: NUCLEOS(T)IDE ANALOGUES

9-1 For HBeAg-positive patients, treatment can be stopped with HBeAg seroconversion with undetectable HBV DNA levels has been maintained for at least 12 months [moderate quality, conditional]. For HBeAg-negative patients, treatment can be stopped when HBsAg becomes negative [moderate quality, strong]. However, in patients with minimal or no fibrosis who have been treated for at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart, discontinuation of therapy may be considered. Close monitoring for relapse should be done [moderate quality, conditional]. For compensated cirrhotic patients, indefinite therapy is recommended unless there is documented HBsAg seroconversion, regression of fibrosis on liver biopsy or development of drug-related adverse events [high quality, strong].

9-2 For patients with suboptimal viral response at week 24 of therapy with LAM, LdT, ADV or CLV, a switch to a more potent drug or add-on of a drug without cross-resistance is recommended [moderate quality, strong].

NAs are usually administered until specific endpoints are achieved because the incidence of drug resistance increases with prolonged treatment.^{1,2} In HBeAg-positive patients, treatment can be discontinued after >12 months of HBeAg seroconversion and undetectable HBV DNA.² On the other hand, optimal endpoints in HBeAg-negative patients, primarily in those who remain HBsAg-positive, are less clearly established.

Studies suggest the durability of response in LAM-treated HBeAg-positive patients who had completed at least 12 months of consolidation therapy after achieving HBeAg seroconversion and undetectable HBV DNA was 70% to 90%.^{1,2} This was consistent with another study which showed that virological response was durable in those who were on LAM for >12 months after HBeAg clearance or seroconversion.³ The need for at least 12 months of consolidation therapy after HBeAg seroconversion is further evidenced by studies with ADV and ETV which demonstrated higher relapse rates after shorter periods of consolidation.⁴ Treatment may be continued in patients who have not achieved HBeAg seroconversion but in whom HBV DNA levels remain suppressed because HBeAg seroconversion may occur with continued treatment.^{3,5}

The endpoint of NA treatment in HBeAg-negative patients is less clear since relapse rates remain very high (>90%) even when patients continue treatment for 1 year after serum HBV DNA has been undetectable.⁶⁻⁸ Studies show that extending LAM, ADV or ETV treatment for at least 2 years while maintaining undetectable HBV DNA levels on at least three separate occasions taken 6 months apart may improve relapse rates to 50% to 60%.⁹⁻¹² This can be used as an alternative endpoint in HBeAg-negative patients with minimal or no fibrosis who are unable to continue NA treatment either for economic reasons or due to drug-related adverse events. HBsAg clearance with or without the anti-HBs seroconversion is associated with a very low relapse rates and is an ideal endpoint for HBeAg-negative patients.

Continuous treatment with NAs is recommended in patients with compensated cirrhosis but may be discontinued after at least 12 months of consolidation therapy in HBeAg-positive patients who achieve HBeAg seroconversion. In HBeAg-negative patients with compensated cirrhosis, treatment can only be discontinued in patients with confirmed HBsAg loss and anti-HBs seroconversion.¹³

Generally, early rescue therapy with another agent is indicated if drug resistance develops.² In patients with a suboptimal viral response (ie, persistently detectable HBV DNA after 24 weeks of oral antiviral therapy in a treatment-compliant patient) to LAM, LdT or ADV, switching to a more potent drug or add-on of a drug without cross-resistance is recommended.² As demonstrated by a study, complete viral suppression and biochemical response can be achieved by patients with suboptimal response to ADV after switching to ETV after 12 months.¹⁴

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PREGNANCY AND BREASTFEEDING

10-1 For female patients of childbearing age, IFN-based therapy is preferred [high quality, strong].

10-2 Category B nucleos(t)ide analogues (LdT and TDF) are recommended for pregnant women who meet treatment criteria [moderate quality, strong]. LAM is an alternative agent [moderate quality, conditional]. IFN is contraindicated in pregnant women [high quality, strong].

10-3a Category B nucleos(t)ide analogues (LdT and TDF) should be offered to pregnant women with high viral load (HBV DNA >107 IU/mL) during the third trimester who do not meet treatment criteria to reduce the risk of perinatal transmission [moderate quality, conditional]. LAM may be used as an alternative [moderate quality, conditional].

