Experts Address FAQs About Chronic Hepatitis B

PIM Postgraduate Institute for Medicine

healthmatterscme A CONTINUING MEDICAL EDUCATION COMPANY

This activity is jointly sponsored by Postgraduate Institute for Medicine and HealthmattersCME.

GILEAD Advancing Therapeutics. Improving Lives.

This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.

A CME/CE-Certified Enduring Material
Release Date: June 15, 2010
Expiration Date: June 15, 2011
Estimated time to complete this activity: 1.5 hours

Postgraduate Institute for Medicine

This activity is jointly sponsored by Postgraduate Institute for Medicine and HealthmattersCME.

Target Audience

This activity has been designed to meet the educational needs of health care providers who care for patients with chronic hepatitis B (CHB), including physicians, physician assistants, nurse practitioners, and registered nurses.

Program Overview

Despite the considerable progress made during the last decade in the understanding and treatment of CHB—particularly the introduction of effective antiviral medications—morbidity and mortality from CHB remains unacceptably high. Most individuals with CHB remain undiagnosed and unaware of their infection until serious complications, such as hepatocellular carcinoma (HCC) and cirrhosis, appear in the later stages of the disease, creating a significant burden of potentially preventable disease. In addition, many clinicians are unfamiliar with recent treatment guidelines, such as those from the American Association for the Study of Liver Diseases (AASLD) or the treatment algorithm developed by a panel of expert hepatologists, that provide recommendations for the prevention, identification, and management of CHB. All providers of CHB care need a practical resource guide to ensure the maximum identification and management of persons living with CHB.

B Aware: Experts Address FAQs About Chronic Hepatitis B is a resource booklet that poses the fundamental questions many clinicians have about screening, diagnosis, and treatment of CHB, and provides brief responses supported by the available data to answer these questions or better inform clinicians about these issues.

Learning Objectives

After completing this activity, participants will be better able to:

- Identify those at risk to screen for hepatitis B infection
- Describe how to diagnose CHB infection
- Outline treatment recommendations for CHB infection
- Describe how to monitor and manage CHB infection
- Explain how to prevent or limit the development of resistance in the treatment of CHB infection

Editors

Willis C. Maddrey, MD, MACP
Professor
UT Southwestern Medical Center
Dallas, TX

Tram T. Tran, MD
Associate Professor of Medicine
Geffen UCLA School of Medicine
Medical Director, Liver Transplant Program
Cedars-Sinai Medical Center
Los Angeles, CA

Physician Continuing Medical Education

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and HealthmattersCME. PIM is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

Postgraduate Institute for Medicine designates this educational activity for a maximum of *1.5 AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nursing Continuing Education

CREDIT DESIGNATION

This educational activity for 1.6 contact hours is provided by Postgraduate Institute for Medicine.

ACCREDITATION STATEMENTS

Postgraduate Institute for Medicine is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CALIFORNIA BOARD OF REGISTERED NURSING

Postgraduate Institute for Medicine is approved by the California Board of Registered Nursing, Provider Number 13485 for 1.9 contact hours.

Disclosure of Conflicts of Interest

Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies mentioned in this activity, and patient care recommendations. PIM is committed to providing its learners with high-quality CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity.

Willis C. Maddrey, MD, MACP

Consulting Fees: Fees for consulting on advisory boards related to drug safety for Merck & Co., Inc., Novartis, Human Genome Sciences

Tram T. Tran, MD

Consulting Fees: Bristol-Myers Squibb, Gilead Sciences, Inc

Fees for Non-CME: Bristol-Myers Squibb, Gilead Sciences, Inc

The following PIM planners and managers, Jan Hixon, RN, BSN, MA; Trace Hutchison, PharmD; Julia Kimball, RN, BSN; Samantha Mattiucci, PharmD; Patricia Staples, MSN, NP-C, CCRN; and Jan Schultz, RN, MSN, CCMEP, hereby state that they or their spouse/life partner

do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

The following HealthmattersCME planner/manager, James Murphy, hereby states that he or his spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months; and HealthmattersCME ANCC planner, Carla Molliner, PA-C, MHS, has disclosed the following financial relationship: consulting fees for Schering-Plough (Hepatitis C Advisory Board).

Method of Participation and Request for Credit

There are no fees for participating and receiving CME credit for this activity. During the period May 31, 2010 through May 31, 2011, participants must read the learning objectives and faculty disclosures and study the educational activity.

PIM supports Green CME by offering your Request for Credit online. If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID "7216". Upon your registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

MEDIA: monograph

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Postgraduate Institute for Medicine (PIM), HealthmattersCME, and Gilead Sciences do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, HealthmattersCME, and Gilead Sciences. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.

Dear Health Care Professional:

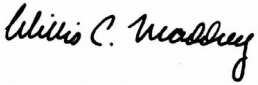
Chronic hepatitis B (CHB) is a serious illness that can lead to severe consequences, such as cirrhosis and hepatocellular carcinoma. In many patients, CHB remains undiagnosed until signs and symptoms of more advanced liver disease become apparent. Until recently, there were few treatment options for patients with CHB, but now there are a number of antiviral agents available that are both effective against hepatitis B virus (HBV) and tolerable for the patient. However, many clinicians have questions about prevention, diagnosis, and treatment selection and duration.

This program provides answers for clinicians about the management of CHB derived from recommendations from experts and key organizations, including the American Association for the Study of Liver Diseases. Topics addressed include screening of individuals at risk for HBV infection, prevention and vaccination, selection of first-line antiviral agents, treatment criteria, treatment duration and monitoring, and strategies to manage antiviral resistance. In addition, this program discusses the most recent information and recommendations available on the treatment of special populations with CHB, such as pregnant women; patients 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 answering key questions they may have about screening, diagnosis, and management of care for patients with CHB. In turn, this CME activity will benefit patients with CHB by increasing awareness of this disease among health care providers, thereby encouraging screening, which will in turn prompt earlier diagnosis and more optimal treatment.

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

Sincerely,



Willis C. Maddrey, MD, MACP
Professor of Internal Medicine
UT Southwestern Medical Center
Dallas, TX

Tram T. Tran, MD
Associate Professor of Medicine
Geffen UCLA School of Medicine
Medical Director, Liver Transplant Program
Cedars-Sinai Medical Center
Los Angeles, CA

HBaware

table of contents

editors

Willis C. Maddrey, MD, MACP
Professor of Internal Medicine
UT Southwestern Medical Center
Dallas, TX

Tram T. Tran, MD
Associate Professor of Medicine
Geffen UCLA School of Medicine
Medical Director, Liver Transplant Program
Cedars-Sinai Medical Center
Los Angeles, CA

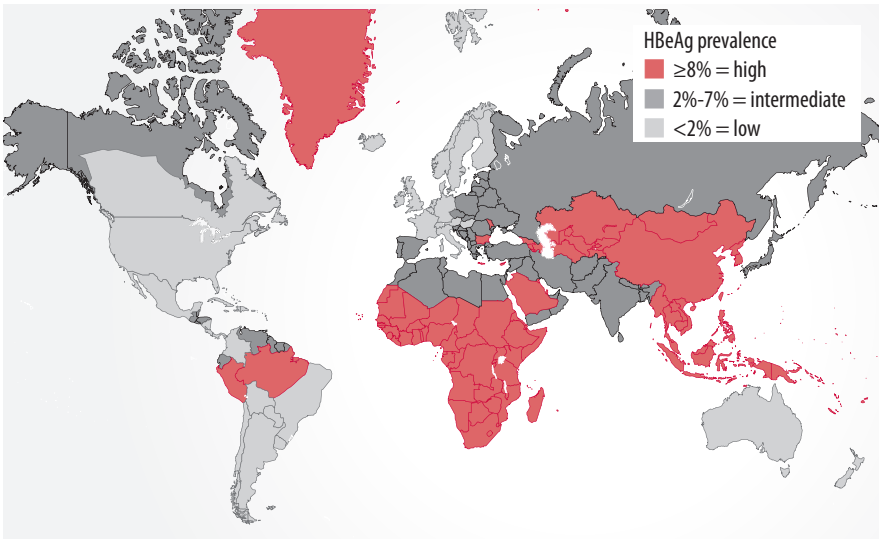
INTRODUCTION

Chronic hepatitis B (CHB) is a serious and prevalent disease in the United States.[1] Approximately 1.25 million-2 million persons living in the US have CHB, but many are not diagnosed or treated.[2-4] Because CHB can lead to severe complications, including cirrhosis and liver cancer, this lack of timely identification and treatment leads to a high burden of potentially preventable disease.[2] CHB is responsible for approximately 2000 to 4000 deaths per year and individuals with CHB are the primary source of new hepatitis B virus (HBV) infections.[2] However, timely screening, diagnosis, and treatment can reduce the burden of this disease and improve outcomes.[2,5]

Hepatitis B virus routes of transmission

HBV is transmitted through mucosal or percutaneous exposure to infectious blood or body fluids.[2] The primary routes of transmission are sexual contact, perinatal exposure to a mother with CHB, needle sharing by injection drug users (IDUs), or needlestick injuries in health care settings. In the US, most of the burden of CHB is borne by individuals who emigrated from countries where HBV is of intermediate or high endemicity. As shown in **Figure 1**, HBV prevalence rates vary by region.[2] As described further below, individuals from these countries should be routinely screened for CHB.[2]

Figure 1. Estimated worldwide distribution of CHB infection—2006



HBeAg, hepatitis B e antigen.

