

SPECIAL REPORT

A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2008 Update

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Chronic HBV infection is an important public health problem worldwide and in the United States. A treatment algorithm for the management of this disease, published previously by a panel of U.S. hepatologists, has been revised on the basis of new developments in the understanding of the disorder, the availability of more sensitive molecular diagnostic tests, and the licensure of new therapies. In addition, a better understanding of the advantages and disadvantages of new treatments has led to the development of strategies for reducing the rate of resistance associated with oral agents and optimizing treatment outcomes. This updated algorithm was based primarily on available evidence by using a systematic review of the literature. Where data were lacking, the panel relied on clinical experience and consensus expert opinion. The primary aim of antiviral therapy is durable suppression of serum HBV DNA to low or undetectable levels. Assays can now detect serum HBV DNA at levels as low as 10 IU/mL and should be used to establish a baseline level, monitor response to antiviral therapy, and survey for the development of drug resistance. Interferon alfa-2b, lamivudine, adefovir, entecavir, peginterferon alfa-2a, telbivudine, and tenofovir are approved as initial therapy for chronic hepatitis B and have certain advantages and disadvantages. Although all of these agents can be used in selected patients, the preferred first-line treatment choices are entecavir, peginterferon alfa-2a, and tenofovir. Issues for consideration for therapy include efficacy, safety, rate of resistance, method of administration, and cost.

Chronic hepatitis B (CHB) remains an important public health problem and a leading cause of liver-related morbidity and mortality worldwide.¹ In the United States, an estimated 1.25 million individuals, or 0.4% of the population, are infected with hepatitis B virus (HBV).² During the last 2 decades, the influx of foreign-born persons immigrating to the United States from areas of high endemicity, including Asia, the Middle East, and Africa, has contributed to an increased presence of CHB, particularly in urban areas and communities with

a high immigrant population.^{3,4} Thus, it is likely that the incidence of CHB is considerably higher than the estimated 1.25 million. When left untreated, individuals with CHB are at increased risk for developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). It is estimated that up to 5000 people die each year in the United States of these complications of HBV infection.¹ The cumulative rate of morbidity and mortality from cirrhosis and liver cancer related to CHB is highest among individuals who acquire HBV infection as neonates or in early childhood.¹

To help guide clinicians in treating patients with CHB, a panel of U.S. hepatologists published a treatment algorithm in 2004,⁵ which was subsequently revised in 2006 on the basis of new developments in the field.⁶ These advances have included a better understanding of the natural history of CHB and the availability of more sensitive molecular diagnostic tests. The number of antiviral agents for the treatment of patients with CHB has expanded from 5 to 7 with the approval of telbivudine in 2006 and tenofovir in 2008 by the U.S. Food and Drug Administration (FDA). In addition, there are now better defined strategies for optimizing patients' responses to oral antiviral therapy.⁷ Emerging data on promising antiviral therapies in late stages of clinical development, along with the potential likely demonstration of the safety and efficacy of combination therapy, suggest that there will be future management options in addition to the agents that are currently used as monotherapy for the treatment of CHB. Finally, data are accumulating on special patient populations who pose unique challenges and special requirements for antiviral therapy.

In light of these advances, the panel met again to reassess and revise its recommendations. The aim was to build on the

Abbreviations used in this paper: AFP, alpha-fetoprotein; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; cccDNA, covalently closed circular DNA; CDC, Centers for Disease Control and Prevention; CHB, chronic hepatitis B; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HR, hazard ratio; PCR, polymerase chain reaction; REVEAL, Risk Evaluation Viral Load Elevation and Associated Liver Disease; RR, relative risk; ULN, upper limit of normal.