10-3b All infants born to HBsAg-positive mothers should receive immunoprophylaxis with standard hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within the first 12 hours of birth and two additional doses of vaccine to prevent perinatal transmission [high quality, strong].

10-4 Breastfeeding is not contraindicated in mothers with chronic hepatitis B provided recommendations on hepatitis B immunization have been followed [low quality, strong]. Breastfeeding can be continued in mothers on antiviral therapy [low quality, conditional].

Mother-to-infant HBV transmission and the potential risks to the fetus or infant must be discussed with all women of childbearing age being considered for HBV treatment.^{1,2} IFN-based therapy is preferred due to its finite treatment duration. Additionally, peg-IFN has distinct advantages over conventional IFN therapy because of its once-weekly administration and possibly better efficacy.^{2,3} However, IFN-based therapy is contraindicated in pregnancy and patients must be advised to avoid becoming pregnant while on treatment.^{1,2}

For pregnant women who require HBV treatment, use of Category B nucleos(t)ides (LdT or TDF) may help minimize possible teratogenic effects and are the preferred first-line agents. LAM, ETV and ADV are currently listed as Category C drugs (Table 5). Of these, LAM has been well studied for its safety in pregnancy. However, because resistance rates are greatest with LAM, it may be considered as an alternative when LdT or TDF are poorly tolerated.⁴

Vertical transmission is greatest in the perinatal period. Post-natal administration of HBIG and HBV vaccination reduces HBV infection rates in infants by 90% to 95% and should be given within 12 to 24 hours of birth to all newborns of mothers with HBV infection.^{5,6} Subsequent HBV booster doses for the infant should then follow the Department of Health Expanded Program on Immunization guidelines. Despite immunoprophylaxis, there is a residual risk of vertical transmission specifically from women who are HBeAg-positive or who have high viral loads.⁷⁻⁹ To further prevent perinatal transmission, Category B NAs or LAM should be offered in the third trimester to women with HBV DNA >107 IU/mL.^{1,2,10-13}

HBsAg is detectable in breast milk of mothers with HBV infection but hepatitis B immunoprophylaxis provides substantial protection for breastfed infants.² Breastfeeding in infants given hepatitis B immunoprophylaxis has no significant effect on immunoprophylaxis failure or HBV infection rates.¹⁴⁻¹⁶ TDF is also detectable in breast milk but because of its low bioavailability, only minimal amounts reach the infant.¹⁷ Thus, mothers with HBV infection with or without antiviral treatment may continue to breastfeed provided that her infant has received appropriate hepatitis B immunoprophylaxis.

Table 5. Advantages and disadvantages of anti-HBV agents during pregnancy⁴

Antiviral agent	FDA pregnancy category	Defects/Live birth when exposed		Advantages/Disadvantages of using during pregnancy
		1ST TRIMESTER % (n/N)	2ND/3RD TRIMESTER % (n/N)	
Adefovir	C	0 (0/43)	0 (0/0)	Not recommended
Entecavir	C	3 (1/30)	0 (0/2)	Not recommended
Clevudine	?	-	-	Only when clearly indicated
Lamivudine	C	3.1 (122/3,966)	2.8 (178/6,427)	Extensive human safety data Not a preferred first-line agent in treatment guidelines Associated with high rates of antiviral resistance
Telbivudine	B	0 (0/8)	0 (0/9)	Positive human data, pregnancy class Fewer data than lamivudine or tenofovir Not a preferred first-line agent in treatment guideline
Tenofovir	B	2.2 (27/1,219)	2.1 (15/714)	Extensive human safety data, pregnancy class

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PATIENTS CO-INFECTED WITH HEPATITIS C

11-1 For patients with concurrent HCV with detectable HCV-RNA, peg-IFN plus ribavirin is the preferred treatment [moderate quality, conditional].

HCV and HDV co-infections are transmitted in the same manner as HBV. There is an increased risk of developing fulminant hepatitis, liver cirrhosis and HCC in HBV patients with HCV and/or HDV co-infections.¹⁻⁸ Management of hepatitis co-infections is complex and requires close monitoring. The predominant infection needs to be determined by measuring the level of viremia for both hepatitis B and C. In HCV-dominant dual infections, HCV responds well to peg-IFN plus ribavirin. However, rebound HBV infection and acute hepatitis B flares may occur after elimination of HCV.⁹⁻¹³ Referral to a specialist experienced in managing hepatitis co-infections is advised.

