CHB COMMON GROUND GAZETTE
VOL I/III
FROM PAPER TO PRACTICE
CLINICAL APPLICATIONS OF AASLD GUIDELINES FOR OPTIMAL MANAGEMENT

Inside

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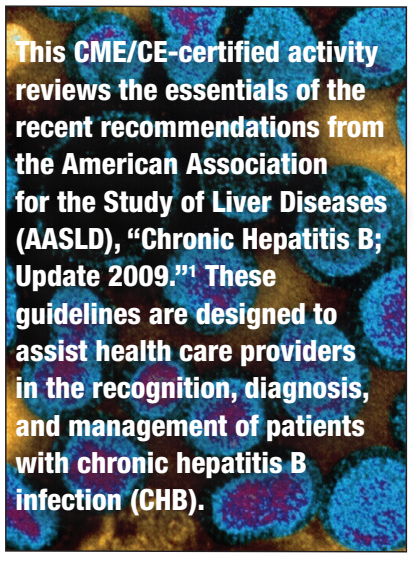

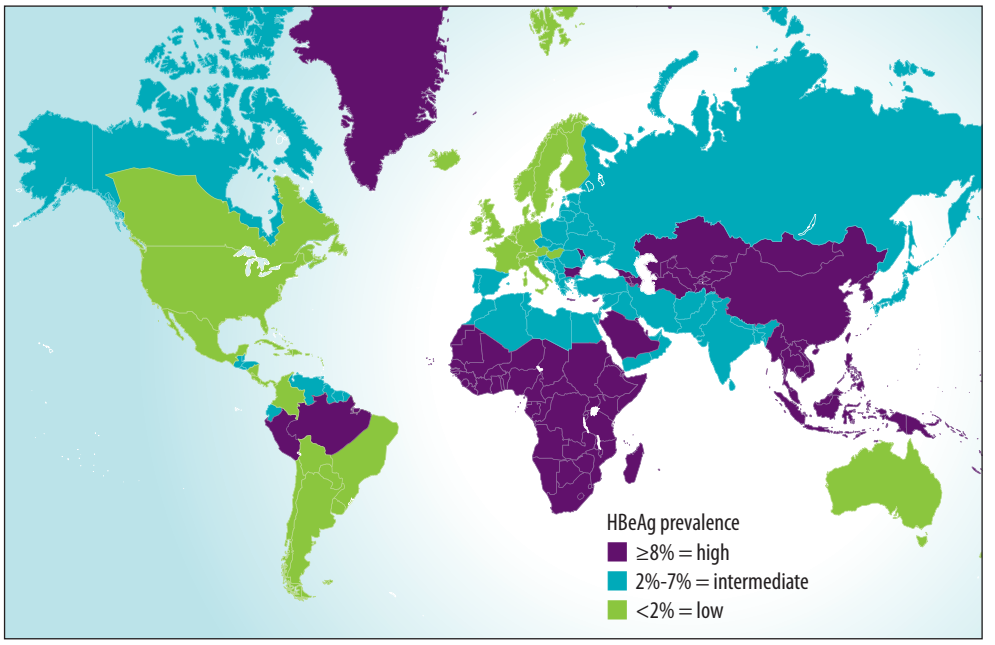

Figure 1. Estimated CHB cases worldwide, 2006
Abbreviations: HBeAg, hepatitis B e antigen.
Source: Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57:(RR-8)1-20.

Chronic hepatitis B: a serious and prevalent disease in the United States

Cover Story

Chronic hepatitis B infection (CHB) is a serious disease affecting approximately 350 million individuals worldwide; acute or chronic infection causes an estimated 600,000 deaths each year.[2] The Centers for Disease Control and Prevention (CDC) estimates that approximately 800,000 to 1.4 million US residents have CHB and that the disease causes 2000-4000 deaths each year.[3] However, according to the Hepatitis B Foundation, if individuals excluded from surveillance studies, such as recent immigrants from areas where hepatitis B virus (HBV) is endemic, are included, the prevalence of CHB may actually be closer to 2 million.[4] HBV-related expenditures have risen markedly since 1990, and estimated hospitalization costs alone in the United States amounted to $1.3 billion in 2006.[5]

The American Association for the Study of Liver Diseases (AASLD)[1] and the European Association for the Study of the Liver (EASL)[6] have released updated guidelines on the prevention, identification, and control of viral hepatitis. This newsletter discusses important features of the AASLD guidelines for clinicians who manage the treatment of patients with CHB. Subsequent newsletters will discuss the EASL guidelines and highlight any key differences between the AASLD and EASL recommendations that may influence clinical practice.

HBV transmission. The primary routes of HBV transmission are sexual contact, percutaneous exposure to infectious body fluids (eg, through needle sharing by injection drug users [IDUs] or needlestick injuries in health care settings), prolonged household contact with an infected person, and perinatal exposure to a mother with CHB.[7] Blood is the most infectious body fluid; however the virus is also present in saliva and semen and may be readily transmitted through these fluids as well. Because hepatitis B virions are viable for up to one week outside the body, they can be present in high concentrations on contaminated objects.[7] In some infectivity models, HBV is 50 to 100 times more infectious than the human immunodeficiency virus (HIV).[2]

CHB affects 0.3% of the general US population and occurs at higher rates among subpopulations with certain risk factors, such as those who are IDUs or who are infected with the human immunodeficiency virus (HIV) (Table 1).[7] However most (47%-70%) of the cases of CHB in the United States occur in individuals born in foreign regions that are endemic

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Strategies to accurately identify and diagnose CHB

Early identification of chronic hepatitis B (CHB) through screening allows prompt treatment that may delay or prevent serious complications as well as reduce the transmission of hepatitis B virus (HBV) infection from the infected person.[7] Universal screening is not recommended because the overall prevalence rate is low (0.3%) in the general population in the United States.[7] Instead, as described below, the Centers for Disease Control and Prevention (CDC) recommends targeted screening in high-risk populations (eg, injection drug users [IDUs], men who have sex with men [MSM], and immigrants from regions of high endemicity).[7]

Recommended screening tests. Assays are available for all HBV serologic markers except hepatitis B core antigen (HBcAg); free HBcAg does not circulate in blood.[7] There are no currently available rapid or oral tests for any HBV markers. Table 2, page 3 shows the interpretation of HBV serologic tests used to differentiate an acute from a chronic infection.[7,13] The American Association for the Study of Liver Diseases (AASLD) recommends testing for both hepatitis B surface antigen (HBsAg) and antibody to hepatitis B surface antigen (anti-HBs) to screen for CHB.[1] Chronic infection is indicated by the presence of HBsAg, the

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Coming Soon

CHB COMMON GROUND
FROM PAPER TO PRACTICE

VOL II: EASL GUIDELINES

VOL III: CASE STUDIES COMPARING AASLD AND EASL GUIDELINES

Paul Martin, MD

Mark Sulkowksi, MD

Letter from the Editors

Dear Health Care Professional:

Chronic hepatitis B (CHB) is a serious disease that can lead to severe complications, including decompensated cirrhosis and hepatocellular carcinoma. CHB often goes undetected until the affected individual is seriously ill and experiences significant hepatic morbidity. Until recently, treatment options for patients with CHB were limited, but a number of antivirals effective against CHB are now available that can delay or prevent serious hepatic complications. However, important questions still remain about treatment selection, timing, and duration.

As described in this newsletter, the American Association for the Study of Liver Diseases (AASLD) issued revised guidelines in 2009 on the recognition, diagnosis, and management of CHB, "AASLD Practice Guidelines: Chronic hepatitis B: Update 2009." These guidelines replace the previously released 2007 guidelines and were developed in response to new knowledge about CHB and the licensure of new antivirals for CHB treatment. The 2009 AASLD guidelines are reviewed in this newsletter and provide updated recommendations on screening individuals at risk for CHB, selection of first-line antiviral agents, criteria for initiating treatment, duration of treatment, and strategies to manage antiviral resistance. In addition, the 2009 AASLD guidelines provide recommendations on the treatment and management of special populations, such as pregnant women; patients with CHB who are coinfected with hepatitis C virus, human immunodeficiency virus, or hepatitis D virus; and patients undergoing immunosuppressive therapy or chemotherapy.