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 phases

Most cases of acute HBV in adults resolve with patients clearing hepatitis B surface antigen (HBsAg) from the blood and developing antibodies to HBsAg; however, a small percentage (< 5%) of adults will go on to develop CHB. CHB is more common in those infected as infants or young children; evidence suggests that more than 90% of infants infected perinatally and 25% to 50% of children infected between ages 1 to 5 years develop CHB.[2] Furthermore, these patients who develop CHB are at high risk of dying from CHB complications; approximately 25% of all persons infected as young children eventually die of liver cancer or cirrhosis.[2]

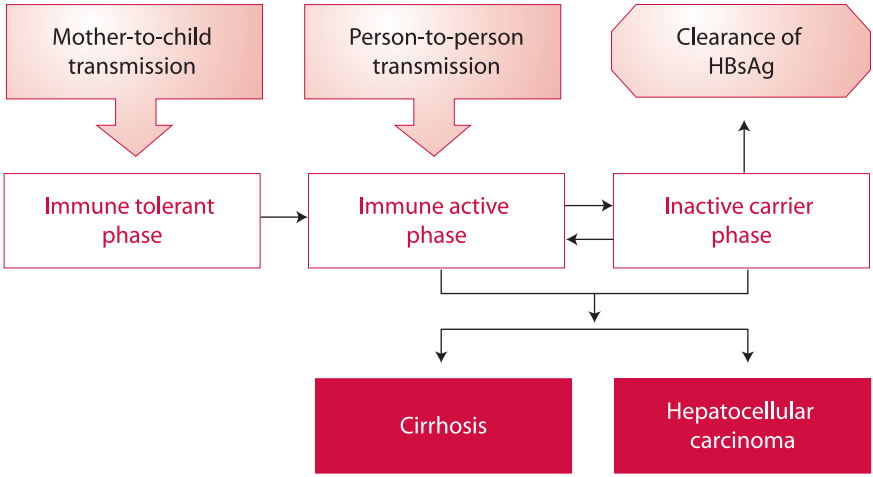
CHB typically evolves through different phases (**Figure 2**).[1,6] The National Institutes of Health Consensus Development Conference on Management of Hepatitis B defined the 3 main phases of CHB as immune tolerant, immune active, and inactive carrier.[1] Movement between phases is not necessarily in one direction; patients may move from the immune active phase to the inactive carrier phase and then experience an HBV reactivation and transition to CHB.[1-6] Terms commonly used to describe the clinical course of HBV infection, such as HBV reactivation, are defined in **Table 1**.[7]

- The immune tolerant phase, which commonly occurs in individuals with perinatally acquired HBV infection, is characterized by high levels of HBV DNA, normal or minimally elevated alanine aminotransferase (ALT) levels, and hepatitis B e antigen (HBeAg)-positive status. Although the immune tolerant phase may persist for decades, most individuals eventually move into the immune active phase. In regions where most individuals contract HBV as adults, such as the United States, most patients enter directly into the immune active phase and do not pass through the immune tolerant phase.[1,6]

- The immune active phase is characterized by either HBeAg-positive or HBeAg-negative status, elevated HBV DNA levels, elevated ALT levels, and liver inflammation.[1] Patients in the immune active phase of CHB have the greatest risk of progressive liver disease.[1] Many patients in the immune active phase eventually undergo HBeAg seroconversion, develop antibodies to HBeAg (anti-HBe), and enter the inactive carrier phase.[1]

- The inactive carrier phase is characterized by presence of anti-HBe, low HBV DNA levels (< 2000 IU/mL), persistently normal ALT levels, and minimal liver inflammation.[1,6] Although inactive carriers have a low risk for progression to more severe liver disease, they remain at risk for HBV reactivation and progression to cirrhosis or hepatocellular carcinoma (HCC).[1,6]

Figure 2. Phases of CHB infection



HBsAg, hepatitis B surface antigen.

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.

Table 1. Terms commonly used to describe HBV infection

HBV acute exacerbation or flare	Intermittent increase of ALT to > 10 x ULN and > 2 x baseline
HBV reactivation	Reappearance of active necroinflammatory disease of the liver in a person known to be in the inactive HBsAg carrier state or to have resolved hepatitis B
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; associated with a reduction in serum HBV DNA to <20,000 IU/mL
HBeAg reversion	Reappearance of HBeAg in a person who was previously HBeAg-negative and anti-HBe-positive
Resolution	Loss of HBsAg and no further virologic, biochemical, or histologic evidence of active virus infection or disease

Anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limits of normal.

Reprinted from *Clinical Gastroenterology and Hepatology*, Vol 6(12), Keeffe EB, Dieterich DT, Han SB, et al, A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 Update, 1315-1341, © 2008, with permission from Elsevier.

SCREENING & PREVENTION

Who should be screened for CHB?

The Centers for Disease Control and Prevention (CDC) recently revised its recommendations for CHB screening.[2] The objective of screening individuals is to reduce HBV transmission and prevent or delay serious complications of untreated CHB.[2] The CDC recommends risk-based rather than universal screening because the CHB prevalence rate is low (0.3%) in the US general population.[2]

Screening is recommended for members of populations at high risk for HBV infection, including injection drug users, men who have sex with men, and immigrants from regions of high endemicity. Areas with HBsAg prevalence ≥ 2% include all Asian, African, and South Pacific Island countries except Australia and New Zealand; all countries in the Middle East except Cyprus and Israel; Malta and Spain on the European Mediterranean; indigenous populations in Alaska, Northern Canada, and Greenland; Ecuador, Guyana, Suriname, Venezuela, and the Amazon regions of Bolivia, Brazil, Colombia, and Peru in South America; all countries in Eastern Europe except Hungary; Antigua and Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos in the Caribbean; and Guatemala and Honduras in Central America.[2,8] Although the CDC continues to recommend screening of indigenous populations in Alaska, routine childhood immunization for HBV during the past 25 years has reduced the incidence of CHB in Alaskan Natives to a level comparable with that of the general US population.[9-11]

In addition, all pregnant women, patients undergoing hemodialysis, those infected with human immunodeficiency virus (HIV), and any patients scheduled for immunosuppressive therapy or chemotherapy should be tested for CHB. **Table 2** lists groups recommended for routine CHB screening.[2]

Table 2. CHB screening recommendations for US population

■ Blood, organ, plasma, semen, tissue donors
■ Hemodialysis patients
■ All pregnant women
■ Infants born to HBsAg-positive mothers
■ Household contacts, needle-sharing or sex partners of HBV-infected persons
■ Sources of blood or body fluid exposures that might warrant postexposure prophylaxis
■ Persons born in countries with HBsAg prevalence ≥2%
■ HIV-infected persons
■ Persons with select medical conditions (eg, elevated ALT or AST levels of unknown etiology)
■ Persons with behavioral exposures (eg, injection drug users, men who have sex with men)
■ Unvaccinated children of persons from countries with ≥8% prevalence

ALT, alanine aminotransferase; AST, aspartate aminotransferases; HBsAg, hepatitis B virus surface antigen; HIV, human immunodeficiency virus.

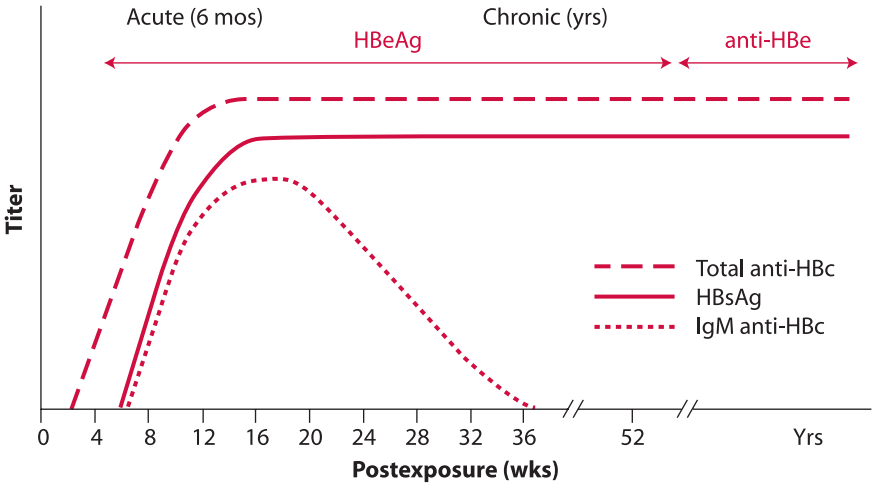
Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57:(RR-8)1-20.

