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. Universal screening is not recommended because the overall prevalence rate is low (0.3%) in the general population in the United States. 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).

Recommended screening tests. Antibodies except hepatitis B core antigen (HbcAg); free HbcAg does not circulate in blood. There are no currently available rapid 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. 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. Chronic infection is indicated by the presence of HbsAg, the abnormal liver function tests, the history of exposure to HBV, and positive hepatitis B surface antibody (anti-HBs). Recommended screening tests. As presents for all HBV serologic markers except hepatitis B core antigen (HbcAg); free HbcAg does not circulate in blood. There are no currently available rapid 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. 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. Chronic infection is indicated by the presence of HbsAg, the abnormal liver function tests, the history of exposure to HBV, and positive hepatitis B surface antibody (anti-HBs).
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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Cover story continued from page 1

For HBV, where the virus is primarily transmitted through perinatal exposure (Figure 1, page 1), although perinatal transmission is now relatively uncommon in the United States because of the immunoprophylaxis of newborns and children, sporadic cases continue to occur (see below for the management of care for pregnant women with CHB). 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. 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%), whereas >90% of infants infected perinatally and 25% to 50% of children infected between the ages of 1-5 will develop CHB. 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. Phases of CHB. CHB can evolve through several different phases (Figure 2). 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. The 3 main phases are immune tolerant, immune active, and inactive carrier.

The immune tolerant phase typically occurs in individuals with perinatally acquired HBV infection. 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; 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. Active viral replication is a major determinant of progressive liver disease. 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. Many HBeAg-positive patients in the immune active phase will clear HBeAg and develop antibodies to HBeAg (anti-HBe). 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. 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 hepatic decompensation, cirrhosis, or hepatocellular carcinoma.

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. 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). However progression to HCC or cirrhosis has been reported in some of these patients. 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). 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. In patients who recover from HBV infection, HBsAg and HBV DNA are cleared from the blood and anti-HBs is present. In contrast, in

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Chronic HBV infection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ever infected with HBV&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>0.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>95% CI = 0.2%-0.4%</td>
<td>95% CI = 4.2%-5.5%</td>
</tr>
<tr>
<td>HIV-positive individuals</td>
<td>4%-17%</td>
<td>24%-76%</td>
</tr>
<tr>
<td>Injection drug users</td>
<td>3%-6%</td>
<td>20%-70%</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>1%-3%</td>
<td>10%-40%</td>
</tr>
<tr>
<td>Sexual contacts of HBsAg-positive</td>
<td>3.5%-9%</td>
<td>25%-59%</td>
</tr>
<tr>
<td>individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household contacts of persons with</td>
<td>3%-20%</td>
<td>15%-60%</td>
</tr>
<tr>
<td>chronic HBV infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>a</sup>Antibody to hepatitis B core antigen-positive includes persons with resolved and chronic infections.

<sup>b</sup>HBsAg, hepatitis B surface antigen-positive.


Figure 2. Natural history of chronic hepatitis B infection

Abbriviations: HBsAg, hepatitis B surface antigen.

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.
Identification and diagnosis

Table 2. Interpretation of HBV serologic test results

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total anti-HBc</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Immune due to HBV vaccination</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Chronically infected</td>
</tr>
</tbody>
</table>

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.


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-HBs, antibody to hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen; IgM, immunoglobulin M.


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-negative 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.

Serological 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.

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

| Asian 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
- Persons 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; IgM, immunoglobulin M.


Factors for human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) coinfection, family history of liver disease and liver cancer, and alcohol use. Patients should also be asked about tobacco use because smoking increases the risk of liver cancer.

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 confections, notably HCV antibodies, hepatitis D virus [HDV] antibody, and HIV antibody.

Assessment of active hepatitis B

Please see IDENTIFICATION AND DIAGNOSIS page 4
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). 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. Any elevations in ALT levels require more frequent monitoring of HBV DNA. 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. 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 sustained suppression of ALT levels below 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. 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. Any elevations in ALT levels require more frequent monitoring and HBV DNA testing. 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. Patients with ALT levels ≥2 times ULN and HBV DNA ≥20,000 IU/mL should be treated as needed if 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. While antiviral treatment does not typically eradicate HBV, 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. Therefore the goals of antiviral treatment for CHB are the sustained suppression of HBV replication and the remission of liver fibrosis.

**Strategies for optimal management of 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.
- 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 HBsAg-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 HBV antibody; and serum HBV DNA, HBsAg, and anti-HBeAg tests.

**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 HBsAg-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 HBV antibody; and serum HBV DNA, HBsAg, and anti-HBeAg tests.