This continuing medical education (CME) activity will benefit clinicians by informing them about recommendations from the AASLD concerning all aspects of screening, diagnosis, and management of patients with CHB. In turn, this CME activity will benefit patients with CHB by increasing awareness of this condition among health care providers, encouraging earlier identification and diagnosis, and optimizing treatment.

We hope that you will find this newsletter to be a useful part of your continuing education about this challenging disease.

Sincerely,

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Table 1. Estimated prevalence of HBV in the United States by subgroup

	Chronic HBV infection[a]	Ever infected with HBV[b]
General population	0.3% 95% CI = 0.2%-0.4%	4.8% 95% CI = 4.2%-5.5%
Subgroup		
HIV-positive individuals	4%-17%	24%-76%
Injection drug users	3%-6%	20%-70%
Men who have sex with men	1%-3%	10%-40%
Sexual contacts of HBsAg-positive individuals	3.5%-9%	25%-59%
Household contacts of persons with chronic HBV infection	3%-20%	15%-60%

Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

[a]Hepatitis B surface antigen-positive.

[b]Antibody to hepatitis B core antigen-positive includes persons with resolved and chronic infections.

Source: Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57:(RR-8)1-20.

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for HBV, where the virus is primarily transmitted through perinatal exposure (Figure 1, page 1).[7] Although perinatal transmission is now relatively uncommon in the United States because of the immunoprophylaxis of newborns and children,[7,8] sporadic cases continue to occur (see below for the management of care for pregnant women with CHB).[8]

Most cases of acute HBV infection in adults are self-limited and resolve with the patient eventually producing antibodies directed against hepatitis B surface antigen (HBsAg) and clearing HBsAg from blood.[9] The risk of developing CHB is inversely related to the age at which the infection was acquired; a small percentage of those persons acutely infected as adults develop CHB (< 5%),[9] whereas > 90% of infants infected perinatally and 25% to 50% of children infected between the ages of 1-5 will develop CHB.[7] The lifetime risk of serious complications from CHB is high among those infected at a young age; an estimated 25% of all persons infected as infants or young children eventually die of liver cancer or cirrhosis.[7]

Phases of CHB. CHB can evolve through several different phases (Figure 2).[1,9] Each phase has a certain pattern of HBV replication, biomarkers, and liver enzyme concentrations determined by the patient's immune status and the extent of liver disease.[10] The 3 main phases are immune tolerant, immune active, and inactive carrier.[9]

The immune tolerant phase typically occurs in individuals with perinatally acquired HBV infection.[1] In this phase, the patient is hepatitis B e antigen (HBeAg)-positive but has high levels of HBV DNA but normal or minimally elevated alanine aminotransferase (ALT) levels. This phase can last for decades;[10] however most patients eventually move into the immune active phase.

In the immune active phase, patients are typically HBeAg-positive with elevated HBV DNA levels, elevated ALT levels, and liver inflammation.[9,10] Active viral replication is a major determinant of progressive liver disease,[11,12] and patients who remain in the immune active phase for a long time have the greatest risk of progressive liver disease.[9] Patients who become infected as adults through person-to-person transmission often enter into the immune active phase after experiencing only a brief or no immune tolerant phase.[1,9,10] Many HBeAg-positive patients in the immune active phase will clear HBeAg and develop antibodies to HBeAg (anti-HBe).[9] Following HBeAg seroconversion, the patient usually enters the inactive carrier phase.

In the inactive carrier phase, the patient is anti-HBe-positive, has low HBV DNA levels (< 2000 IU/mL), persistently normal ALT levels, and little or no significant liver inflammation.[1,9] Patients in this phase are unlikely to progress to more severe liver disease. However they remain at risk for reactivation of HBV infection with the possible emergence of mutant forms of HBV DNA and the progression of liver disease. Any patient who remains HBsAg-positive remains at risk for hepatocellular carcinoma (HCC).

Patients typically pass from one phase to the next, but there can be bidirectional movement of the disease. Patients may move from being immune active to an inactive carrier and then experience a reactivation and transition to CHB.[1,9] Approximately 0.5% of inactive carriers will clear HBsAg from the serum each year and produce an antibody to hepatitis B surface antigen (anti-HBs).[1] However progression to HCC or cirrhosis has been reported in some of these patients.[1,9] The variable and often unpredictable natural history of CHB underscores the need for lifelong monitoring of infected patients.

HBV serologic markers. The different phases of CHB are associated with changes in serologic markers, specifically HBsAg, anti-HBs, HBeAg, anti-HBeAg, total antibody to hepatitis B core antigen (anti-HBc), and immunoglobulin M antibody to hepatitis B core antigen (IgM anti-HBc).[7] As shown in Figure 3, levels of HBV serologic markers change as the disease progresses from acute to chronic infection.

In newly infected individuals, HBsAg is the only serologic marker detected during the first few weeks following infection. Total anti-HBc appears approximately 1-2 months into acute HBV infection and has a lifelong presence in most patients irrespective of whether the infection resolves or not. IgM anti-HBc is generally an indication of a recent acute (≤ 6 months) rather than a chronic infection. However, among patients with CHB, a low level of IgM anti-HBc can be detected during active viral replication in individuals with the reactivation of chronic infection.[7] In patients who recover from HBV infection, HBsAg and HBV DNA are cleared from the blood and anti-HBs is present. In contrast, in

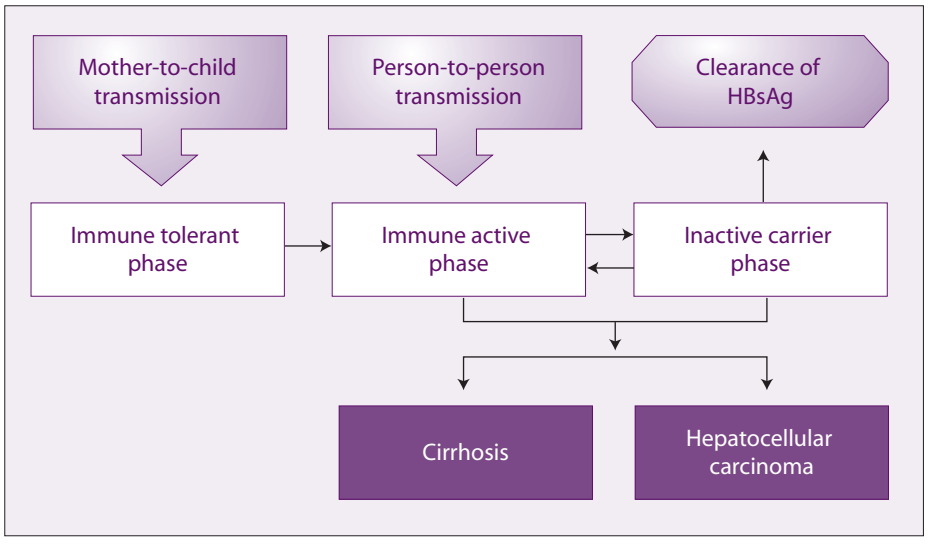

Figure 2. Natural history of chronic hepatitis B infection

Abbreviations: HBsAg, hepatitis B surface antigen.

Source: Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis B. *Ann Intern Med.* 2009;150(2):104-110. Reproduced with permission.