How are serologic markers for HBV interpreted?

Detectable serologic profiles change as HBV infection progresses from acute to chronic infection (**Figure 3**).[2] Measurable serologic markers of HBV infection include HBsAg, anti-HBs, HBeAg, anti-HBe, immunoglobulin M antibody to hepatitis B core antigen (IgM anti-HBc), total hepatitis B core antibody (total anti-HBc; includes IgM anti-HBc and immunoglobulin G antibody to HBc antigen), and HBV DNA (**Table 3**).[2,12] The typical interpretation of common tests for HBV infection is shown in **Table 4**.[2,13]

HBsAg is the only serologic marker detected during the first few weeks following acute infection. Approximately 1-2 months after the initial acute HBV infection, total anti-HBc appears; total anti-HBc persists for the duration of life in most patients. Acute infection within 6 months is indicated by presence of IgM anti-HBc. Patients who recover from HBV infection clear HBsAg and HBV DNA from the blood and develop anti-HBs. Patients with CHB do not clear HBsAg and HBV DNA from the blood, and do not develop anti-HBs.

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



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.

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.

HBeAg can be detected during both acute HBV infection and CHB. Most CHB patients will eventually clear HBeAg from the blood and develop anti-HBe. The presence of HBeAg is generally associated with more active disease;[2] however, HBeAg-negative status should not be interpreted to mean that the disease is inactive. HBeAg-negative patients can have mutations in the core or precore regions of the HBV genome that allow active viral replication and disease progression with abolished or diminished

Table 3. Serologic markers of hepatitis B virus infection	
Hepatitis B surface antigen (HBsAg)	■ Protein on the surface of hepatitis B virus (HBV) ■ Can be detected at high levels in serum during acute HBV infection or in chronic hepatitis B (CHB) ■ Presence indicates the patient is infectious ■ Used to make HBV vaccine
Hepatitis B surface antibody (anti-HBs)	■ Antibody to HBsAg ■ Presence usually indicates recovery and immunity from HBV infection ■ Also develops in patients successfully vaccinated against HBV
Total hepatitis B core antibody (anti-HBc)	■ Antibody to core antigen of hepatitis B virus; the core antigen cannot be directly measured in the blood ■ Appears at the onset of symptoms in acute HBV infection and remains throughout life ■ Presence indicates previous or ongoing HBV
IgM antibody to hepatitis B core antigen (IgM anti-HBc)	■ Immunoglobulin M antibody to the core antigen of the hepatitis B virus ■ Presence indicates recent acute infection with HBV (≤ 6 months)
Hepatitis B e antigen (HBeAg)	■ Protein produced by the virus when it is actively replicating ■ Can be detected in serum during acute HBV infection and CHB ■ Some strains of HBV do not make e antigen
Hepatitis B e antibody	■ Antibody to HBeAg ■ Can be used to monitor the infection and treatment in patients with CHB
HBV DNA	■ Genetic material of the hepatitis B virus ■ Number of HBV DNA copies in the blood is used to detect active HBV infection and to monitor response to antiviral therapy

Table 4. Interpretation of common tests for hepatitis B virus infection		
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

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.

production of HBeAg. Therefore, those with HBeAg-negative CHB have detectable HBV DNA and active disease and now make up a significant proportion of patients.[14,15]

What tests should I use for screening?

The American Association for the Study of Liver Diseases (AASLD) recommends using both HBsAg and anti-HBs as a primary screen for CHB; other expert guidelines recommend using HBsAg alone.[6,7] Total anti-HBc is not recommended as a primary screening test but may be used as an alternative test only if positive results are followed up by tests for HBsAg and anti-HBs.[6] Tests for HBeAg, anti-HBe, and serum HBV DNA levels are also not recommended as primary screening tools; however, they may be used to evaluate patients for treatment, to monitor disease progression, and to assess response.[6]

Who should be vaccinated?

The CDC recommends HBV vaccination of all newborns and children up to 18 years of age, and all adults at risk for HBV infection (**Table 5**).[16,17] In addition, vaccination is recommended for all individuals who are positive only for total anti-HBc, come from areas of low HBV endemicity, and have no HBV risk factors.[6]

How effective is the vaccine and is it safe?

The HBV vaccine is highly effective and safe; more than a billion doses of vaccine have been administered throughout more than 150 countries.[18] The 3-dose vaccine series

Table 5. Adult groups recommended for HBV vaccination

Persons at risk for HBV infection through sexual exposure	■ Sex partners of HBsAg-positive persons ■ Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than one sex partner during the previous 6 months) ■ Persons seeking evaluation or treatment for a sexually transmitted disease ■ Men who have sex with men
Persons at risk for HBV infection through percutaneous or mucosal exposure to blood	■ Current or recent injection drug users ■ Household contacts of HBsAg-positive persons ■ Residents and staff of facilities for developmentally disabled persons ■ Health care workers and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids ■ Persons with end-stage renal disease (eg, predialysis, hemodialysis, peritoneal dialysis, and home dialysis)
Others	■ International travelers to regions with HBsAg prevalence of > 2% ■ Persons with chronic liver disease ■ Persons with HIV infection ■ All other persons seeking protection from HBV infection

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Mast EE, Margolios HS, Fiore HE, et al. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); part 1: immunization of infants, children, and adolescents. *MMWR Morb Mortal Wkly Rep*. 2005;54(RR-16):1-33.

(given over 6 months) provides > 90% protection against HBV infection in most responders.[17] Approximately 5% to 10% of healthy immunocompetent individuals will not develop anti-HBs in response to the vaccine;[18] however, response rates ranging from 44% to 100% have been reported in nonresponders who received revaccination with the 3-dose series.[17]

What is the vaccine schedule for adults?

The vaccine schedule for adults is shown in **Table 6**.[17] As indicated, immunocompromised patients and patients undergoing hemodialysis require a higher dose and/or a different dosing schedule, depending on the vaccine used.[17] Patients who do not initially complete the vaccine series do not have to restart the series but only need to get their remaining shots.[17] Table 6 also includes the recommended dosing and schedule for a combination HBV and hepatitis A virus (HAV) vaccine, which is recommended for individuals aged ≥18 years who have risk factors for both HAV and HBV.[17]

Patients who are coinfected with HIV should be vaccinated when CD4 cell counts are >200/mm^3; those patients with a CD4 cell count <200/mm^3 should be treated for HIV first, and then vaccinated when the CD4 count is <200/mm^3.[6] (CHB treatment for patients coinfected with HIV is discussed in more detail in the section on special populations.)

Table 6. Hepatitis B vaccine recommended dosing and schedules for adults (age ≥20 years)

	Single-antigen HBV vaccine				Combination vaccine	
	Recombivax HB®[a]		Engerix-B®[b]		Twinrix®[bc]	
	Dose (µg)[d]	Vol (mL)	Dose (µg)[d]	Vol (mL)	Dose (µg)[d]	Vol (mL)
Adults	10	1.0	20	1.0	20	1.0
Hemodialysis patients and other immunocompromised persons	40[f]	1.0	40[g]	2.0	NA	NA
Recommended schedule	0, 1, 6 months, or 0, 1, 4 months, or 0, 2, 4 months		0, 1, 6 months, or 0, 1, 4 months, or 0, 2, 4 months 0, 1, 2, 12 months[e]		0, 1, 6 months	

[a]Merck &Co., Inc., Whitehouse Station, New Jersey.

[b]GlaxoSmithKline Biologicals, Rixensart, Belgium.

[c]Combined hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccine, recommended for persons aged ≥18 years at increased risk for both HBV and HAV infections.
[d]Recombinant hepatitis B surface antigen protein dose.

[e]A four-dose schedule of Engerix-B® is licensed for all age groups.

[f]Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

[g]Two 1.0-mL doses administered in 1 or 2 injections on a 4-dose schedule at 0, 1, 2, and 6 months.

Mast EE, Margolios HS, Fiore HE, et al. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); part 1: immunization of infants, children, and adolescents. *MMWR Morb Mortal Wkly Rep*. 2005;54(RR-16):1-33.

Testing of anti-HBs levels following completion of the vaccine series is not needed for most adults, but is recommended for those at risk for exposure, such as health care and public safety workers, and needle-sharing or sexual contacts of HBsAg-positive individuals.[17] Individuals at continued exposure risk should be tested 1 to 2 months after completing the vaccine series for adults; annual testing is recommended for chronic hemodialysis patients.[6]

When are HBV vaccine booster shots needed?

Booster shots of the HBV vaccine are not recommended for previously vaccinated individuals with normal immune status. Booster doses are recommended for hemodialysis patients when anti-HBs levels decline to < 10 mIU/mL. The need for booster shots in other immunocompromised persons, such as HIV-infected persons, hematopoietic stem-cell transplant recipients, and those undergoing chemotherapy, has not been determined. However, according to the CDC recommendations, when anti-HBs levels decline to < 10 mIU/mL in immunocompromised patients, booster doses should be considered for those with an ongoing risk of HBV exposure.[12]

What other steps can be taken to prevent transmission?