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PATIENTS CO-INFECTED WITH HIV

12-1 For patients with HBV-HIV co-infection, co-management with an infectious disease specialist is strongly recommended [low quality, strong].

12-2 Antiretroviral therapy (ART) containing TDF and LAM plus EFV is the therapy of choice for those with CD4 T-cell count ≤ 500 cells/mm³ or those with severe chronic liver disease regardless of CD4 count [low quality, strong].

12-3 If TDF cannot be safely used, alternative regimen includes: ETV plus AZT/LAM/EFV [high quality, strong], ADV or LdT plus AZT/LAM/EFV [low quality, conditional].

12-4 If the CD4 count is >500 cells/mm³ and ART is not indicated but meet the criteria for HBV therapy, TDF plus LAM-containing regimen is preferred [moderate quality, conditional].

HIV infection is associated with higher HBV-related morbidity and mortality and HIV treatment can cause immune reactivation and HBV flares.^{1,2} Referral and co-management with an infectious disease specialist is recommended.

CD4 count should be evaluated every 6 months. Treatment for both HIV and HBV is indicated in patients with CD4 T-cell counts ≤ 500 cells/mm³ or those with severe chronic liver disease regardless of CD4 count.² Several NAs have activity against both HBV and HIV, but sensitivity and resistance profiles for HBV and HIV differ. Thus, treatment entails careful selection of antiviral combinations that avoid selection of HIV- or HBV-resistant strains.

The 2013 World Health Organization (WHO) recommendations and the 2014 Department of Health (DOH) Revised Antiretroviral Therapy (ART) Guidelines support TDF/LAM/EFV therapy as first-line treatment due to its good anti-HBV and anti-HIV activity and less risk for hepatotoxicity. Alternative first-line regimens include TDF/LAM/nevirapine (NVP) (if the patient cannot tolerate EFV) or a regimen containing AZT and LAM plus EFV or NVP (if TDF cannot be safely used).^{2,3} EFV and NVP may be substituted with a boosted protease inhibitor (ie, lopinavir/ritonavir) if both drugs are poorly tolerated.

There is less data to support HIV treatment in patients with CD4 counts > 500 cells/mm³ and anticipated risks of early HIV antiviral therapy (eg, hepatotoxicity, immune reconstitution inflammatory syndrome and hepatic flares) may outweigh treatment benefit.² For patients in whom HIV treatment is not indicated but otherwise meet HBV treatment criteria (see Statement 4), single-agent NAs are discouraged because of the risk of developing drug resistance.⁴⁻⁸ TDF plus LAM is the currently preferred treatment of choice.^{2,6}

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PATIENTS WITH DECOMPENSATED LIVER DISEASE

13-1 For patients with hepatic decompensation, treatment should be initiated promptly with ETV or TDF [high quality, strong]. LdT, LAM or ADV can also be used in nucleos(t)ide naive patients [high quality, conditional]. IFN should not be used in this setting [high quality, strong]. Referral and evaluation for liver transplantation should be done.

Decompensated liver cirrhosis that is untreated carries a high risk of progressing to HCC and hepatic failure with an estimated 5-year survival rate of only 14%.^{1,2} The underlying cause of liver deterioration (HBV antiviral resistance, presence of HCC, etc) must be determined. Child-Turcotte-Pugh (CTP) or Model for End-Stage Liver Disease (MELD) scores are used to monitor liver function. Management includes addressing liver complications (eg, ascites, bleeding, hepatic encephalopathy), administering antiviral therapy and continued HCC surveillance. Prompt assessment and referral for liver transplantation is also warranted.³

Current Asian Pacific Association for the Study of the Liver (APASL) and EASL guidelines recommend antiviral treatment irrespective of HBV DNA level.^{4,5} Kidney disease is common in these patients and should be considered when planning the choice and dosage of antiviral treatment. ETV and TDF have demonstrated efficacy in improving or stabilizing liver function. A 12-month course of ETV significantly improved pretreatment CTP and MELD scores in patients with decompensated CHB.⁶ However, patients should be monitored

for ETV-associated lactic acidosis.⁷ TDF monotherapy is comparable in efficacy to TDF plus emtricitabine or ETV monotherapy. Data showed similar rates of reduction in HBV DNA (<400 IU/mL) and a decrease or improvement in MELD scores across all three groups after 48 weeks of treatment.⁸

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DRUG RESISTANCE

14-1a For resistance to LAM, LdT or CLV, add-on ADV therapy [high quality, strong] OR switching to TDF is indicated [moderate quality, strong].