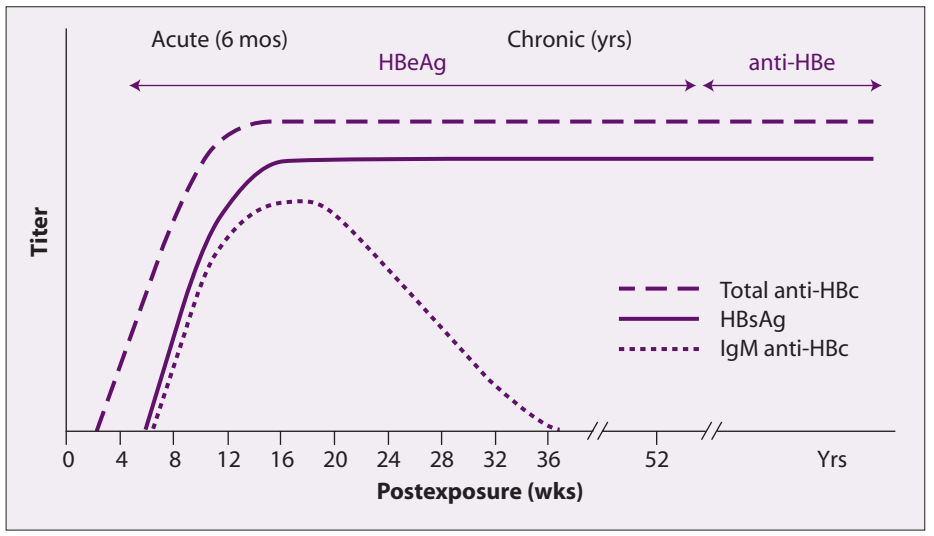

Figure 3. Typical serologic course of acute hepatitis B virus infection with progression to chronic hepatitis B virus infection

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

Source: Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57:(RR-8)1-20.

those who develop chronic infection, HBsAg and HBV DNA persist and anti-HBs does not develop. In persons with resolved CHB, HBsAg becomes undetectable, anti-HBs develops, and total anti-HBc persists.

HBeAg can be detected in both acute HBV infection and CHB. In most patients with CHB, HBeAg is eventually cleared and anti-HBeAg appears. In general, the presence of HBeAg is associated with more active disease;[7] however, the absence of HBeAg cannot be interpreted as indicative of inactive disease since such patients can harbor mutations in the core or precore regions of the HBV genome that permit active viral replication and disease without the production of HBeAg.[6] ■

Key Points: Cover story

- Many of the CHB cases in the United States now occur in individuals from communities that are endemic for HBV
- The lifetime risk of serious complications of CHB is highest in those infected at a young age; an estimated 25% of all persons infected < 5 years eventually die of liver cancer or cirrhosis
- The 3 main phases of CHB are immune tolerant, immune active, and inactive carrier. In the immune tolerant phase the patient is HBeAg-positive and has high levels of HBV DNA but normal or minimally elevated ALT levels. In the immune active phase, the patient is HBeAg-positive and has elevated HBV DNA levels, elevated ALT levels, and liver inflammation. In the inactive carrier phase, the patient is anti-HBe-positive, has low HBV DNA levels (< 2000 IU/mL), persistently normal ALT levels, and no significant liver inflammation. Patients typically pass from one phase of the disease to the next, but there can be bidirectional movement of the disease
- Serologic markers typically used to test for CHB are HBsAg, anti-HBs, total anti-HBc, and IgM anti-HBc. Patients with an acute HBV infection (≤ 6 months) are positive for IgM anti-HBc, HBsAg, and total anti-HBc but negative for anti-HBs. Patients with CHB are positive for HBsAg and negative for anti-HBs. Persons with resolved CHB have undetectable HBsAg and are positive for anti-HBs and total anti-HBc.

Identification and diagnosis continued from page 1

Table 2. Interpretation of HBV serologic test results

HBsAg **Total anti-HBc** **Anti-HBs**	Negative Negative Negative	Susceptible
HBsAg **Total anti-HBc** **Anti-HBs**	Negative Positive Positive	Immune due to natural infection
HBsAg **Total anti-HBc** **Anti-HBs**	Negative Negative Positive	Immune due to HBV vaccination
HBsAg **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Positive Positive Positive Negative	Acutely infected
HBsAg **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Positive Positive Negative Negative	Chronically infected

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgM, immunoglobulin M.

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Interpretation of hepatitis B serologic test results. http://www.cdc.gov/HEPATITIS/HBV/PDFs/SerologicChartv8.pdf. Accessed February 1, 2010.

absence of anti-HBs, and negative immunoglobulin M antibody to hepatitis B core antigen (IgM anti-HBc).

Testing for total anti-HBc is not recommended by AASLD as an initial screening test. It may be used as an alternative test only if a positive result is followed up by tests for HBsAg and anti-HBs.[1] Hepatitis B e antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe), and HBV DNA tests are not recommended as primary screening tools but rather to evaluate patients for treatment, to monitor disease progression, and to assess the patient's response.[1]

Populations recommended for screening. The AASLD guidelines reflect the CDC 2008 recommendations for CHB screening by risk group (Table 3).[1,7] All individuals from countries of high or intermediate HBV endemicity should be screened for CHB (Figure 1).[7, 14] Screening is also recommended for individuals in groups with an increased risk for HBV, such as injection drug users (IDUs) and MSM. In addition, screening is recommended for all pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected individuals, individuals who are the source of blood or body fluid exposures that warrant postexposure prophylaxis (eg, needlestick injury to a health care worker), and those infected with HIV.[7]

Recommendations for Diagnosis. The diagnostic criteria for CHB recommended by the AASLD are listed in Table 4, page 4.[1] Patients are diagnosed with CHB if they have been HBsAg-positive for at least 6 months and have a serum HBV DNA level > 20,000 IU/mL; however, lower values (2,000-20,000 IU/mL) are common in HBeAg-negative patients. In addition, patients with CHB may have persistent or intermittent elevation in alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels, and if a liver biopsy is performed, may have evidence of liver injury with moderate or severe necroinflammation.

The initial evaluation of a patient with CHB should include a patient history and physical examination with attention to risk factors for human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) coinfection, family history of liver disease and liver cancer, and alcohol use.[1] Patients should also be asked about tobacco use because smoking increases the risk of liver cancer.[15] Laboratory tests should include an assessment of hepatic dysfunction (eg, ALT level, serum albumin test, prothrombin time [international normalized ratio or INR], bilirubin test, and tests for coinfections, notably HCV antibody, hepatitis D virus (HDV) antibody, and HIV antibody. Assessment of active hepatitis B

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Table 3. HBV screening recommendations for US populations from the Centers for Disease Control, 2008

Individuals born in areas of high[a] or intermediate HBV prevalence[b] (includes immigrants and adopted children[cd])

- Asia: all countries
- Africa: all countries
- South Pacific Islands: all countries
- Middle East (except Cyprus and Israel)
- European Mediterranean: Malta and Spain
- The Arctic (indigenous populations of Alaska, Canada, and Greenland)
- South America: Ecuador, Guyana, Suriname, Venezuela, and Amazonian regions of Bolivia, Brazil, Colombia, and Peru
- Eastern Europe: All countries except Hungary
- Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos
- Central America: Guatemala and Honduras

Other groups recommended for screening

- U.S. born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥ 8%)
- Infants born to HBsAg-positive mothers
- Household and sexual contacts of HBsAg-positive persons[d]
- Persons who have ever injected drugs[d]
- Persons with multiple sexual partners or history of sexually transmitted diseased
- Men who have sex with men[d]
- Inmates of correctional facilities[d]
- Individuals with chronically elevated ALT or AST levels[d]
- Individuals infected with HCV or HIV[d]
- Patients undergoing renal dialysis[d]
- Persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis
- All pregnant women
- Persons needing immunosuppressive therapy

[a]HBsAg prevalence ≥ 8%. [b]HBsAg prevalence 2%-7%.

[c]If HBsAg-positive persons are found in the first generation, subsequent generations should be tested.

[d]Those who are seronegative should receive hepatitis B vaccine.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Source: Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57:(RR-8)1-20.

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Table 4. Diagnostic criteria for CHB

Chronic hepatitis B
■ HBsAg-positive > 6 months ■ Serum HBV DNA > 20,000 IU/mL (10^5copies/mL), lower values 2,000-20,000 IU/mL (10^4-10^5 copies/mL) are often seen in HBeAg-negative chronic hepatitis B ■ Persistent or intermittent elevation in ALT/AST levels ■ Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation
Inactive HBsAg carrier state
■ HBsAg-positive > 6 months ■ HBeAg–, anti-HBe + ■ Serum HBV DNA < 2000 IU/mL ■ Persistently normal ALT/AST levels ■ Liver biopsy confirms absence of significant hepatitis
Resolved hepatitis B
■ Previous known history of acute or chronic hepatitis B or the presence of anti-HBc +/- anti-HBs ■ HBsAg-negative ■ Undetectable serum HBV DNA[a] ■ Normal ALT levels

[a] Very low levels using sensitive PCR assays.