Patients should be counseled to notify all sexual partners or needle-sharing partners and household contacts that they need to be tested for HBV infection and vaccinated if they are susceptible.[2,6] In addition, patients should be informed that they need to use barrier protection during sexual contact with susceptible persons, to cover all open sores, and clean all blood spills with bleach or detergent. Finally, patients should be informed that they cannot donate blood, plasma, semen, or tissue.[2] HBsAg-positive patients, however, should be informed that they can participate in all types of social activities involving casual contact, including contact sports, and that they can share food and utensils.[6] **Table 7** summarizes preventive measures for HBsAg-positive patients to reduce HBV transmission.[2,6]

Table 7. Preventive measures for all persons who are HBsAg-positive to reduce HBV transmission

■ 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, organs, or semen

HBsAg, hepatitis B surface antigen.

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

DIAGNOSIS

What are the recommended tests for diagnosis?

Recommended pretreatment assessments and tests are listed in **Table 8**.[7] The initial evaluation for CHB includes a patient history, physical examination, determination if there is a family history of HBV, liver cancer or cirrhosis, and determination of alcohol use.[6,7]

Laboratory tests for liver disease should include ALT level, serum albumin level, prothrombin time, and bilirubin level. Patients should be evaluated for common coinfections such as HCV, hepatitis D virus (HDV), and HIV. HBV replication should be assessed with HBV DNA assays and tests for HBeAg and anti-HBe. Routine testing for HBV genotype is not recommended by the AASLD; however, several experts suggest that determining the HBV genotype may be useful if treatment with pegylated interferon (peg-IFN) is being considered.[6,7] Evidence suggests that genotypes A and B are associated with a better antiviral response to interferon therapy than genotypes C and D.[19–21]

The AASLD recommends performing a liver biopsy to determine the presence and extent of liver disease for patients who do not clearly meet their criteria for treatment.[6] Decisions concerning whether to perform a liver biopsy should take into account the patient's age, HBV DNA levels, ALT levels, and HBeAg status. A liver biopsy may be most helpful in HBsAg-positive patients older than 35 to 40 years whose HBV DNA levels are ≥ 20,000 IU/mL and who have normal ALT levels.[7]

How do I know if the patient has CHB?

According to a panel of expert hepatologists, patients may be diagnosed with CHB if HBsAg persists in the serum 6 months beyond the onset of acute HBV infection, or if patients present with clinical manifestations and/or epidemiologic factors associated with CHB and have detectable HBsAg in the blood.[7] In addition, patients with CHB usually have detectable levels of total anti-HBc but not IgM anti-HBc, which is associated with acute HBV infection.[7] Clinical manifestations of CHB include persistent or intermittent elevations in ALT/AST levels and chronic hepatitis with moderate or severe necroinflammation.[6] It is important to note that CHB can still be present in a patient with a normal ALT level, which is an especially common finding in patients > 40 years old.[6]

How often should I screen my patients for hepatocellular carcinoma?

The AASLD recommends screening for HCC at baseline and then every 6 to 12 months.[6] Ultrasonography is preferred for screening, and testing for α-fetoprotein should be used only if ultrasonography is not available.[22]

Patients at high risk for HCC for whom surveillance is recommended include Asian men ≥ 40 years of age, Asian women ≥ 50 years of age, Africans > 20 years of age, those with cirrhosis, a family history of HCC, or any HBsAg carrier with persistent or intermittent ALT level elevations and/or HBV DNA level >2,000 IU/mL.[6,22] However, evidence indicates that

Table 8: Recommended pretreatment assessments and tests for CHB evaluation

History and physical examination	■ Risk factors for viral hepatitis ■ Duration of infection ■ Route of transmission ■ Risk factors for HIV coinfection ■ Alcohol history ■ Presence of comorbid diseases ■ Family history of liver cancer ■ HBV testing of family members and vaccination of susceptible household and sexual contacts ■ Patient counseling about transmission prevention
Pretreatment tests	■ Serial testing of ALT level and HBV DNA level during 6-month period ■ Liver function tests ■ Complete blood count with platelets ■ Hepatic function panel ■ Prothrombin time ■ HBeAg and anti-HBe ■ HBV genotype ■ Tests to rule out other causes of liver disease ■ Anti-HCV ■ Anti-HDV, if from endemic area ■ HAV antibody ■ HIV antibody ■ Screen for HCC in high-risk patients: AFP and ultrasonography ■ Liver biopsy examination to grade and stage liver disease[a] ■ Urinalysis; if abnormal, perform 24-hour urine for creatinine and protein

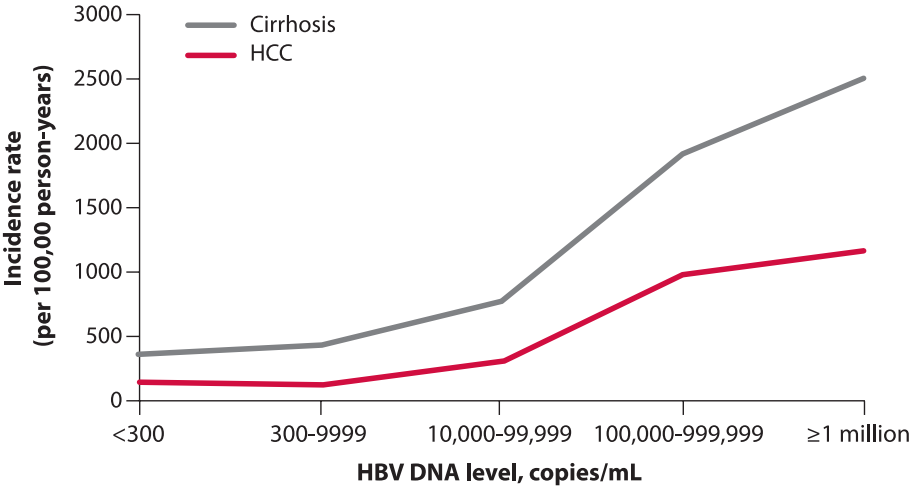
[a]Liver biopsy is optional for patients meeting treatment criteria but should be considered in patients aged > 35-40 years with normal ALT levels.

AFP, α-fetoprotein; ALT, alanine transaminase; anti-HBe, antibody to HBe; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

Reprinted from *Clinical Gastroenterology and Hepatology*, Vol 6(12), Keeffe EB, Dieterich DT, Han SB, et al, A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 Update, 1315-1341, © 2008, with permission from Elsevier.

persistently elevated HBV DNA levels are an independent risk factor for HCC (**Figure 4**).[6,23–25] The large-scale, prospective Risk Evaluation Viral Load Elevation and Associated Liver Disease (REVEAL) study found that the risk of progression to cirrhosis and HCC increases with higher levels of HBV DNA.[23–25]

Figure 4. Incidence of hepatocellular carcinoma and liver cirrhosis in the REVEAL study cohort



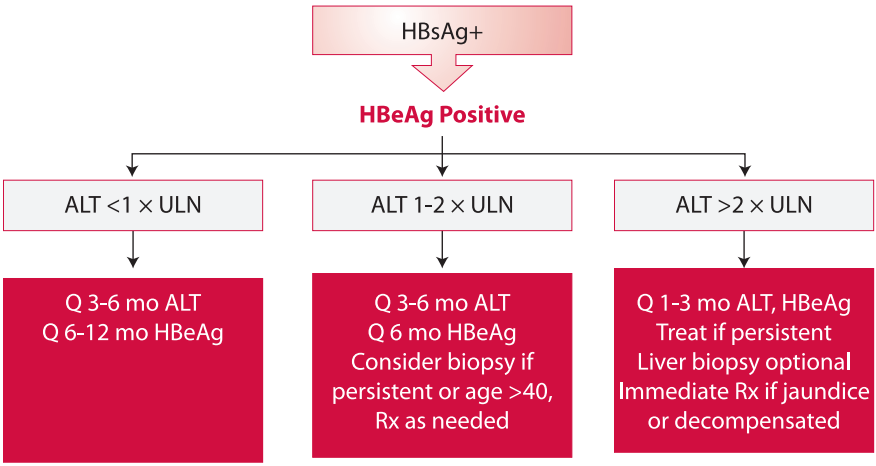
Reprinted from *Clinics in Liver Disease,* Vol 11(4), Chen CJ, Iloeje UH, Yang HI, Long-term outcomes in hepatitis B: The REVEAL-HBV Study, 797-816. ©2007, with permission from Elsevier.

How do I monitor patients with chronic hepatitis B?