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Table 1. Phases of Chronic HBV Infection

| Phase | ALT | Liver histology | HBV DNA | HBeAg | HBsAg |
|---|--|---|---|-----------------------------|----------------|
| Immune tolerance phase | Normal or minimally elevated | Minimal activity; absent or scant fibrosis | High levels: serum HBV DNA >20,000 IU/mL | Positive; anti-HBe–negative | Positive >6 mo |
| Immune clearance phase (HBeAg-positive CHB) | Elevated, usually persistently or with intermittent elevations | Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥ 4) ^a | High levels: serum HBV DNA >20,000 IU/mL | Positive; anti-HBe–negative | Positive >6 mo |
| Inactive HBsAg carrier state | Persistently normal | Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score <4) ^a | Low or undetectable levels: serum HBV DNA negative or <2000 IU/mL | Negative; anti-HBe–positive | Positive >6 mo |
| Resolution | Normal | Inactive; scant fibrosis | No detectable serum HBV DNA (low levels might be detectable in the liver) | Negative; anti-HBe–positive | Negative |
| Reactivation phase (HBeAg-negative CHB ^b) | Elevated, often fluctuating levels | Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥ 4) ^a | Moderate, often fluctuating levels: serum HBV DNA >2000 IU/mL | Negative; anti-HBe–positive | Positive >6 mo |

^aLiver biopsy optional.

^bMost of these patients have precore or core promoter variants. Data from Hoofnagle et al¹⁸ and Yim and Lok.¹⁷

existing algorithm, preserving its practical approach and comprehensiveness, and update the guidelines for the diagnosis, treatment, and monitoring of patients with chronic HBV infection in the United States. The panel used the same methods of evaluation as for the previous algorithm by reviewing the literature and current international guidelines.^{6,8-10} A comprehensive, structured literature review was conducted by using the PubMed computerized bibliographic database for English-language articles published between August 1, 2005 and March 28, 2008 that addressed the treatment of CHB. The panel also reviewed abstracts from the following conferences and included them in the evidence table: Digestive Disease Week 2006 and 2007, the American Association for the Study of Liver Diseases Annual Meeting 2006 and 2007, the European Association for the Study of the Liver Annual Meeting 2007 and 2008, and the Asian Pacific Association for the Study of Liver Disease 2007 and 2008. Where possible, the panel based their recommendations solidly on evidence, but where data were lacking, panel members relied on their own clinical experience and expert opinion.

The goal of the revised algorithm presented here is to provide physicians with the most current information on the screening, diagnosis, and treatment of CHB. Specifically, the algorithm provides answers to several practical questions: (1) which patients are candidates for antiviral therapy?, (2) what are the advantages and disadvantages of available treatment options?, (3) when should therapy be initiated?, (4) when can therapy be stopped?, (5) what is the role of on-treatment monitoring?, and (6) which strategies should be used to modify therapy to decrease the risk for antiviral resistance? As a background to an application of the recommendations, this article reviews the current understanding of the clinical aspects of chronic HBV infection and presents updated algorithm recommendations for the management of CHB.

Natural History of Chronic Hepatitis B Virus Infection

The accurate and early diagnosis of chronic HBV infection is an important step in patient management. An understanding of the natural history of CHB is fundamental to the evaluation and management of CHB, playing a critical role in the assessment of patient status and in guiding decisions regarding candidacy for treatment and treatment end points. The natural course of HBV infection is a dynamic interplay of complex interactions involving the virus, the hepatocyte, and the host immune response, which, together with the influence of various external factors, determine disease severity and progression.¹¹⁻¹⁵ The natural history of HBV infection can be divided into distinct phases: immune tolerance, immune clear-

Table 2. Definitions of Clinical Terms Used in the Course of HBV Infection

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|---|
| Acute exacerbation or flare of hepatitis B: intermittent increase of aminotransferase activity to $>10 \times$ ULN and $>2 \times$ baseline |
| Reactivation of hepatitis B: 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 decrease in serum HBV DNA to $<20,000$ IU/mL |
| HBeAg reversion: reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe–positive |
| Resolution: loss of HBsAg and no further virologic, biochemical, or histologic evidence of active virus infection or disease |

ance, inactive carrier of HBsAg, and reactivation.^{16,17} Each phase is characterized by distinct patterns of serologic markers, HBV DNA levels, and changes in serum levels of ALT and AST that indicate the immunologic and necroinflammatory status of the patient. The clinical terms and definitions used to characterize the stages of CHB adopted at the National Institutes of Health conference on the Management of Hepatitis B are summarized in Table 1.¹⁸ Other clinical terms relating to HBV infection are summarized in Table 2.