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; CHB, chronic hepatitis B; HBeAg, antibody to hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

virus (HBV) replication should include tests for serum HBV DNA, HBeAg, and anti-HBe.

In addition, patients with active HBV infection should undergo liver imaging with ultrasonography or another modality to screen for hepatocellular carcinoma (HCC). A biopsy of the liver may also be useful to evaluate necroinflammatory activity and the fibrosis stage, which may guide HBV treatment decisions as well as identify persons at high risk for HCC (eg, those with significant fibrosis).[16] Accordingly, the AASLD recommends a liver biopsy for patients who do not clearly meet criteria for HBV treatment as the additional information obtained by histologic evaluation may influence the decision about whether to treat or observe the patient.[1] The decisions to pursue a biopsy of the liver should take into account the patient's age, HBV DNA levels, ALT levels, HBeAg status, and other clinical features as well as the need for antiviral therapy. Many clinicians will not pursue a liver biopsy of patients for whom HBV treatment is clearly indicated (eg, those with elevated serum ALT and HBV DNA levels).

HCC screening. Because every patient with CHB is at risk for HCC, all patients should be screened for this cancer. Additional risk factors for HCC include a family history of HCC, male gender, older age, history of reversion from anti-HBe to HBeAg, cirrhosis, and coinfection with HCV.[1] Recent evidence suggests that the presence of persistently elevated HBV DNA levels is an independent risk factor for HCC in HBeAg-negative and -positive individuals.[1,11] A recent large prospective cohort study evaluated the risk of HCC or cirrhosis among untreated Taiwanese with CHB.[11, 12] The mean follow-up was 11.4 years. After adjustment for other HCC risk factors, such as seropositivity for HBeAg, cirrhosis, and elevated ALT levels, the hazard ratio for HCC significantly increased with rising HBV DNA levels (Table 2).[11] An increasing or sustained elevated HBV DNA level was the strongest independent predictor of progression to HCC.[11]

Measures to prevent transmission. Because individuals with CHB are the primary source of new HBV infections,[7] all patients should be counseled on preventive measures to reduce the risk of HBV transmission. The AASLD recommendations for preventive measures are shown in Table 5.[1]

Patients should notify all sexual partners or needle-sharing partners and household contacts that they should be tested for HBV infection and vaccinated if they are susceptible.[1,7] All patients with CHB should use barrier protection during sexual contact with susceptible persons. Because exudates from wounds and lesions can transmit HBV,[7] patients should be advised to cover all open sores. In addition, because HBV can remain viable for a week outside the body,[7] all blood spills must be cleaned with bleach or detergent. Persons with CHB infections should be advised not to donate blood, plasma, semen, or tissue.[7] HBV is not transmitted by casual contact, such as hugging; therefore persons with CHB should not be excluded based on their HBsAg status from any workplace, school, or other settings where casual contact may occur.[7] ■

Table 5. AASLD-recommended preventive measures

For persons who are HBsAg-positive:
■ Have sexual contacts vaccinated ■ Use barrier protection during sexual intercourse if partner is not vaccinated or naturally immune ■ Cover open cuts and scratches ■ Do not share toothbrushes or razors ■ Clean blood spills with bleach or detergent ■ Do not donate blood, plasma, semen, or tissue
For adults and children who are HBsAg-negative:
■ Can participate in all activities including contact sports ■ Should not be excluded from activities involving casual contact ■ Can share food and utensils

Abbreviations: HBsAg, hepatitis B surface antigen.

Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

Strategies for optimal management of CHB

The American Association for the Study of Liver Diseases (AASLD) has developed algorithms for managing hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients (Figure 4).[1] HBeAg-positive patients with hepatitis B virus (HBV) DNA > 20,000 IU/mL and normal alanine aminotransferase (ALT) levels should be monitored at 3- to 6-month intervals for any changes in ALT levels, and every 6 to 12 months for HBeAg status.[1] Any elevations in ALT levels require more frequent monitoring.[1] Patients with persistently borderline normal or slightly elevated ALT levels may be advised to undergo a liver biopsy, especially if the patient is greater than 40 years of age.[1] These patients should be treated as needed if the liver biopsy shows moderate to severe inflammation or fibrosis. Patients with chronic hepatitis B (CHB) who have a persistent elevation of ALT > 2 times the upper limits of normal (ULN) who remain HBeAg-positive and have HBV DNA levels > 20,000 IU/mL require treatment; a liver biopsy may be considered optional for these patients.[16] Treatment should also be implemented for all HBeAg-positive patients with ALT levels > 2 times the ULN and HBV DNA > 20,000 IU/mL and with jaundice or decompensated liver disease.

For HBeAg-negative patients with normal ALT levels and HBV DNA < 2000 IU/mL, ALT levels should be monitored every 3 months for a year to confirm their inactive carrier status, and then every 6 to 12 months.[1] Any elevations in ALT levels require more frequent monitoring and HBV DNA testing.[1] HBeAg-negative patients with ALT elevations and HBV DNA between 2000 IU/mL and 20,000 IU/mL should be monitored every 3 months; a liver biopsy and treatment may be considered if elevations in ALT levels are persistent.[1] Patients with ALT levels ≥ 2 times ULN and HBV DNA ≥ 20,000 IU/mL should be considered for treatment. A liver biopsy is optional for these patients.

Treatment of CHB. Active viral replication causes the progression of CHB, which provides a rationale for treating active CHB with antivirals to delay or prevent complications.[10] While antiviral treatment does not typically eradicate HBV,[1] durable and effective suppression of HBV DNA has been shown to slow disease progression or reverse hepatic fibrosis and cirrhosis and thereby decrease the risk of hepatic decompensation for patients with advanced cirrhosis and fibrosis.[17] Therefore the goals of antiviral treatment for CHB are the sustained suppression of HBV replication and the remission of liver disease to prevent cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC).[1]

Markers used to assess treatment response include a decrease in the serum HBV DNA level, loss of HBeAg with or without seroconversion as marked by the development of an antibody to hepatitis B e antigen (anti-HBe), the normalization of ALT levels, and an improvement in liver histology.[1] As shown in Table 6, there are different categories of response to antiviral treatment for CHB: biochemical, virologic, primary nonresponse, virologic relapse, histologic, and complete.[1] These categories are used in clinical trials and are also useful in routine practice when assessing a patient's response to an antiviral agent.[18]

Patient selection for treatment. The AASLD recommends treating patients who are at high risk for liver-related morbidity and mortality within the next 5-10 years who

Key Points: Strategies to accurately identify and diagnose CHB

- Early identification of CHB through screening allows prompt treatment that may delay or prevent serious complications as well as reduce the transmission of HBV infection from the infected person
- The AASLD recommends testing for both HBsAg and anti-HBs to screen for CHB
- The AASLD recommends CHB screening for individuals from countries of high or intermediate HBV endemicity, IDUs, MSM, all pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected individuals, individuals who are the source of blood or body fluid exposures that warrant postexposure prophylaxis (eg, needlestick injury to a health care worker), and those with HIV infection
- According to the AASLD, patients should be diagnosed with CHB if they are HBsAg-positive for at least 6 months and have a serum HBV DNA level > 20,000 IU/mL. However lower HBV DNA values (2,000-20,000 IU/mL) are common in HBeAg-negative patients. In addition, patients with CHB may have a persistent or intermittent elevation of ALT/AST levels, and if a liver biopsy is performed, may show evidence of liver injury with moderate or severe necroinflammation
- The initial evaluation of a patient with CHB should include a patient history and physical examination with attention to risk factors for HIV and/or HCV coinfection, family history of HBV and liver cancer, and alcohol and tobacco use. Laboratory tests should include the ALT level, serum albumin test, prothrombin time, bilirubin test; tests for HCV antibody, HDV antibody, and HIV antibody; and serum HBV DNA, HBeAg, and anti-HBeAg tests
- The AASLD recommends a liver biopsy for patients who do not clearly meet criteria for HBV treatment since the additional information obtained by histologic evaluation may influence the decision whether to intervene with treatment or continue to observe the patient
- All patients with CHB should be screened for HCC
- To reduce and prevent HBV transmission, patients with CHB should notify all sexual partners or needle-sharing partners and household contacts that they should be tested for HBV infection and vaccinated, as required; use barrier protection during sexual contact with susceptible persons; cover all open sores; clean all blood spills with bleach or detergent; and not donate blood, plasma, semen, or tissue