The AASLD has developed algorithms for monitoring patients with CHB who are HBeAg-positive and HBeAg-negative (**Figure 5**).[6]

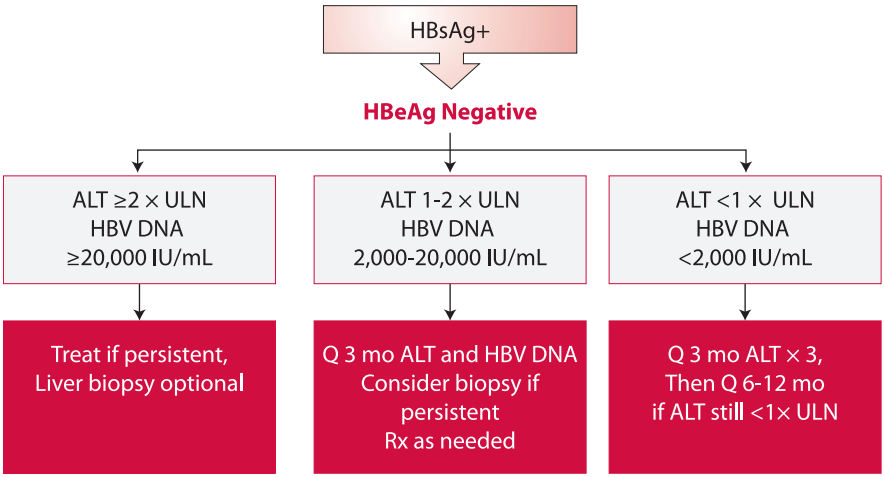
Figure 5. AASLD algorithms for managing HBeAg-positive and HBeAg-negative patients

Management of HBeAg-positive patients[a]



[a]HCC surveillance if indicated.

Management of HBeAg-negative patients[a]



[a]HCC surveillance if indicated.

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.

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

HBeAg-positive patients with HBV DNA levels > 20,000 IU/mL and normal ALT levels should have their ALT levels tested every 3 to 6 months and their HBeAg status assessed every 6 to 12 months.[6] A liver biopsy should be considered for patients with persistently borderline normal or slightly elevated ALT levels, especially if the patient is > 40 years of age.[6] Treatment should be considered for HBeAg-positive patients with persistent ALT elevations > 2 times ULN and HBV DNA levels > 20,000 IU/mL.[6] A liver biopsy is optional with these patients; immediate treatment is needed if jaundice or decompensation is present.

HBeAg-negative patients with normal ALT levels and HBV DNA levels < 2000 IU/mL should have their ALT levels monitored every 3 months for a year to verify their inactive carrier status, and then every 6 to 12 months.[6] Those with ALT elevations 1-2 times the ULN and HBV DNA levels between 2000 IU/mL and 20,000 IU/mL should have their ALT levels monitored every 3 months; if ALT elevations persist, performing a liver biopsy and treatment should be considered. Treatment should be considered for HBeAg-negative patients with ALT levels ≥ 2 times ULN and HBV DNA levels ≥ 20,000 IU/mL; a liver biopsy is optional for these patients.[6]

If CHB is incurable, then what are the goals of treatment?

The goals of antiviral treatment are sustained suppression of HBV replication and remission of liver disease to prevent cirrhosis, hepatic failure, and HCC.[6] Antiviral treatment does not completely eradicate HBV,[6] but effective and sustained suppression of HBV DNA slows progression or may reverse hepatic fibrosis and cirrhosis.[26]

Who should be treated for CHB?

The AASLD guidelines recommend treatment for HBeAg-positive patients with HBV DNA levels > 20,000 IU and ALT levels > 2 times ULN; for HBeAg-negative patients with HBV DNA levels between 2000 and 20,000 IU/ml the guidelines recommend that treatment be considered.[6] In addition, patients > 40 years old who have ALT level elevations between 1 to 2 times ULN and moderate to severe liver histology should be considered for treatment.[6] However, because significant liver disease can be present in patients with lower or fluctuating HBV DNA levels, other experts recommend making decisions to treat on an individual basis and not strictly adhering to viral thresholds.[7]

Do not treat patients with a low risk of liver-related morbidity or mortality within the next 20 years and a low probability of achieving sustained viral suppression after a defined period of treatment.[6] Long-term monitoring and periodic reassessment for treatment is needed for all patients with CHB.

What treatments are available?

Seven antiviral agents are approved for treatment of CHB, 5 of which are oral therapies and 2 of which are injectable therapies. The available nucleoside or nucleotide analogues (NAs) are lamivudine, adefovir, entecavir, telbivudine, and tenofovir. In addition, the combination of emtricitabine+tenofovir is under investigation for the treatment of CHB, and, as described below, may be used to manage antiviral resistant disease.[6,27] Interferons available in

the United States are standard interferon and pegylated interferon alpha-2a (peg-IFN). Long-acting peg-IFN, which is administered once weekly, has largely replaced standard interferons, which are usually given once a day or 3 times a week.[28]

How do oral therapies and interferons compare?

There are advantages and disadvantages to both categories of treatments. Oral therapies have greater efficacy with regard to viral suppression and a more favorable side-effect profile but carry a risk of resistance and require either long or indefinite treatment periods for most patients.[6,15,26] Interferons are administered for a finite treatment period and carry no risk of resistance, but they have a lower efficacy and a decreased probability of response relative to NAs.[6,15,26] **Table 9** summarizes the response rates and the durability of response in HBeAg-positive and HBeAg-negative patients for NAs and interferons from multiple clinical trials.[6]

What does the AASLD recommend for treatment?

First- and second-line agents as recommended by the AASLD are shown in **Table 10**.[6] Factors to consider in selecting a CHB treatment include safety and efficacy, antiviral resistance, cost, patient preference, and patient comorbidities.

For oral therapy, the AASLD recommends entecavir or tenofovir as first-line options.[6] Entecavir and tenofovir are highly effective against HBV and have a high genetic barrier to resistance.[7] Except for patients requiring a short course of therapy, lamivudine and telbivudine are not first-line agents because of the risk of resistance.[6] Adefovir is not a first-line agent because it has lower potency against HBV and is associated with low response rates; 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.[6] Moreover, adefovir is associated with increasing resistance after one year of therapy.[6] NAs are generally well tolerated[26] but in rare circumstances have been associated with lactic acidosis.[29–31]

The AASLD recommends peg-IFN as a first-line interferon therapy. HBeAg-positive patients who are more likely to respond to peg-IFN include those with pretreatment ALT levels > 2 times ULN, lower HBV DNA levels, and infection with HBV genotype A; there are no known predictors of response for HBeAg-negative patients. Peg-IFN is associated with some side effects, including an initial influenza-like illness, weight loss, loss of appetite, fatigue, and mild alopecia.[6]

How do I know if the treatment is working?

Treatment response can be measured by a decrease in serum HBV DNA level, loss of HBeAg with or without seroconversion marked by the development of anti-HBe, normalization of ALT levels, or improvement in liver histology.[6] As shown in **Table 11**, there are 6 categories of response to treatment for CHB: biochemical response, virologic response, primary nonresponse, virologic relapse, histologic response, and complete response.[6] These categories of response are often used in clinical trials but can also be

Table 9. Responses to nucleos(t)ide analogues and pegylated interferon among previously untreated patients

	Placebo/ Control Groups from Multiple Studies	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
HBeAg-positive CHB							
Loss of serum HBV DNA[a]	0%–17%	40%–44%	21%	67%	76%	60%	25%
Loss of HBeAg	6%–12%	17%–32%	24%	22%	NA	26%	30%/34%[b]
HBeAg seroconversion	4%–6%	16%–21%	12%	21%	21%	22%	27%/32%[b]
Loss of HBsAg	0%–1%	1%	0%	2%	3.2%	0%	3%
Normalization of ALT levels	7%–24%	41%–75%	48%	68%	68%	77%	39%
Histologic improvement	NA	49%-56%	53%	72%	74%	65%	38%[c]
Durability of response	NA	50%–80%[d]	~90%[d]	69%[d]	NA	~80%	NA
HBeAg-negative CHB							
Loss of serum HBV DNA[a]	0%–20%	60%–73%	51%	90%	93%	88%	63%
Normalization of ALT	10%–29%	60%–79%	72%	78%	76%	74%	38%
Histologic improvement	33%	60%-66%	64%	70%	72%	67%	48%
Durability of response	Control	<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. 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.
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, not available; Peg-IFN-α, pegylated interferon-alfa; qd, daily; tiw, three times a week.
Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

Table 10. First- and second-line options for CHB treatment		
Antiviral agent	First-line	Second-line
Tenofovir	✓	
Entecavir	✓	
Lamivudine		✓
Telbivudine		✓
Adefovir		✓
Pegylated interferon	✓	

Adapted from: Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36.

Table 11. Categories of response to antiviral treatment of CHB	
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

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.
Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

useful in practice to monitor the treatment response of patients.[32] Because increasing evidence suggests that even HBV DNA levels > 300 IU/mL are associated with an increased risk of disease progression,[33] the objective of antiviral therapy is sustained suppression of HBV DNA to the lowest possible level.[7]

How do I manage the care of patients who do not respond to treatment?