14-1b For resistance to ADV, add-on LAM, LdT or ETV, or switching to TDF is indicated [moderate quality, strong].

14-1c For resistance to ETV, add-on ADV or TDF is indicated [moderate quality, strong].

14-1d For resistance to both LAM or LdT or CLV AND ADV, switching to ETV plus TDF is indicated [moderate quality, strong].

14-2 For resistance to any nucleos(t)ide analogue, switching to IFN-based therapy may be considered [moderate quality, strong].

14-3 Management of drug resistance in the treatment of HBV is complex. Referral to a specialist is recommended.

Drug resistance is identified by an initial non-response to treatment or virological breakthrough in the presence of established treatment compliance.¹ Ideally, drug resistance testing is performed to tailor rescue therapy but may not be feasible in resource-limited settings. Alternatively, add-on treatment or switching to different antivirals is guided by available cross-resistance data.²

Among antiviral agents, LAM yields the highest year-on-year rates of HBV resistance in treatment-naïve patients.¹ ETV and TDF have the lowest documented resistance rates, although there is currently limited data for TDF.³ In patients with LAM resistance, add-on ADV enhances viral suppression, prevents virologic breakthrough and is more effective than switching to ADV alone.^{4,5} Moreover, LAM plus ADV was significantly more favorable than ETV monotherapy (1 mg/day) for reducing viral suppression and virologic breakthrough rates.⁶ However, ETV may still be offered to patients not amenable to other antivirals. Switching to TDF monotherapy has been shown to be effective for LAM or ADV resistance.⁷ ETV plus TDF should be considered for patients resistant to combined nucleoside and nucleotide analogues.

IFN-based treatment has also been used for patients with NA resistance. A 48-week course of peg-IFN versus continuous ADV treatment in HBeAg-positive patients with LAM resistance showed that peg-IFN was superi-

or to ADV in inducing HBeAg seroconversion after 72 weeks (or 6 months after peg-IFN treatment) (p=0.01). However, only 10.6% of peg-IFN treated patients had HBV DNA <80 IU/mL versus 22.5% in ADV-treated patients during the same time period.⁸

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PATIENTS ON IMMUNOSUPPRESSION OR CHEMOTHERAPY

15-1 Screening for HBsAg and anti-HBc should be done in all patients being evaluated for any form of immunosuppression or chemotherapy. If HBsAg-positive, HBV DNA determination must be done and prophylactic therapy with nucleos(t)ide analogues started before or together with chemotherapy to prevent HBV reactivation [high quality, strong]. Depending on the HBV DNA level and duration of immunosuppression or chemotherapy, ETV or TDF [moderate quality, strong]. LAM may also be used [moderate quality, conditional].

15-2 For those with isolated anti-HBc-positivity, HBV DNA determination should be done to test for occult HBV infection particularly in those who will receive biologic agents (eg, rituximab) and steroid-containing regimens. For those with detectable HBV DNA, prophylactic treatment is recommended [moderate quality, strong].

15-3 For those on prophylactic therapy, treatment should be continued for 6 to 12 months post-immunosuppression/chemotherapy [moderate quality, strong].

15-4 For those who meet treatment criteria (Statement 4) prior to immunosuppression or chemotherapy, treatment should be continued until appropriate endpoints are met (Statement 9) [high quality, strong].

15-5 Monitoring of HBV DNA and ALT should be done every 3 to 6 months while on treatment and upon discontinuation of treatment [high quality, strong].