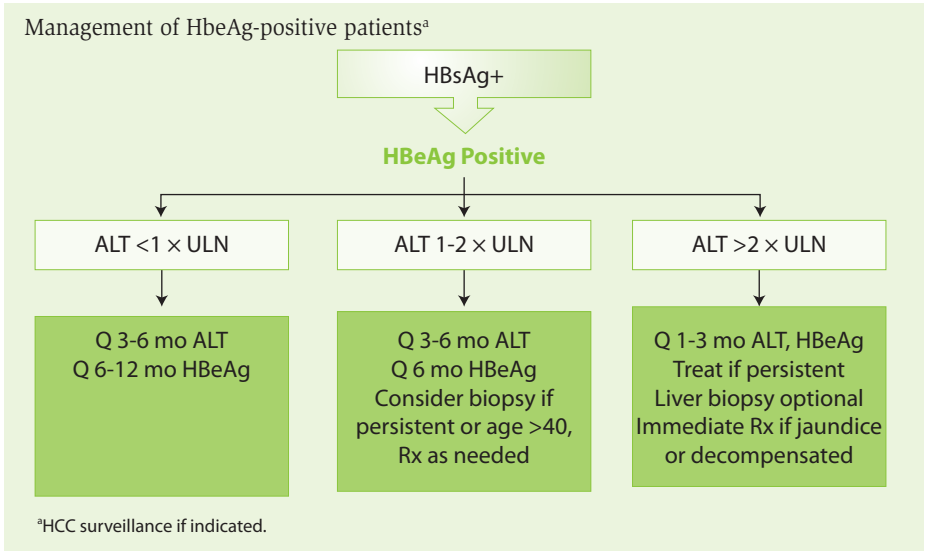

Figure 4. AASLD algorithms for managing HBeAg-positive and HBeAg-negative patients

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatcellular carcinoma; Q, every; ULN, upper limits of normal.

Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

have a high probability of achieving maintained viral suppression during continued treatment.[1] Treatment is also indicated for patients who have a high risk of liver-related morbidity and mortality within the next 10-20 years and a high probability of achieving sustained viral suppression after a defined period of treatment.

Treatment is not indicated for patients who have a low risk of liver-related morbidity or mortality within the next 20 years and have a low probability of achieving sustained viral suppression after a defined period of treatment.[1] As patients progress through the different phases of CHB, the risk of liver-related morbidity and mortality and the probability of the response to treatment may change, and therefore, long-term monitoring is needed for all patients with CHB independent of active treatment.

Available antiviral agents. There are 7 antiviral agents approved for treatment of CHB: 5 oral nucleos(t)ide analogues (NAs) (adefovir, entecavir, lamivudine, telbivudine, and tenofovir) and 2 injectable therapies (standard interferon [IFN] and pegylated interferon [peg-IFN]). Long-acting peg-IFN has largely replaced standard interferons;[19] only peg-IFN-alpha 2a is currently licensed for HBV therapy in the United States. Emtricitabine, which is used alone and in combination with tenofovir for human immunodeficiency virus (HIV) treatment, is under investigation for the treatment of coinfected patients in combination with tenofovir.[20] As discussed below, the AASLD recommends combination therapy with tenofovir plus emtricitabine for certain patients with CHB who are coinfected with HIV and for patients who develop resistance to specific NAs.[1] Data on responses from clinical trials of approved antiviral agents for HBeAg-positive and HBeAg-negative patients are summarized in Tables 7 and 8 (page 6).[1] The durability of response for each agent is also shown.

Factors to consider when selecting an antiviral regimen include safety and efficacy, risks of antiviral drug resistance, costs, patient preference, and patient comorbidities.[1]

Table 6. AASLD definition of response to antiviral treatment of chronic hepatitis B

Response	Description
Biochemical	■ Decrease in serum ALT to within the normal range
Virologic	■ Decrease in serum HBV DNA to undetectable levels by PCR assays, *and* ■ Loss of HBeAg in patients who were initially HBeAg positive
Primary nonresponse (not applicable to interferon therapy)	■ Decrease in serum HBV DNA by < 2 log10 IU/mL after at least 24 weeks of therapy
Virologic relapse	■ Increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least 2 determinations more than 4 weeks apart
Histologic	■ Decrease in histology activity index by at least 2 points *and* ■ No worsening of fibrosis score compared to pretreatment liver biopsy
Complete	■ Fulfill criteria of biochemical and virologic response *and* ■ Loss of HBsAg

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

Because resistance is a concern with long-term treatment for all NAs, it is important to choose an agent that has a low intrinsic risk of resistance.[1] Moreover, an agent with a potent antiviral effect is optimal because studies show that sustained HBV replication is significantly associated with an increased risk of HCC and cirrhosis (Figure 5).[21]

Please see STRATEGIES FOR OPTIMAL MANAGEMENT page 6

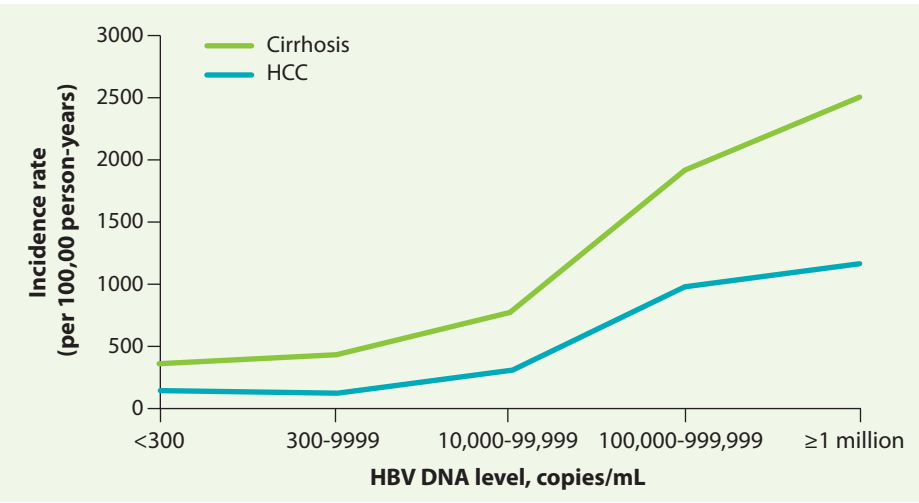

Figure 5. Incidence of hepatocellular carcinoma and liver cirrhosis in the REVEAL study cohort

Source: Reprinted from *Clinics in Liver Disease*, Vol 11(4), Chen CJ, Iloeje UH, Yang HI, Long-term outcomes in hepatitis B: The REVEAL-HBV Study, 797-816. ©2007, with permission from Elsevier.

Table 7. Responses to approved antiviral therapies among previously untreated HBeAg-positive patients with CHB

	Placebo/ Control Groups from Multiple Studies	Standard IFN-α 5 MU qd or 10 MU tiw 12-24 wk	Lamivudine 100 mg qd 48-52 wk	Adefovir 10 mg qd 48 wk	Entecavir 0.5 mg qd 48 wk	Tenofovir 300 mg qd 48 wk	Telbivudine 600 mg qd 52 wk	Peg-IFN-α 180 mcg qw 48 wk
Loss of serum HBV DNA[a]	0%–17%	37%	40%–44%	21%	67%	76%	60%	25%
Loss of HBeAg	6%–12%	33%	17%–32%	24%	22%	NA	26%	30%/34%[b]
HBeAg seroconversion	4%–6%	Difference of 18%	16%–21%	12%	21%	21%	22%	27%/32%[b]
Loss of HBsAg	0%–1%	7.80%	1%	0%	2%	3.2%	0%	3%
Normalization of ALT levels	7%–24%	Difference of 23%	41%–75%	48%	68%	68%	77%	39%
Histologic improvement	NA	NA	49%-56%	53%	72%	74%	65%	38%[c]
Durability of response	NA	80%–90%	50%–80%[d]	≈90%[d]	69%[d]	NA	≈80%	NA

[a]Hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/mL or 5-6 log copies/mL) in standard IFN-α studies and some lamivudine studies, and PCR assays (lower limit of detection approximately 50 IU/mL or 250 copies/mL) in other studies. NA = not available.