Patients who respond to NA therapy with < 2-log decrease in HBV DNA level after a minimum of 6 months of treatment are primary nonresponders and should be switched to an alternative treatment or receive additional treatment. Patients initially treated with interferons who do not respond to treatment should be treated with NAs.[6]

What is the best way to monitor treatment?

All patients should be monitored during and after therapy. Measurement of the HBV DNA level is crucial to assessing the patient's response to therapy.[6] Other key parameters to monitor periodically include the ALT level and HBeAg status. Recommended monitoring tests and timings of treatments with interferons and NAs for HBeAg-positive and HBeAg-negative patients are shown in **Table 12**.[6]

When can I stop treatment?

Peg-IFN is typically administered for a finite period of 48 weeks. The duration of NA treatment is less well defined and continues until certain end points are reached. In HBeAg-positive patients, NA treatment should be continued until the patient achieves HBeAg seroconversion, has undetectable serum HBV DNA levels, and has completed at least 6 months of additional treatment following the emergence of anti-HBe. In HBeAg-negative patients, NA treatment should be continued indefinitely or until the patient has achieved anti-HBs clearance.[6]

Table 12. Recommended monitoring tests and timing during and after CHB antiviral therapy

Antiviral Therapy	HBeAg Status	Test	Treatment Period	
			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	

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.
Data from Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36.

RESISTANCE PREVENTION & MANAGEMENT

Does antiviral resistance occur with all treatments? How is it defined?

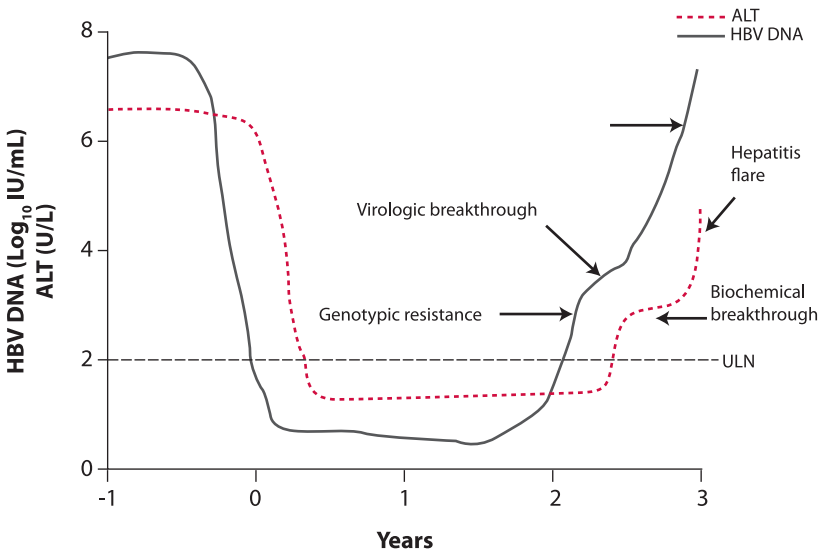
Resistance is a concern with long-term treatment with all NAs, and it is important to select an agent that has a low risk of resistance.[6,26] Interferons are not associated with antiviral resistance.

Emergence of antiviral resistance generally follows a pattern (**Figure 6**).[6] Genotypic resistance develops first with the emergence of resistant mutations. Virologic breakthrough follows, which is defined as a > 10-fold increase in HBV DNA in patients who had achieved a virologic response and are continuing therapy. Viral rebound with an increase in serum HBV DNA eventually becomes evident. Biochemical breakthrough typically occurs with virologic breakthrough. Biochemical breakthrough is the occurrence of an elevation in ALT during treatment in a patient who had achieved an initial response. Reversal of biochemical and histologic improvements can precipitate hepatic flares and decompensation in some patients.[6,7]

How can I prevent resistance?

Antiviral resistance and lack of adherence are the primary contributors to NA treatment failure in patients with CHB.[34] The best way to prevent resistance is to select the

Figure 6. Serial changes in serum HBV DNA and ALT levels in association with emergence of antiviral resistant HBV mutants



ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limits of normal.
Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):1-36. Reproduced with permission.

most potent agent with the highest genetic barrier to resistance.[6] Resistance to NAs can generally be divided between the nucleotides (adefovir, tenofovir) and the nucleosides (lamivudine, telbivudine, and entecavir). Nucleotides are associated with mutations in the HBV polymerase domains B and D and the nucleosides are associated with mutations in the polymerase domain C and compensatory mutations in domains A and B.[28] Cross-resistance occurs among NAs, and resistance to one can limit future options for treatment substitutions.[6] The sequential use of NA monotherapies can allow for the selection of mutant variants that are resistant to the initial NA and subsequent NAs that may be used.[34]

Resistance rates for NAs approved to treat CHB are shown in **Table 13**.[28,35,36] Among patients not previously treated with NAs, there is no reported resistance with tenofovir to date and the risk of resistance with entecavir is low.[28,35,36] Both entecavir and tenofovir have a high genetic barrier to resistance.[15] For NAs used to treat CHB, a genetic barrier to resistance 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.[34] Resistance rates during long-term therapy are high with adefovir, and approach 70% with lamivudine monotherapy at 5 years.[28] Telbivudine has a low genetic barrier to resistance and is associated with high rates of resistance in patients with high HBV DNA levels at baseline or detectable levels after 6 months of therapy.[15]

In addition to choosing an agent with a high genetic barrier to resistance, preventive strategies include avoiding unnecessary treatment (eg, do not treat patients who are unlikely to achieve a sustained virologic response, such as patients younger than age 30 or those with minimal disease) and emphasizing the importance of adherence to therapy to patients. Furthermore, HBV DNA levels should be monitored every 3 to 6 months for the emergence of antiviral response.[6]

Table 13. Hepatitis B virus resistance rates for available nucleos(t)ides

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

[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]In lamivudine-resistant patients, viral resistance was 7% during year 1 of therapy and up to 43% at year 4.
HBeAg, hepatitis B e antigen.
Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36. Reproduced with permission.

How do I manage resistance if it develops?

When patients develop a breakthrough infection during NA therapy, it is necessary to first confirm their adherence to therapy. If there has been a long lapse in adherence, treatment can be resumed. If adherence is not a concern, tests should be performed, when possible, to determine whether antiviral-resistant mutations are present since this determination can help differentiate between a primary nonresponse and a breakthrough infection. These tests can also determine whether multidrug resistance may be present in patients who have been treated with more than one NA treatment. Once antiviral resistance is confirmed, the treatment regimen must be adjusted. Preferred treatment strategies recommended by the AASLD to address the development of resistance to specific NAs are shown in **Table 14**.[6]

For patients who develop lamivudine resistance, adefovir or tenofovir may be added. Alternatively, lamivudine may be discontinued and the patient switched to combination therapy with tenofovir and emtricitabine. It is important to note that emtricitabine alone or in combination with tenofovir is not indicated for this use; however, emtricitabine is currently under investigation for treatment of CHB.[27] There are several strategies to address development of adefovir resistance. In patients with adefovir resistance who have no prior exposure to other NAs, lamivudine or entecavir may be added. Alternatively, adefovir may be discontinued and the regimen switched to combination therapy with tenofovir and emtricitabine. Patients who develop resistance to entecavir should be switched to either tenofovir monotherapy or combination therapy with tenofovir and emtricitabine. For patients with telbivudine resistance, adefovir or tenofovir may be added to the regimen. Alternatively, telbivudine may be discontinued and the regimen switched to combination therapy with tenofovir and emtricitabine.[6]

Table 14. Treatment options to address development of antiviral resistance

Antiviral resistance	Treatment options
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[†]
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
Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1-36. Reproduced with permission.

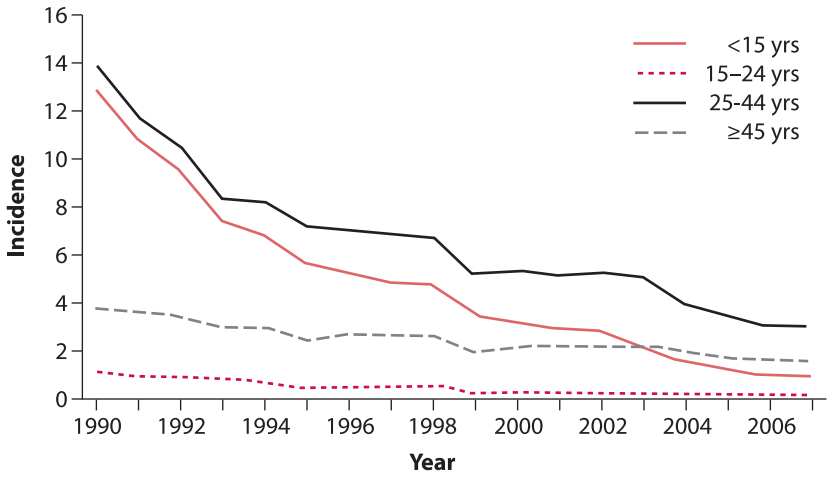
How should I treat women who are pregnant?