**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.

Management of HBeAg-positive patients

- **HBeAg Positive**
  - ALT <1 × ULN
  - ALT 1-2 × ULN
  - ALT >2 × ULN

- Q 3-6 mo ALT
- Q 6 mo HBeAg
- Consider biopsy if persistent or age >40, Rx as needed

- Q 1-3 mo ALT, HBeAg
- Test if persistent Liver biopsy optional Immediate Rx if jaundice or decompensated

Management of HBeAg-negative patients

- **HBeAg Negative**
  - ALT ≥2 × ULN
  - HBV DNA ≥20,000 IU/mL
  - ALT <1 × ULN
  - HBV DNA 2,000-20,000 IU/mL

- Treat if persistent, Liver biopsy optional

- Q 3 mo ALT and HBV DNA
- Consider biopsy if persistent Rx as needed

- Q 3 mo ALT × 3, Then Q 6-12 mo if ALT still <1 × ULN

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

<table>
<thead>
<tr>
<th>Response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical</strong></td>
<td>Decrease in serum ALT to within the normal range</td>
</tr>
<tr>
<td><strong>Virologic</strong></td>
<td>Decrease in serum HBV DNA to undetectable levels by PCR assays, and Loss of HBeAg in patients who were initially HBeAg positive</td>
</tr>
<tr>
<td>Primary nonresponse (not applicable to interferon therapy)</td>
<td>Decrease in serum HBV DNA by &lt;2 log10 IU/mL after at least 24 weeks of therapy</td>
</tr>
<tr>
<td><strong>Virologic relapse</strong></td>
<td>Increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least 2 determinations more than 4 weeks apart</td>
</tr>
<tr>
<td><strong>Histologic</strong></td>
<td>Decrease in histology activity index by at least 2 points and No worsening of fibrosis score compared to pretreatment liver biopsy</td>
</tr>
</tbody>
</table>

**Complete**
- Fulfill criteria of biochemical and virologic response and Loss of HBsAg

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

<table>
<thead>
<tr>
<th>Placebo/Control Groups from Multiple Studies</th>
<th>Standard IFN-α 5 MU tiw 12-24 wk</th>
<th>Lamivudine 100 mg qd 48-52 wk</th>
<th>Adefovir 10 mg qd 48 wk</th>
<th>Entecavir 0.5 mg qd 48 wk</th>
<th>Tenofovir 300 mg qd 48 wk</th>
<th>Teltuvudine 600 mg qd 52 wk</th>
<th>Peg-IFN-α 180 mcg qw 48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of serum HBV DNA*</td>
<td>0%–17%</td>
<td>37%</td>
<td>40%–44%</td>
<td>24%</td>
<td>22%</td>
<td>60%</td>
<td>25%</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>6%–12%</td>
<td>33%</td>
<td>17%–32%</td>
<td>16%–21%</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>HBeAg serocconversion</td>
<td>4%–6%</td>
<td>Difference of 18%</td>
<td>16%–21%</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Loss of HBsAg</td>
<td>0%–1%</td>
<td>7.80%</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
<td>3.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Normalization of ALT levels</td>
<td>7%–24%</td>
<td>Difference of 25%</td>
<td>41%–75%</td>
<td>48%</td>
<td>68%</td>
<td>68%</td>
<td>77%</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Durability of response</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

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; IFN-α, standard interferons; Peg-IFN-α, pegylated interferon.

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


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

Figure 6. Clinical trials of approved antiviral agents for HBeAg-positive and HBeAg-negative patients

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; only peg-IFN-α1a 2 μg 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. 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. 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). 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.

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. 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). Please see STRATEGIES FOR OPTIMAL MANAGEMENT page 6.
Table 9. AASLD recommendations for treatment of chronic hepatitis B infection

<table>
<thead>
<tr>
<th>HBV DNA (PCR)</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>&gt;20,000 IU/mL</td>
<td>≤2x ULN</td>
</tr>
<tr>
<td></td>
<td>&gt;2x ULN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;2x ULN</td>
</tr>
<tr>
<td></td>
<td>≤2x ULN</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;2,000 IU/mL</td>
<td>&gt;2x ULN</td>
</tr>
<tr>
<td></td>
<td>≤2x ULN</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;2,000 IU/mL</td>
<td>&gt;2x ULN</td>
</tr>
<tr>
<td></td>
<td>≤2x ULN</td>
<td></td>
</tr>
<tr>
<td>Positive or negative</td>
<td>Detectable</td>
<td>Cirrhosis: Compensated</td>
</tr>
<tr>
<td></td>
<td>HBV DNA&gt;2000 IU/mL</td>
<td>—Treat: NAs (TDF or ETV preferred)</td>
</tr>
<tr>
<td></td>
<td>HBV DNA&lt;2000 IU/mL</td>
<td>—Consider treatment if ALT is elevated</td>
</tr>
<tr>
<td></td>
<td>—Refer for liver transplant</td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>Cirrhosis: Compensated</td>
<td>—Refer for liver transplant</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis: Decompensated</td>
<td>—Refer for liver transplant</td>
</tr>
<tr>
<td></td>
<td>—Treat with LAM (or LdT)+ADV, TDF, or ETV</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADV, adefovir; ALT, alanine aminotransferase; ETV, entecavir; HBcAg, hepatitis B c antigen; HBsAg, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; LAM, lamivudine; LdT, telbivudine; LAM, lamivudine; NA, not available; Peg-IFN, pegylated interferon-alfa; PCR, polymerase chain reaction; peg-IFN, pegylated interferon; TDF, tenofovir; ULN, upper limits of normal.