[b]Responses at week 48/week 72 (24 weeks after stopping treatment).

[c]Posttreatment biopsies obtained at week 72.

[d]Lamivudine and entecavir – no or short duration of consolidation treatment; adefovir and telbivudine – most patients had consolidation treatment.

Abbreviations: ALT, alanine aminotransferase; HBeAg, antibody to hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN-α, interferon-alfa; MU, million units; NA, no answer; Peg-IFN-α, pegylated interferon-alfa; qd, daily; tiw, three times a week.

Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

Strategies for optimal management continued from page 5

Table 9 summarizes the AASLD recommendations for treatment and duration by HBeAg status, HBV DNA count, and ALT levels. For oral NA therapy, the AASLD recommends tenofovir or entecavir as first-line options for patients who meet the treatment criteria.[1] Entecavir and tenofovir each provide greater efficacy and a high barrier to resistance compared to other oral agents.[10] Lamivudine and telbivudine are not preferred agents because of the risk of resistance unless only a finite course of therapy is planned.[1] The AASLD recommends using adefovir as a second-line agent for previously untreated patients because it is less potent than other NAs and has an increasing risk of rate of resistance after one year of therapy.[1] For example, approximately 30% of previously untreated patients do not respond to adefovir and will not show a 2-log reduction in HBV DNA after 6 months of treatment.[1] All NAs are generally well tolerated.[17]

If interferon therapy is selected, the AASLD recommends peg-IFN.[1] Some patients may be more likely to respond to peg-IFN than others. Predictors of response to peg-IFN in HBeAg-positive patients include pretreatment ALT levels >2 times ULN, lower HBV DNA levels, and infection with HBV genotype A; there are no established predictors of sustained response in HBeAg-negative patients.[1] Adverse effects of peg-IFN include an initial influenzalike illness, fatigue, anxiety, depression, weight loss, loss of appetite, and mild alopecia.[1]

Management of nonresponders. Patients initially treated with either IFN or peg-IFN who do not respond to therapy may be treated with NAs.[1] Response rates to NAs for patients who do not respond to interferons are similar to those of previously untreated patients.[17] Patients initially treated with NAs who achieve a <2 log decrease in their HBV DNA level after a minimum of 6 months of therapy should have their regimen altered, preferably with the addition of a second more potent agent with a nonoverlapping resistance profile.[1]

Duration of therapy. Interferons are given for a finite period; peg-IFN is typically administered for 48 weeks.[1] The treatment duration for NAs is less well defined and continues until certain end points are reached, which also vary depending on HBeAg status.[1] For HBeAg-positive patients, treatment should continue until the patient achieves HBeAg seroconversion, has undetectable serum HBV DNA, and has completed at least 6 months of additional treatment following seroconversion, marked by the emergence of anti-HBe.[1] Patients should be closely monitored for relapse after treatment withdrawal.[1] For HBeAg-negative patients, NA treatment should be continued until the patient has achieved hepatitis B surface antigen (HBsAg) clearance.[1]

All patients should be monitored throughout therapy and, for those treated with interferons, for 24 weeks after treatment. The AASLD-recommended monitoring tests for interferons and NAs for HBeAg-positive and HBeAg-negative patients are shown in Table 10.[1] ■

Table 8. Responses to approved antiviral therapies among previously untreated HBeAg-negative CHB patients

	Placebo/ Control Groups from Multiple Studies	Standard IFN-α 5 MU qd or 10 MU tiw 12-24 wk	Lamivudine 100 mg qd 48-52 wk	Adefovir 10 mg qd 48 wk	Entecavir 0.5 mg qd 48 wk	Tenofovir 300 mg qd 48 wk	Telbivudine 600 mg qd 52 wk	Peg-IFN-α 180 mcg qw + lamivudine 100 mg 48 wk
Loss of serum HBV DNA[a]	0%–20%	60%-70%	60%–73%	51%	90%	93%	88%	63%
Normalization of ALT	10%–29%	60%-70%	60%–79%	72%	78%	76%	74%	38%
Histologic improvement	33%	NA	60%-66%	64%	70%	72%	67%	48%
Durability of response	Control	10%–20%	<10%	≈5%	3%	NA	NA	≈20%

[a]Hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/mL or 5-6 log copies/mL) in standard IFN- α studies and some lamivudine studies, and PCR assays (lower limit of detection approximately 50 IU/mL or 250 copies/mL) in other studies. Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; IFN-α, interferon-alfa; MU, million units; NA, not available; Peg-IFN-α, pegylated interferon-alfa; qd, daily; tiw, three times a week.
Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36. Reproduced with permission.

Table 9. AASLD recommendations for treatment of chronic hepatitis B infection

HBeAg	HBV DNA (PCR)	ALT	Treatment Strategy
Positive	>20,000 IU/mL	≤ 2x ULN	■ Observe; consider treatment when ALT becomes elevated ■ Consider biopsy in persons >40 years, ALT persistently high normal-2x ULN, or with family history of HCC. ■ Consider treatment if HBV DNA >20,000 IU/mL and biopsy shows moderate/severe inflammation or significant fibrosis
Positive	>20,000 IU/mL	>2x ULN	■ Observe for 3-6 months and treat if no spontaneous HBeAg loss ■ Consider liver biopsy prior to treatment if compensated. Immediate treatment if icteric or clinical decompensation ■ Initial therapy: NAs (TDF or ETV preferred), IFN or peg-IFN (preferred) ■ End point of treatment: seroconversion from HBeAg to anti-HBe ■ Duration of therapy: —IFN: 16 weeks —Peg-IFN: 48 weeks —NAs: minimum 1 year, continue for at least 6 months after HBeAg seroconversion
Negative	>2,000 IU/mL	>2x ULN	■ Initial therapy: NAs (TDF or ETV preferred) or IFN or peg-IFN (preferred) ■ End point of treatment: not defined ■ Duration of therapy: —IFN/peg-IFN: 1 year —NAs: >1 year
	>2,000 IU/mL	1-2x ULN	■ Consider liver biopsy and treat if liver biopsy shows moderate/severe necroinflammation or significant fibrosis
	≤ 2,000 IU/mL	1 ≤ ULN	■ Observe, treat if HBV DNA or ALT becomes higher
Positive or negative	Detectable	Cirrhosis: Compensated	■ HBV DNA >2000 IU/mL: —Treat: NAs (TDF or ETV preferred) ■ HBV DNA <2000 IU/mL: —Consider treatment if ALT is elevated ■ Refer for liver transplant
		Cirrhosis: Decompensated	■ Treat with LAM (or LdT) + ADV, TDF, or ETV ■ Refer for liver transplant
	Undetectable	Cirrhosis: Compensated	■ Observe
		Cirrhosis: Decompensated	■ Refer for liver transplant

Abbreviations: ADV, adefovir; ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, standard interferon; LAM, lamivudine; LdT, telbivudine; NAs, nucleoside/nucleotide analogues; PCR, polymerase chain reaction; peg-IFN, pegylated interferon; TDF, tenofovir; ULN, upper limits of normal.
Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36. Reproduced with permission.

Table 10. Recommended monitoring tests and timing during CHB antiviral therapy and posttreatment

			Treatment Period	
Antiviral Therapy	HBeAg Status	Test	During Therapy	Posttreatment
Interferon	HBeAg+ and HBeAg-	Blood counts Liver panel	Every 4 weeks	Every 12 weeks for first 24 weeks
		TSH HBV DNA	Every 12 weeks	Every 12 weeks for first 24 weeks
	HBeAg+ only	HBeAg Anti-HBe	Every 24 weeks	Every 12 weeks for first 24 weeks
Oral nucleos(t)ides	HBeAg+ and HBeAg-	Liver panel HBV DNA	Every 12 weeks Every 12-24 weeks	
	HBeAg+ only	HBeAg Anti-HBe	Every 24 weeks	
	HBeAg- with persistently undetectable HBV DNA	HBsAg	Every 6 to 12 months	

Abbreviations: Anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TSH, thyroid stimulating hormone.
Source: Data from Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36.