As mentioned above, all pregnant women should be screened for HBsAg. Pregnancy is not a contraindication for vaccination, and all susceptible pregnant women at risk for HBV exposure should be vaccinated.[16,17,37] Although the incidence of acute HBV infection in infants and children has declined in the United States since the implementation of universal vaccination recommendations (**Figure 7**), cases of perinatal transmission still occur, and closer adherence to vaccination and immunoprophylaxis measures is needed.[2,38,39]

The AASLD recommends the immediate administration of hepatitis B immune globulin and HBV vaccination following delivery to all children born to HBsAg-positive women.[6] Studies show that these immunoprophylaxis measures reduce the risk of perinatal transmission by 85% to 95%.[16] However, efficacy of immunoprophylaxis measures may be lower for women with very high HBV DNA levels.[6] Following delivery, patients should be monitored to ensure completion of the 3-dose vaccine series for infants. Administration of NAs to the newborn is not recommended.

Guidance is lacking from the AASLD on the treatment of HBsAg-positive women during pregnancy. However, some experts suggest that treatment may be warranted for pregnant women with high HBV DNA serum levels or for women who have already given birth to an HBsAg-positive child.[7] A recent prospective observational study reported an HBV transmission rate of approximately 9% in children born to women with HBV DNA levels > 10^8 copies/

Figure 7. Incidence[a] of acute hepatitis B, by age group and year—United States, 1990–2007



[a]per 100,000 population.

Daniels D, Grytdal S, Wasley A; Centers for Disease Control and Prevention. Surveillance for Acute Viral Hepatitis—United States, 2007. *MMWR Surveillance Summ*. 2009;58(No. SS-3)1-27.

mL.[40] Clinicians deciding whether to treat pregnant women must consider the risks of treatment, the stage of liver disease, and the potential benefit to the patient. Treatment may be deferred until after pregnancy for younger patients who are more likely to have mild disease.[7]

The preferred agents for use in pregnant women are lamivudine, telbivudine, or tenofovir administered during the third trimester.[7] Limited studies have found that lamivudine treatment in the third trimester of women with high HBV DNA decreases the risk of intrauterine and perinatal transmission, and lamivudine is the most commonly used antiviral medication for treatment of CHB in pregnant women.[7,15,41,42] Both lamivudine and tenofovir have accumulated substantial safety data in the treatment of pregnant women with HIV.[15]

Lamivudine, adefovir, and entecavir are pregnancy category C drugs; tenofovir and telbivudine are category B drugs.[41] Category B drugs are medications that, according to data from animal studies, have no teratogenic or embryogenic risk and for which there have been no controlled human studies or for which animal studies may indicate a risk but controlled human studies do not support these findings. Category C drugs are medications that have shown teratogenic or embryocidal effects in animals and for which there are no controlled studies in humans. Use of NAs during pregnancy remains controversial and more data are needed.

For women who are in the immune tolerant phase of CHB and plan to become pregnant, a liver biopsy should be performed.[7] If liver biopsy results show significant fibrosis, the patient may be treated with peg-IFN because it requires a finite period of treatment.[7]

How do I treat women who become pregnant while on NA therapy?

Treatment may be withdrawn or continued in women who become pregnant while on NA therapy.[7] The decision on when to stop treatment must take into account several factors, including the risk to the fetus, the stage of liver disease in the mother, the risk of HBV reactivation if treatment is discontinued, as well as the potential benefit of therapy. Switching to a medication in pregnancy category B (tenofovir or telbivudine) or with an established history of safety in pregnancy (lamivudine or tenofovir) should be considered.

How do I treat patients who are coinfected with HIV?

Given that HIV and HBV share routes of transmission, it is not surprising that approximately 6% to 13% of all HIV-positive patients also have CHB.[6] Studies show that coinfected patients are at greater risk of the complications of CHB, including liver-related mortality and cirrhosis (**Figure 8**).[43–45] The criteria for treatment of patients with CHB who are coinfected with HIV are the same as for CHB patients without HIV.[7] Selection of antiviral therapy must be designed to reduce the risk of developing resistance to either virus.[7]

Expert guidelines recommend that, when possible, treatment for CHB and HIV should begin at the same time with a regimen that includes 2 drugs that are active against both HIV and HBV.[6,7,15] In patients not previously treated for HIV or HBV, combination therapy with tenofovir and lamivudine or tenofovir and emtricitabine is recommended.[6,7,46,47] Entecavir can be used as an alternative to tenofovir where needed.[7] For patients who develop lamivudine resistance, tenofovir should be added to their regimens.[6,48]

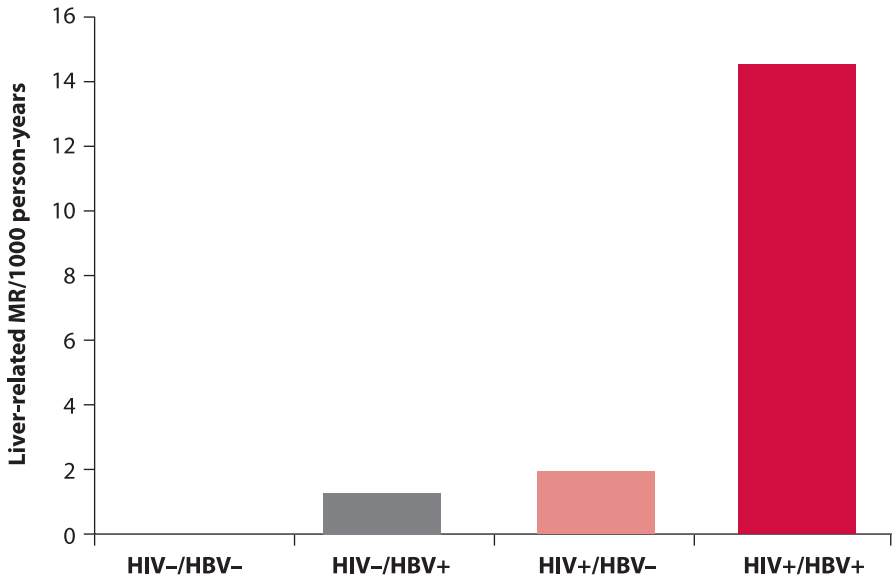
Coinfected patients already on an effective antiviral regimen for HIV that does not include an agent with activity against HBV may be treated with either peg-IFN or adefovir, depending on the CD4 cell count.[6] Response to peg-IFN is more likely in HBeAg-positive patients who are young, immunocompetent, and who have high ALT levels but low HBV DNA levels.[6,7]

For coinfected patients not scheduled to start HIV treatment in the near future, those who are HBeAg-positive may be treated with either peg-IFN or adefovir.[6] Earlier initiation of antiviral therapy for HIV should be considered in CHB patients who are HBeAg-negative.[6]

How do I treat patients who are coinfected with hepatitis C virus?

Data suggest that approximately 14% of CHB patients are coinfected with HCV.[49] Patients coinfected with HBV and HCV are at greater risk for cirrhosis and HCC than patients only

Figure 8. Liver-related mortality rate (MR) per 1000 person-years in 5293 men with (+) or without (-) hepatitis B virus (HBV) or HIV infection



HBV, hepatitis B virus; HIV, human immunodeficiency virus; MR, mortality rate.

Adapted from *The Lancet*, 360, Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS) pp. 1921-1926, © 2002, with permission from Elsevier.

infected with HBV or HCV. Compared with patients with a monoinfection, patients coinfected with HBV and HCV have more severe liver disease, a higher probability of liver cirrhosis and hepatic decompensation, and a greater incidence of HCC.[50,51]

Because data are lacking from randomized clinical trials, the AASLD guidelines do not provide recommendations on treatment of CHB patients coinfected with HCV.[6] HBV DNA levels can be suppressed in HCV coinfected patients, and targeting therapy at HCV may be beneficial. [15] Some studies suggest that treatment of HCV infection with standard IFN or peg-IFN and ribavirin for up to 48 weeks is as effective in treating HBV/HCV coinfected patients as in patients with HCV alone.[50–53] A rebound in serum HBV DNA and reactivation of HBV have been reported in coinfected patients treated with interferons and ribavirin.[51–53] HBV reactivation should be treated with NAs.[15]

How do I treat patients who are coinfected with HDV?

Hepatitis D virus (HDV) is a virus that is dependent on active HBV replication. IFN is the only currently approved treatment for chronic hepatitis D;[6] however, certain trials show peg-IFN may be effective.[54,55] Lamivudine treatment alone or in combination with interferon has no benefit in the treatment of HDV,[56] and oral medications in general are not effective.[57]

What do I need to consider in treating CHB if the patient has to undergo chemotherapy or immunosuppressive therapy?