The clinical course of CHB is variable, and not all patients will experience every phase of infection. Acquisition of HBV at birth or in early childhood is associated with a long latency period of immune tolerance, which might last for 2–3 decades before immune clearance characterized by HBeAg seroconversion to antibody to HBeAg (anti-HBe), whereas infection later in life is associated with a very short immune tolerance phase or none at all.^{16,19} The onset of chronic HBV infection is marked by the continued presence of HBsAg, high levels of serum HBV DNA, and the presence of HBeAg in serum. A 5-year follow-up study involving HBsAg-positive individuals in the immune tolerance phase found that these patients exhibit minimal histologic changes, and those remaining in the immune tolerance phase experience no or minimal disease progression.^{17,20} Transition to the immune clearance phase is characterized by fluctuating or generally high HBV DNA levels, with frequent hepatitis flares or ongoing hepatic necroinflammatory damage that might lead to variable degrees of fibrosis or cirrhosis. The immune clearance phase ends when the patient undergoes HBeAg seroconversion, with loss of HBeAg and development of anti-HBe. Loss of HBeAg and seroconversion to anti-HBe usually are preceded by a marked decrease in serum HBV DNA levels to <20,000 IU/mL, although often still detectable, and are typically followed by the normalization of ALT levels.²¹ Thus, HBeAg seroconversion usually represents a transition from the immune clearance phase to an inactive carrier state, although some patients directly transition to the reactivation phase clinically called HBeAg-negative CHB and associated with the presence of the precore and/or double basal core promoter mutant virus.

During the inactive carrier state, there is little evidence of hepatitis by clinical and laboratory evaluation, and serum HBV DNA levels are markedly reduced or undetectable.^{17,22–24} A minority of patients (annual incidence, 0.1%–0.8% for Asians and 0.4%–2% for whites) will lose HBsAg, which is referred to as resolution of the carrier state. It is not uncommon for a small proportion of patients in the inactive carrier state to experience reversion back to HBeAg positivity or reactivation of disease, either spontaneously or through immune suppression after years of inactivity.^{25,26} This is most likely caused by the presence of detectable HBV DNA levels in the liver in the form of covalently closed circular DNA (cccDNA).²⁷ These findings underscore the fact that even HBsAg clearance is not tantamount to the complete resolution of HBV infection.

In addition, one third or more of inactive carriers experience a return of high levels of HBV DNA and persistent or intermittent increases in ALT levels, despite the absence of HBeAg.^{22,28,29} This form of chronic HBV infection, referred to as the reactivation phase or HBeAg-negative CHB, is associated with the selection of viral mutants that fail to produce HBeAg or have reduced HBeAg production.³⁰ The most common mutation is a guanine to adenine substitution at nucleotide 1896 in the

precore region. This mutation results in a TAG stop codon at codon 28 of the precore protein, thereby preventing HBeAg production, and is termed the precore mutant. A second dual mutation, the double basal core promoter mutant involving 2 nucleotide substitutions (A1762T and G1764A), leads to the down-regulation of HBeAg production.³¹ Alone or in combination, these mutations account for the majority of HBeAg-negative CHB. The HBeAg-negative form of CHB has been reported to occur more frequently in patients with HBV genotypes B, C, and D compared with genotype A, with genotype D having a particularly strong association with the precore mutation.³²