Key Points: Strategies for optimal management of CHB

- Monitor HBeAg-positive patients with HBV DNA > 20,000 IU/mL and normal ALT levels at 3- to 6-month intervals for changes in ALT levels and every 6 to 12 months for HBeAg status. Consider a liver biopsy for patients with persistently borderline normal or slightly elevated ALT levels, especially those > 40 years of age
- Treat HBeAg-positive patients with persistent elevation of ALT > 2 times the ULN who remain HBeAg-positive and have HBV DNA levels > 20,000 IU/mL; a liver biopsy is optional
- Treat all HBeAg-positive patients with ALT > 2 times the ULN and HBV DNA > 20,000 IU/mL and with jaundice or decompensated liver disease
- Monitor ALT levels in HBeAg-negative patients with normal ALT levels and HBV DNA < 2000 IU/mL every 3 months for a year to confirm their inactive carrier status, and then every 6 to 12 months
- Monitor HBeAg-negative patients with elevated ALT levels and HBV DNA between 2000 IU/mL and 20,000 IU/mL every 3 months; a liver biopsy and treatment may be considered if ALT elevations are persistent. Consider treatment for patients with ALT levels ≥ 2 times ULN and HBV DNA ≥ 20,000 IU/mL; a liver biopsy is optional
- Treat patients who have a high risk of liver-related morbidity and mortality within the next 5-10 years and a high probability of achieving maintained viral suppression during continued treatment or who have a high risk of liver-related morbidity and mortality within the next 10-20 years and a high probability of achieving sustained viral suppression after a defined period of treatment
- Do not treat patients who have a low risk of liver-related morbidity or mortality within the next 20 years and with a low probability of achieving sustained viral suppression after a defined period of treatment
- For oral NA therapy, the AASLD recommends tenofovir or entecavir as first-line options because they provide greater efficacy and a high barrier to resistance compared to the other oral agents. Lamivudine and telbivudine are not preferred because of the risk of resistance, and adefovir is a second-line agent because it is less potent than other NAs and has an increasing risk of inducing resistance after one year of therapy
- For injection therapy, the AASLD prefers peg-IFN as the first-line medication
- Peg-IFN treatment duration is finite and typically lasts for 48 weeks; treatment duration for NAs may be indefinite. For HBeAg-positive patients, continue NA treatment until the patient achieves HBeAg seroconversion, has undetectable serum HBV DNA, and has completed at least 6 months of additional treatment following seroconversion. For HBeAg-negative patients, continue NA treatment until the patient has achieved HBsAg clearance

Strategies to prevent and manage antiviral resistance

Selection of antiviral resistant mutations is a concern with long-term nucleoside/nucleotide analogues (NAs) therapy but not with interferons.[1,17] Antiviral resistance and lack of adherence are the primary contributors to NA treatment failure among patients with chronic hepatitis B (CHB).[16]

Development of resistance leads to viral rebound and eventual reversal of biochemical and histological improvements and, in some cases, can precipitate hepatic flares and decompensation.[1,10] In addition, because cross-resistance occurs among agents, resistance to one agent can limit substitution for another later in therapy.[1] Furthermore, sequential use of NA monotherapies can lead to the sequential selection of mutations that confer resistance to the initial NA and subsequent NAs used as rescue therapy.[16] Therefore, reducing the risk of resistance is essential to successful, long-term HBV treatment.

Resistance rates for approved NAs are shown in Table 11.[19,22,23] Both entecavir and tenofovir are potent agents with a high genetic barrier to resistance,[6] which for NAs used to treat HBV is defined as the presence of unique nucleotide and corresponding deduced amino acid mutations in the HBV polymerase gene that have been previously demonstrated to be associated with antiviral resistance.[16] Among previously untreated patients, there is no reported resistance with tenofovir to date and the risk of resistance with entecavir is low for patients not previously treated with NAs.[19,22,23] Telbivudine has a low genetic barrier to resistance and is associated with high rates of resistance among patients with high HBV DNA levels at baseline or detectable levels after 6 months of therapy.[6] Resistance rates during long-term therapy are high with adefovir and approach 70% with lamivudine monotherapy at 5 years.[19]

The American Association for the Study of Liver Diseases (AASLD) recommends several strategies to prevent and manage antiviral resistance (Table 12).[1] These include choosing the most potent agent with the highest genetic barrier to resistance, avoiding unnecessary treatment (eg, do not treat patients with minimal disease or those who are unlikely to achieve a sustained virologic response, such as patients younger than age 30), and reinforcing adherence to therapy. Patients should be educated regarding the risks associated with missed doses of antiviral therapy, such as reduced efficacy and the potentially increased risk of resistance, and adherence should be discussed and documented at each patient visit. Other strategies include the use of automated prescription services, daily pill boxes, and/or other memory aids. In addition, HBV DNA levels should be monitored every 3 to 6 months for antiviral response.[1,6] Table 12 also shows treatment strategies to address the development of resistance to specific NAs.[1] ■

Table 11. Viral resistance rates for available nucleosides and nucleotides

		Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
HBeAg-positive patients	At 1 year	15%-30%[a]	None[a]	None in nucleoside-naïve patients[ab]	6%[a]	0%[a]
	At > 1 year	70% at 5 years[a]	No data[a] available	< 1% up to 4 years in nucleside-naïve patients[a]	25 at 2 years[c]	0%[d]
HBeAg-negative patients	At 1 year	15%-30%[a]	None[a]	None[a]	4%[a]	0%[a]
	At > 1 year	70% at 5 years[a]	29% at 5 years[a]	< 1% up to 4 years[a]	11% at 2 years[b]	0%[d]

[a]Dienstag JL. Hepatitis B virus infection. *N Engl J Med*. 2008;359:1490,1491.
[b]Liaw YF, Gane E, Leung N, et al. 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology*. 2009;136:490.
[c]Marcellin P, Healthcote EJ, Jacobson I, et al. Safety and tolerability of 96 weeks of tenofovir disoproxil fumarate (TDF) treatment in HBeAg negative and positive patients infected with chronic hepatitis B (CHB). Poster presented at: 44th Annual Meeting of the European Association for the Study of the Liver; Copenhagen, Denmark, April 22–26, 2009; Copenhagen, Denmark.
[d]In lamivudine-resistant patients, viral resistance was 7% during year 1 of therapy and up to 43% at year 4.
Abbreviations: HBeAg, hepatitis B e antigen.

Table 12. Management of resistance

Prevention	
■ Avoid unnecessary treatment ■ Initiate treatment with potent antiviral that has low rate of drug resistance or with combination therapy ■ Switch to alternative therapy in patients with primary nonresponse	
Monitoring	
■ Test for serum HBV DNA (PCR assay) every 3-6 months during treatment ■ Check for medication compliance in patients with virologic breakthrough ■ Confirm antiviral resistance with genotypic testing	
Treatment	
Lamivudine resistance	■ Add adefovir or tenofovir ■ Stop lamivudine, switch to tenofovir + emtricitabine[a]
Adefovir resistance	■ Add lamivudine[b] ■ Stop adefovir, switch to tenofovir + emtricitabine[a] ■ Switch to or add entecavir[b]
Entecavir resistance	■ Switch to tenofovir or tenofovir + emtricitabine[a]
Telbivudine resistance[c]	■ Add adefovir or tenofovir ■ Stop telbivudine, switch to tenofovir + emtricitabine[a]

[a]In HIV coinfected persons; minimal data are available in non–HIV-infected persons.
[b]Durability of viral suppression unknown, especially in patients with prior lamivudine resistance.
[c]Clinical data not available.
Abbreviations: HBV, hepatitis B virus; PCR, polymerase chain reaction.
Source: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36. Reproduced with permission.