All patients with risk factors for HBV infection who are scheduled for chemotherapy or immunosuppressive therapy should be screened for HBsAg.[6] Immunosuppressive therapy or chemotherapy (eg, with corticosteroids or rituximab) can cause a reactivation in HBV carriers.[6,58] It is important to note that reactivation can occur in patients with resolved CHB who are HBsAg-negative and are anti-HBsAg and anti-HBc positive.[7] Hepatitis flares associated with HBV reactivation can be asymptomatic or they can lead to serious, life-threatening events that require immediate treatment.[7,59]

Expert guidelines recommend prophylactic treatment of patients who are HBsAg-positive with NAs before and after chemotherapy or immunosuppressive therapy.[6,7] If the patient is scheduled for a short period of immunosuppressive treatment (< 12 months) and the baseline HBV DNA is undetectable, then lamivudine or telbivudine may be used for prophylaxis.[6] If immunosuppressive therapy is planned for a longer duration, then tenofovir or entecavir is preferred. 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.[6,7] For patients with a baseline HBV DNA level > 2000 IU/mL, NA treatment should be continued until the ALT level is normalized and HBV DNA is undetectable.[7] Avoid interferon therapy in this setting because of the associated bone marrow suppression.[6]

REFERENCES

1. Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis B. *Ann Intern Med.* 2009;150:104-110.
2. Weinbaum CM, Williams I, Mast EE, et al. Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR* 2008;57:(RR-8)1-20.
3. Cohen C, Evans AA, London WT, et al. Underestimation of chronic hepatitis B virus infection in the United States of America [letter]. *J Viral Hepat.* 2008;15:12-13.
4. MacMahon BJ. Selecting appropriate management strategies for chronic hepatitis B: who to treat. *Am J Gastroenterol.* 2006;101:S7-S12.
5. Colvin H, Mitchell A, eds. Institute of Medicine of the National Academies. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.* Washington, DC: The National Academies Press; 2010.
6. Lok ASF, McMahon B. Chronic hepatitis B update: 2009. *Hepatology.* 2009;50:1-36.
7. Keeffe EB, Dieterich DT, Han SB, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 Update. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.
8. Centers for Disease Control and Prevention. *2010 Yellow Book.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention. http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx. Accessed February 3, 2010.
9. Singleton R, Holve S, Groom A, et al. Impact of immunizations on the disease burden of American Indian and Alaska native children. *Arch Pediatr Adolesc Med.* 2009;163:446-453.
10. Menzies RI, Singleton RJ. Vaccine preventable diseases and vaccination policy for indigenous populations. *Pediatr Clin North Am.* 2009;56:1263-1283.
11. Harpaz R, McMahon BJ, Margolis HS, et al. Elimination of new chronic hepatitis B virus infections: results of the Alaska immunization program. *J Infect Dis.* 2000;181:413-418.
12. Centers for Disease Control and Prevention. Division of Viral Hepatitis. Hepatitis B FAQs for health professionals. http://cdc.gov/hepatitis/HBV/HBVfaq.htm. Accessed April 5, 2010.
13. 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.
14. Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. *J Viral Hepat.* 2002;9:52-61.
15. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol.* 2009;50:227-242.
16. Mast EE, Margolis HS, Fiore AE, et al. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 1: Immunization of Infants, Children, and Adolescents. *MMWR.* 2005;54(RR-16):1-33.
17. Mast EE, Weinbaum CM, Fiore AE, et al. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 2: Immunization of Adults. *MMWR.* 2006;55(RR-16):1-33.
18. Zuckerman JN. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. *J Med Virol.* 2006;78:169-177.
19. Kao JH, Wu NH, Chen PJ, et al. Hepatitis B genotypes and the response to interferon therapy. *J Hepatol.* 2000;33:998-1002.

20. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut.* 2007;56:699-705.
21. Kao JH. Hepatitis B viral genotypes: clinical relevance and molecular characteristics. *J Gastroenterol Hepatol.* 2002;17:643-650.
22. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology.* 2005;42:1208-1236.
23. Chen C-J, Yang H-I, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA.* 2006;295:65-73.
24. Iloeje UH, Yang H-I, Su J, et al; and Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology.* 2006;130:678-686.
25. Chen C-J, Iloeje UH, Yang H-I. Long-term outcomes in hepatitis B: the REVEAL-HBV study. *Clin Liver Dis.* 2007;11:797-816.
26. Dienstag JL. Benefits and risks of nucleoside analog therapy for hepatitis B. *Hepatology.* 2009;49:S112-S121.
27. National Institute of Diabetes and Digestive and Kidney Diseases. Tenofovir alone versus tenofovir with emtricitabine to treat chronic hepatitis B. http://clinicaltrials.gov/ct2/show/NCT00524173?term=emtricitabine&rank=7. Accessed February 11, 2010.
28. Dienstag JL. Hepatitis B virus infection. *N Engl J Med.* 2008;359:1486-1500.
29. Cohen SM, Levy RM, Jovanovich JF, et al. Fatal lactic acidosis associated with the use of combination oral medications to treat reactivation of hepatitis B. *J Clin Gastroenterol.* 2009;43:1008-1010.
30. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology.* 2009;50:2001-2006.
31. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology.* 2009;49(5 Suppl):S185-S195.
32. Hoofnagle JH, Doo E, Liang TJ, et al. Management of hepatitis B: summary of a clinical research workshop. *Hepatology.* 2007;45:1056-1075.
33. Iloeje U, Yang H-I, Su J, et al. HBV viral load less than 10^4 copies/mL is associated with significant risk of hepatocellular carcinoma in chronic hepatitis B patients: an update from the R.E.V.E.A.L.-HBV study. *Hepatology.* 2007;46:640A.
34. Lok AS, Zoulim F, Locarnini S, et al. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology.* 2007;46:254-265.
35. Liaw Y-F, Gane E, Leung N, et al. 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology.* 2009;136:486-495.
36. Marcellin P, Heathcote 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.
37. Centers for Disease Control and Prevention. Guidelines for Vaccinating Pregnant Women. http://www.cdc.gov/vaccines/pubs/preg-guide.htm#3. Accessed March 30, 2010.
38. Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis—United States, 2007. *MMWR Surveillance Summ.* 2009;58(SS-3)1-27.
39. Willis BC, Wortley P, Wang SA, et al. Gaps in hospital policies and practices to prevent perinatal transmission of hepatitis B virus. *Pediatrics.* 2010 Mar 8. [Epub ahead of print.]
40. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust.* 2009;190:489-492.

41. Terrault NA, Jacobson IM. Treating chronic hepatitis B infection in patients who are pregnant or are undergoing immunosuppressive chemotherapy. *Semin Liver Dis.* 2007;27(suppl 1):18-24.

42. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat.* 2009;16:94-103.

43. Thio CL. Hepatitis B treatment in HIV-infected patients. *Top HIV Med.* Dec 2006-Jan 2007;14:170-175.

44. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS.* 2004;18:2285-2293.

45. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology.* 2009;49(5 suppl):S138-S145.

46. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and-experienced patients coinfected with HIV-1 and hepatitis B virus. *J Infect Dis.* 2004;189:1185-1192.

47. Hoff J, Bani-Sadr F, Gassin M, et al. Evaluation of chronic hepatitis B virus (HBV) infection in coinfected patients receiving lamivudine as a component of anti-human immunodeficiency virus regimens. *Clin Infect Dis.* 2001;32:963-969.

48. Benhamou Y, Fleury H, Trimoulet P, et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology.* 2006;43:548-555.

49. Liu C-J, Chen P-J, Chen D-S. Dual chronic hepatitis B virus and hepatitis C virus infection. *Hepatol Int.* 2009;3:517-525.

50. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol.* 2008;23:512-520.

51. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology.* 2009;136:496-504, e3.

52. Hung CH, Lee CM, Lu SN, et al. Combination therapy with interferon-alpha and ribavirin in patients with dual hepatitis B and hepatitis C virus infection. *J Gastroenterol Hepatol.* 2005;20:727-732.

53. Potthoff A, Wedemeyer H, Boecher WO, et al. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol.* 2008;49:688-694.

54. Niro GA, Ciancio A, Gaeta GB, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. *Hepatology.* 2006;44:713-720.

55. Castelnau C, Le Gal F, Ripault MP, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology.* 2006;44:728-735.

56. Yurdaydin C, Bozkaya H, Onder FO, et al. Treatment of chronic delta hepatitis with lamivudine vs lamivudine+interferon vs interferon. *J Viral Hepat.* 2008;15:314-321.

57. Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. *Nat Rev Gastroenterol Hepatol.* 2010;7:31-40.

58. Yeo W, Chan TC, Leung NWY, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol.* 2009;27:605-611.

59. Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. *Clin Gastroenterol Hepatol.* 2006;4:1076-1081.

This activity is jointly sponsored by Postgraduate Institute for Medicine and HealthmattersCME.

This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.