Sustained spontaneous remission is uncommon in patients with HBeAg-negative CHB (incidence, 6%–15%), and the long-term prognosis is reportedly poorer compared with that for HBeAg-positive patients, although this might in part reflect a later stage of HBV infection.²⁹ A recent long-term follow-up study involving 1965 asymptomatic inactive HBsAg carriers who were followed for 20,298 person-years showed that HBeAg-negative hepatitis recurred at an annual incidence of 1.5%, with a cumulative probability of 10% at 5 years, 17% at 10 years, and approximately 20% after 15 years.³³ In this study, spontaneous HBsAg seroclearance occurred at an annual incidence of up to 1.15%, with a cumulative probability of 8% at 10 years, 25% at 20 years, and 45% at 25 years of follow-up. It is unclear whether these results can be universally applied to all inactive carriers, because this was a special group of patients with normal ALT levels and serum HBV DNA was not routinely tested. Patients who lose HBsAg have a much better prognosis than do their HBsAg-persistent counterparts.³⁴ Long-term follow-up of HBsAg-positive, HBeAg-negative individuals, involving the serial testing of HBV DNA and ALT levels, is recommended to confirm that the inactive carrier state is maintained.⁸

Hepatitis B Virus DNA and Disease Progression

Large, long-term population-based studies of HBsAg-positive individuals have demonstrated a strong relationship between the risk of progression to cirrhosis, HCC, or both and ongoing HBV replication.^{12,35–37} In both natural history and therapeutic studies, patients with cirrhosis who are seropositive for HBeAg, HBV DNA, or both have an approximately 4-fold higher risk of further disease progression to decompensation, HCC, and death than do patients who are HBeAg seronegative.^{15,38–40}

The relationship between serum HBV DNA levels and risk of disease progression has been most convincingly demonstrated in the Risk Evaluation Viral Load Elevation and Associated Liver Disease (REVEAL) study, a large, prospective cohort study that assessed the natural history of CHB in 3653 untreated HBsAg-positive Asian individuals.¹² Patients were followed for an average of 11.4 years, during which 164 study participants developed HCC. The cumulative incidence of HCC increased progressively in a direct relationship to HBV DNA levels at study entry. The multivariable-adjusted relative risk (RR) of HCC increased from 1.1 at HBV DNA levels of 300 to <10⁴ copies/mL to 6.1 at HBV DNA levels of >10⁶ copies/mL.¹² However, patients with HBV DNA levels of ≥10⁴ to <10⁵ copies/mL also were at a significant risk of HCC (RR, 2.3), and patients with increasing levels of HBV DNA over time or with persistently increased levels during follow-up were at the highest risk for HCC. In contrast, a lowering of HBV DNA levels

from the highest levels was linked with a reduction in risk of HCC, but only when the HBV DNA level decreased to $<10^4$ copies/mL. Reanalysis of the REVEAL study data with more sensitive real-time polymerase chain reaction (PCR) methods for quantifying serum HBV levels showed an increasing risk of HCC up to $>10^6$ copies/mL.⁴¹

In a recent subanalysis of the REVEAL cohort, Iloeje et al³⁵ found that individuals with low levels of HBV DNA ($<10^4$ copies/mL), who are often classified as having “inactive” disease, are also at an increased risk for HCC development, compared with uninfected (HBsAg-negative) individuals. This analysis involved 3584 HBsAg-positive and 18,541 HBsAg-negative patients as controls who were followed for 12 years. Moreover, during follow-up, individuals with persistently low levels of HBV DNA (≥ 300 to $<10^4$ copies/mL) had an increased risk of developing HCC, compared with patients whose HBV DNA levels were persistently undetectable (<300 copies/mL). Another analysis of the REVEAL cohort, involving 3582 participants, found a positive direct relationship between the risk of cirrhosis and serum HBV DNA levels.³⁶ More than 90% of the cohort had serum ALT levels <45 U/L; 85% were HBeAg-negative, and 98% had no sonographic evidence of cirrhosis. The cumulative incidence of cirrhosis increased from 5% for patients with a viral load of <300 copies/mL to 36% for patients with a viral load of $\geq 10^6$ copies/mL ($P < .001$).³⁶ Furthermore, the risk for cirrhosis was independent of HBeAg status and serum ALT level. These studies provide evidence that viral replication plays a critical role in the progression of chronic HBV infection, thus establishing a rationale for antiviral therapy to arrest the progression of liver disease.