Key Points: Strategies to prevent and manage antiviral resisitance

- To prevent resistance, the AASLD recommends choosing the most potent agent with the highest genetic barrier to resistance, avoiding unnecessary treatment, and reinforcing adherence to therapy. Monitor HBV DNA levels every 3 to 6 months for antiviral response
- To manage lamivudine resistance, add adefovir or tenofovir, or stop lamivudine and switch to tenofovir + emtricitabine. For adefovir resistance, add lamivudine, or stop adefovir and switch to tenofovir + emtricitabine, or switch to or add entecavir. For entecavir resistance, switch to tenofovir or tenofovir + emtricitabine. For telbivudine resistance, add adefovir or tenofovir, or stop telbivudine and switch to tenofovir + emtricitabine

SPECIAL POPULATIONS continued from page 8

HBV DNA should be advised regarding the available, albeit limited, data on the use of NA therapy in the third trimester to prevent mother to infant transmission.

Immunosuppression and chemotherapy. Approximately 20% to 50% of hepatitis B carriers experience a reactivation of HBV replication accompanied by rising HBV DNA levels and ALT level elevations during immunosuppressive treatment or chemotherapy.[1] Reactivation is more likely with the use of rituximab or corticosteroids.[1,51,52] Therefore, the AASLD recommends that all patients who are scheduled for chemotherapy or immunosuppressive therapy, and particularly those considering treatment with rituximab, be screened for HBsAg and antibody to hepatitis B core antigen (anti-HBc).[1]

The AASLD also recommends that patients who are HBsAg-positive receive prophylactic NA treatment before and after chemotherapy or immunosuppressive therapy.[1] Interferons should be avoided with this patient population because of hematologic side effects.[1] For patients with a baseline HBV DNA level < 2000 IU/mL, NA treatment should be continued for 6 months following completion of chemotherapy or immunosuppressive therapy.[1] For patients with a baseline HBV DNA level > 2000 IU/mL), NA treatment should be continued until they reach the same treatment end points recommended for immunocompetent patients. If the expected duration of immunosuppressive treatment is short (< 12 months) and baseline HBV DNA is undetectable, lamivudine or telbivudine may be used as prophylactic therapy.[1] Tenofovir or entecavir is preferred if the use of immunosuppressive therapy or chemotherapy for a longer duration is expected. ■

Strategies to manage CHB in special populations

HIV coinfection. Chronic hepatitis B (CHB) coinfection occurs in approximately 6% to 13% of all human immunodeficiency virus (HIV)-positive patients.[1] The criteria for CHB treatment in coinfected patients are the same as for those without HIV,[1] but prompt treatment of patients with HIV and CHB is important for they are at greater risk of liver-related mortality and cirrhosis.[24-27]

The American Association for the Study of Liver Diseases (AASLD) recommends simultaneous treatment for CHB and HIV, with a regimen that includes 2 agents with activity against HIV and hepatitis B virus (HBV).[1,6] In patients not previously treated for HIV or HBV, the AASLD recommends combination therapy with tenofovir and lamivudine or tenofovir and emtricitabine.[1,20,28-31] Tenofovir is effective against lamivudine-resistant HBV[32] and should be added to the regimen of coinfected patients on antiretroviral therapy (ART) with lamivudine resistance.[1]

Patients already on an effective ART regimen for HIV that does not include an agent with activity against HBV may be treated with either pegylated interferon (peg-INF) or adefovir, depending on the CD4 cell count.[1] Patients with CD4 cell counts >500 cells/mm^3 can be treated with peg-IFN;[1,33] adefovir is recommended for those with lower CD4 cell counts or those who are hepatitis B e antigen (HBeAg)-negative.[1] On the other hand, in consultation with the patient's HIV treating clinician, the ART regimen may also be modified to add tenofovir. HBeAg-positive patients not scheduled to start ART for HIV in the near future should be treated for CHB with either peg-IFN or adefovir,[1] although the combination of telbivudine and adefovir can also be an option.[6] However, many HIV experts would consider implementing a regimen for both HIV and HBV for such persons. In addition, earlier initiation of ART for HIV should be considered for HBeAg-negative patients in whom long-term NA therapy is frequently required.[1] It is important to note that HBV monotherapy with lamivudine, emtricitabine, and/or telbivudine should not be prescribed for any coinfected patients because of the unacceptably high risk of selection for HBV-resistant mutations. Whenever ART regimens for HIV are modified, antiviral agents active against HBV should not be discontinued without substituting another antiviral that is also active against HBV, unless the patient has undergone HBeAg seroconversion and has completed an adequate course of consolidation treatment.[1]

HCV coinfection. An estimated 14% of patients with CHB in the United States are coinfected with hepatitis C virus (HCV).[34] Coinfected patients are at greater risk of cirrhosis and hepatocellular carcinoma (HCC) than patients who have either HCV or CHB alone.[34,35]

Because data are lacking, the AASLD guidelines do not provide recommendations on the treatment of patients with CHB who are coinfected with HCV.[1] Available evidence suggests that standard IFN or peg-IFN and ribavirin (RBV) for HCV are as effective in treating patients coinfected with HBV/HCV as in treating patients with HCV infection alone.[36-39] However, rebound in serum HBV DNA levels and reactivation of HBV have been reported.[36,38,39] For a patient coinfected with HBV/HCV, markers of HBV replication (HBV DNA and HBeAg) and HCV replication (HCV RNA) should be obtained. HBV DNA levels are often suppressed in coinfected patients, and it may therefore be more appropriate to focus on therapy for HCV.[6] In the absence of definitive, randomly assigned controlled trials, some experts recommend initial treatment with peg-IFN and RBV at the doses approved for HCV treatment.[6] However, since RBV does not appear to have any effect on HBV response, if the patient demonstrates insufficient HCV RNA response at week 12 or 24, RBV may be discontinued; however the course of peg-IFN should be maintained for 48 weeks targeting the HBV infection. Patients who do not achieve an HBV response following a 48-week course of treatment with peg-IFN may be treated with NAs according to standard guidelines for therapy;[1] it is important to note that these NAs have no activity against HCV.

HDV infection. Hepatitis D virus (HDV) is a satellite virus that is dependent on active HBV replication.[1] IFN is the only approved treatment for chronic hepatitis D;[1] however, recent trials show peg-IFN is also effective against this virus.[40,41] Lamivudine alone or in combination with interferon has no additional benefit in treating HDV infections.[42,43] In addition, most studies indicate that oral NAs are not effective for HDV infection.[6,44]

HBsAg-positive pregnant women. Although the implementation of HBV vaccination recommendations since 1990 has markedly reduced the incidence of acute HBV in infants and children in the United States,[7,8] perinatal transmission still occurs. There were a total of 83 cases of perinatal transmission reported in 2007 in the United States, which most likely represents less than 1 of 10 of the actual infections that occurred.[8]

The AASLD recommends the immediate (<24 hours) administration following delivery of hepatitis B immune globulin (HBIG) and HBV vaccination to all children born to hepatitis B surface antigen (HBsAg)-positive women.[1] In conjunction with completion of the 3-dose HBV vaccine series, these preventive measures have been shown to reduce the risk of perinatal transmission by 85% to 96%.[10, 45-47] However, efficacy may be lower for women with very high HBV DNA levels.[1] All HBsAg-positive women who are pregnant should be counseled to inform their health care providers about their HBsAg status to ensure their newborn receives HBIG and an HBV vaccination. Administration of NAs to the newborn is not recommended. Patients should be closely monitored following delivery because CHB can be exacerbated following pregnancy, even among women treated with lamivudine during the third trimester.[6,48]

Guidance from the AASLD on the treatment of HBsAg-positive women during pregnancy is limited. Some evidence suggests that lamivudine treatment in the third trimester of women with high HBV DNA levels decreases the risk of intrauterine and perinatal transmission.[6,49,50] In addition, substantial data has accumulated on the safety of tenofovir and/or lamivudine or emtricitabine in HIV-positive pregnant women.[49] Lamivudine, adefovir, and entecavir are pregnancy category C drugs; tenofovir and telbivudine are category B drugs.[49] However, it is important to note that the use of NAs during pregnancy remains controversial. At this time, HBV DNA and serum alanine aminotransferase (ALT) levels should be monitored during pregnancy; women with high levels of

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CHB COMMON GROUND GAZETTE
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