**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. Antiviral resistance and lack of adherence are the primary contributors to NA treatment failure among patients with chronic hepatitis B (CHB). 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. In addition, because cross-resistance occurs among agents, resistance to one agent can limit substitution for another later in therapy. 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. Therefore, reducing the risk of resistance is essential to successful, long-term HBV treatment. Resistance rates for approved NAs are shown in Table 11. Both entecavir and tenofovir are potent agents with a high genetic barrier to resistance, 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. 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. Tenofovir has a lower 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. Resistance rates during long-term therapy are high with adefovir and approach 70% with lamivudine monotherapy at 5 years. The American Association for the Study of Liver Diseases (AASLD) recommends several strategies to prevent and manage antiviral resistance (Table 12). These include choosing the most potent agent with the highest genetic barrier to resistance, avoiding unnecessary treatment, and reinforcing adherence to therapy.

### Table 11. Viral resistance rates for available nucleosides and nucleotides

<table>
<thead>
<tr>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg-positive patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>15%–30%</td>
<td>None&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>At &gt; 1 year</td>
<td>70% at 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No data available</td>
<td>&lt;1% up to 4 years&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>HBeAg-negative patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>15%–30%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>At &gt; 1 year</td>
<td>70% at 5 years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29% at 5 years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;1% up to 4 years&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>c</sup>Marcellin P, Heathcote EJ, Jacobson I, et al. Safety and tolerability of 96 weeks of tenofovir disoproxil fumarate (TDF) treatment in HBeAg-negative patients treated 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.
<sup>d</sup>In lamivudine-resistant patients, viral resistance was 7% during year 1 of therapy and up to 43% at year 4.

### Table 12. Management of resistance

#### Prevention

- Avoid unnecessary treatment
- Initiate treatment with potent antiviral that has low rate of drug resistance or 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
- Adefovir resistance: Stop lamivudine, switch to tenofovir + entecavir<sup>a</sup> or switch to or add entecavir<sup>a</sup>
- Entecavir resistance: Switch to tenofovir or tenofovir + entecavir<sup>a</sup>
- Tenofovir resistance: Add adefovir or tenofovir

<sup>a</sup>In HBV infected persons; minimal data are available in non-HBV infected persons.

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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 infection accompanied by rising HBV DNA levels and ALT level elevations during immunosuppressive treatment or chemotherapy. Reactivation is more likely with the use of corticosteroids. Therefore, the AASLD recommends that all patients who are scheduled for chemotherapy or immunosuppressive therapy, and particularly those undergoing treatment with rituximab, be screened for HBSAg and antibody to hepatitis B core antigen (anti-HBc).<sup>2</sup> The AASLD also recommends that patients who are HBeAg-positive receive prophylactic NA treatment before and after chemotherapy or immunosuppressive therapy.<sup>2</sup> Interferons should be avoided with this patient population because of hematologic side effects. 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.<sup>2</sup> 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 tenofovir may be used as prophylactic therapy. 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. The criteria for CHB treatment in coinfected patients are the same as for those without HIV, but prompt treatment of patients with HIV and CHB is important for they are at greater risk of liver-related mortality and cirrhosis. 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). In patients not previously treated for HIV or HBV, the AASLD recommends combination therapy with tenofovir and lamivudine or tenofovir and emtricitabine. Tenofovir is effective against lamivudine-resistant HBV and should be added to the regimen of coinfected patients on antiretroviral therapy (ART) with lamivudine resistance.

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. Patients with CD4 cell counts >500 cells/mm³ can be treated with peg-INF; adefovir is recommended for those with lower CD4 cell counts or those who are hepatitis B e antigen (HBeAg)-negative. 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-INF or adefovir. Although the combination of telbivudine and adefovir can also be an option. 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. 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.

HCV coinfection. An estimated 14% of patients with CHB in the United States are coinfected with hepatitis C virus (HCV). Cofected patients are at greater risk of cirrhosis and hepatocellular carcinoma (HCC) than patients who have either HCV or CHB alone. Because data are lacking, the AASLD guidelines do not provide recommendations on the treatment of patients with CHB who are coinfected with HCV. 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. However, rebound in serum HBV DNA levels and reactivation of HBV have been reported. 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. In the absence of definitive, randomly assigned controlled trials, some experts recommend initial treatment with peg-INF and RBV at the doses approved for HCV treatment. 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-INF 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-INF may be treated with NAs according to standard guidelines for therapy; 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 hepatitis B virus (HBV) for replication. The HDV response following a 48-week course of consolidation treatment still occurs. However, efficacy may be lower for women with very high HBV DNA levels. 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.

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. In addition, substantial data has accumulated on the safety of tenofovir and/or lamivudine or emtricitabine in HBV-positive pregnant women. Lamivudine, adefovir, and entecavir are pregnancy category B drugs; tenofovir and telbivudine are category B drugs. 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 HBV DNA who are positive for HBeAg may require increased monitoring to detect early pregnancy-related increases in HBV DNA.

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