Risk Factors for Disease Progression

Viral and host factors have been shown to influence disease progression to cirrhosis or HCC.¹⁵ In large, long-term, natural history studies of HBsAg-positive individuals, viral and disease factors that were predictive of HCC included the presence of HBeAg (hazard ratio [HR], 4.2), HBV DNA levels $>10^4$ copies/mL (HR, 2.7), and HBV DNA levels $>10^5$ copies/mL (HR, 8.9–10.7).¹² Host factors included male gender (HR, 3.0), advanced age (HR, 3.6–8.3), alcohol consumption (HR, 2.6), and cigarette smoking (HR, 1.7). Other factors that have been reported to negatively influence the course of HBV-related liver disease include coinfection with HCV or HDV (usually as the result of injection drug use or multiple sex partners), human immunodeficiency virus (HIV) coinfection, conditions associated with acute or chronic immunosuppression, HBV genotype (particularly genotype C), the presence of HBV precore and especially core promoter mutations, and the severity and frequency of ALT elevations.¹⁵

Screening and Initial Patient Evaluation

Candidates for Hepatitis B Virus Screening and Vaccination

During the last 2 years, the guidelines for the screening and vaccination of individuals with HBV infection have been revised by the Centers for Disease Control and Prevention (CDC).^{42,43} All persons in high-risk groups for hepatitis B should be screened for serum HBsAg (Table 3).^{40,42,43} Testing for hepatitis B should be performed on any person with risk factors

Table 3. Groups at High Risk for HBV Infection Who Should Be Screened for HBV

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|--|
| Individuals born in areas of high and intermediate prevalence rates for HBV, including immigrants and adopted children |
| <ul style="list-style-type: none"> • Asia-Pacific region • Middle East • European-Mediterranean region, including Greece, Italy, Malta, Portugal, and Spain • Indigenous populations of the Arctic region • South America • Eastern Europe, including Russia and independent states of former Soviet Union • Caribbean region |
| Other high-risk groups recommended for screening |
| <ul style="list-style-type: none"> • Household and sexual contacts of HBsAg-positive persons • Persons who have ever injected drugs • Persons with multiple sexual partners or a history of sexually transmitted disease • Men who have sex with men • Inmates of correctional facilities • Individuals with chronically elevated ALT or AST levels • Individuals coinfecting with HCV or HIV • Patients undergoing renal dialysis • Pregnant women |

Data from Fattovich et al⁴⁰ and Mast EE et al.^{42,43}

for acquiring HBV infection and in persons with elevated liver enzymes or evidence of active liver disease without an identified cause. The administration of hepatitis B vaccine is recommended for individuals in high-risk populations who are HBsAg-seronegative.^{42,43}

Initial Patient Evaluation

Initial evaluation of patients with chronic HBV infection and the suggested follow-up evaluation of patients with CHB are indicated in Table 4. The initial evaluation should include a thorough history and physical examination, with particular attention to family history of HBV infection and liver cancer, risk factors for coinfection, and alcohol use. Laboratory tests should include assessment of liver disease, HBeAg and anti-HBe, markers of HBV replication, tests for coinfection with other viruses for individuals at risk, and HBV genotype in select circumstances, particularly when peginterferon therapy is being considered. A liver biopsy examination also is recommended for patients who have intermittent or persistent increases in ALT levels, but it is not mandatory. Liver biopsy might be particularly useful in patients with elevated serum HBV DNA but normal ALT levels and age >35 –40 years of age (see below). Screening for HCC should be considered in high-risk individuals, particularly family history of HCC and older age. Patients also should be counseled on precautions to prevent the transmission of HBV infection, and sexual and household contacts should be vaccinated. All patients should be discouraged from heavy alcohol use (there is no proven safe level of alcohol use). Abstinence from alcohol is recommended for patients with cirrhosis. All individuals with chronic HBV infection who are not immune to hepatitis A should be vaccinated according to CDC recommendations (ie, 2 doses of hepatitis A vaccine, with an initial injection at baseline and a booster injection at 6–18 months).⁴⁴ A detailed discussion of diagnostic testing for CHB follows.