Monitoring HBV status is warranted in immunocompromised states since HBV reactivation occurs in 20% to 50% of HBV carriers on immunosuppression therapy. HBV-related liver mortality rates range from 5% to 30%.^{1,2} Enhanced HBV replication and reactivation can occur with chronic steroid treatment, cancer chemotherapy, hematopoietic stem cell transplantation or organ transplantation.^{3,4} It can also occur with rituximab therapy and possibly other emerging biological response modifiers (BRMs) (eg, alemtuzumab) which cause B- or T-cell depletion.⁵⁻¹²

Screening for HBsAg and anti-HBc is indicated when chemo- or immunosuppressive therapy is being considered. High viral load is a significant risk factor and baseline HBV DNA testing should be performed in patients who test positive for HBsAg or anti-HBc.¹³ While HBV DNA levels guide treatment, chemotherapy should not

be delayed while awaiting HBV DNA results. HBV antiviral treatment alongside immunosuppressive therapy is advised for patients who meet HBV treatment criteria (see Statement 4) and should be continued until adequate endpoint parameters are achieved (see Statement 9). IFN-based therapy is not recommended because it may cause further bone marrow suppression or hepatic flares.¹

Prophylactic antiviral therapy should be administered to HBsAg-positive carriers.^{1,13,14} It is also recommended for occult HBV infections (ie, HBsAg-negative patients who are anti-HBc-positive and have detectable HBV DNA), particularly in patients on BRMs or steroid-containing regimens.^{13,15} Less commonly, HBV reactivation or seroreversion may develop during or shortly after completion of chemotherapy in patients with isolated anti-HBc but with otherwise undetectable HBV DNA at baseline.^{1,13,16} Hence, HBV DNA and ALT should be closely monitored every 3 to 6 months and antiviral treatment initiated when there is documented elevation in ALT and HBV DNA.

Prophylactic treatment should be given before or with immunosuppressive treatment and maintained for 6 to 12 months after completion.^{1,14} HBV DNA level and the anticipated duration of immunosuppression therapy determine the choice of prophylactic agent. LAM, being the most extensively studied prophylactic agent in this setting, can be used in most cases and has been shown to reduce the risk of HBV reactivation and HBV-related mortality.^{2,3,13,17} However, because of the higher incidence of LAM resistance, NAs with a high barrier of resistance (ie, ETV or TDF) are considered in patients with high HBV DNA levels (>2000 IU/mL) or those requiring prolonged or lifelong immunosuppression (ie, organ transplantation).^{13,14}

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PATIENTS WITH HEPATOCELLULAR CARCINOMA

16-1 For patients with HCC and detectable HBV DNA, treatment with a nucleos(t)ide analogue (preferably with ETV or TDF) should be initiated before any therapy for HCC is considered [high quality, strong].

16-2 For patients with HCC and decompensated liver disease, treatment with a nucleos(t)ide analogue (preferably with ETV or TDF) should be initiated [high quality, strong].

HBV reactivation can occur following HCC liver resection, especially with baseline HBV DNA >104 IU/mL.¹ It has been shown to significantly reduce postoperative recovery of liver function, increase liver failure rates, and worsen 3-year disease-free and overall survival rates.^{2,3} A prospective randomized controlled trial has demonstrated that in patients who had undergone liver resection for HBV-related HCC, LdT reduced the incidence of periorperative HBV reactivation versus controls (HR 0.07 [95% CI 0.01-0.65]; p=0.001).⁴ Rates of hepatitis after transarterial chemo-lipiodolization were also significantly lower with preemptive LAM therapy than without concomitant antiviral treatment (2.8% versus 29.7%; p=0.002).¹ Nonetheless, in light of limited trials on the use of antivirals in these patients, antiviral treatment similar to patients with decompensated liver disease is currently recommended (see Statement 13).⁵ Concurrent evaluation and referral for liver transplantation should also be undertaken.

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ACUTE HEPATITIS B

17-1 Antiviral treatment of acute viral hepatitis is generally not recommended [high quality, strong].

17-2 Treatment with nucleos(t)ide analogues may be considered in severe acute or fulminant hepatitis B [moderate quality, strong].

Acute hepatitis B infection in adults usually resolves without treatment. Anti-HBs seroconversion occurs in 95% to 98% of cases and the risk of progression to CHB is low (0.2% to 13.4%).¹⁻³ However, antiviral treatment is indicated when liver transplantation is being considered.²⁻⁴ Treatment may also be initiated in patients with severe acute hepatitis B; namely, those with two or more of the following: (1) hepatic encephalopathy, (2) serum bilirubin >10.0 mg/dL, and (3) international normalized ratio (INR) >1.6.^{5,6} The goal of treatment is to limit disease duration and prevent liver failure.³ LAM, the most commonly used NA based on available data, has been shown to improve clinical and biochemical parameters in these cases.^{4,6}

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