Table 4. Pretreatment Evaluation and Initial Follow-Up

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|---|
| Pretreatment evaluation |
| History and physical examination |
| <ul style="list-style-type: none"> ● 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 ● General counseling regarding transmission ● Vaccination of at-risk household and sexual contacts ● Family planning |
| Pretreatment tests |
| <ul style="list-style-type: none"> ● Serial testing of ALT and HBV DNA level during 6-mo period ● Liver function tests <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ Anti-HCV ○ Anti-HDV, if from endemic area ● Hepatitis A immunity: anti-HAV ● HIV: anti-HIV ● Screen for HCC in high-risk patients: AFP and ultrasound ● Liver biopsy examination to grade and stage liver disease^a ● Urinalysis; if abnormal, perform 24-hour urine for creatinine and protein |
| Suggested follow-up for patients not considered for treatment |
| <ul style="list-style-type: none"> ● HBeAg-positive CHB with HBV DNA $\geq 20,000$ IU/mL and normal ALT <ul style="list-style-type: none"> ○ ALT every 3–6 mo ○ Consider liver biopsy examination and/or treatment when ALT levels become increased ● HBeAg-negative CHB with HBV DNA ≥ 2000 IU/mL and normal ALT <ul style="list-style-type: none"> ○ ALT every 3–6 mo ○ Consider liver biopsy examination and/or treatment when ALT levels become increased ● Inactive carrier state <ul style="list-style-type: none"> ○ ALT every 6–12 mo ○ If ALT levels become increased, check serum HBV DNA and exclude other causes of disease |

^aLiver biopsy is optional for patients meeting treatment criteria but might be especially helpful in patients with normal ALT levels and age >35–40 y.

Serologic Tests

Serologic tests for virologic markers of HBV infection, including HBsAg and antibodies to the surface antigen (anti-HBs) and core antigen (anti-HBc), can distinguish acute, chronic, or past infection, as well as detect individuals who have been vaccinated. Acute HBV infection can be diagnosed by the detection of HBsAg and IgM anti-HBc along with the presence of total (IgG plus IgM) anti-HBc. A pattern indicative of recent acute infection is isolated total anti-HBc, which occurs in the window between the disappearance of HBsAg and the development of anti-HBs. Isolated anti-HBc might also indicate the presence of occult hepatitis B, and measurement of serum HBV DNA might be helpful in this setting. Patients with this sero-

logic pattern should be followed with repeat testing of HBsAg, anti-HBc, and anti-HBs in 3–6 months to distinguish these possibilities.

The persistence of HBsAg 6 months beyond the onset of acute hepatitis B is adequate for a diagnosis of CHB, although waiting this time period is not necessary in patients presenting de novo with detectable HBsAg and clinical and/or epidemiologic factors suggestive of chronic HBV infection. Patients with the chronic form of the disease also have detectable levels of total anti-HBc but usually not of IgM anti-HBc, which distinguishes them from patients with acute hepatitis B.

Resolved HBV infection is characterized by the absence of HBsAg and the detection of anti-HBs and anti-HBc. Vaccine recipients are differentiated from patients with resolved infection by the detection of anti-HBs without anti-HBc. Although anti-HBs titers after vaccination decline over time, the majority of successfully vaccinated individuals have anamnestic responses to single doses of vaccine.^{45,46}

Hepatitis B Virus DNA Testing

Serum HBV DNA testing is a direct measure of the level of viral replication. This quantification is important for characterizing the status of infection and predicting the risk of cirrhosis and HCC; therefore, it should be obtained for all persons diagnosed with CHB. The introduction of an IU, which is equivalent to approximately 5–6 copies, as the recommended reporting unit for HBV DNA has facilitated standardized reporting and comparison of serum HBV DNA levels in clinical trials and daily practice.⁴⁷ Several HBV DNA assays commonly used for the quantification of serum HBV DNA levels have been normalized to the international standard.⁴⁸

Methods used in the quantification of HBV DNA have evolved rapidly. Considerable variation exists in the reproducibility and sensitivity of the different HBV DNA quantification assays available. The ideal HBV DNA assay should have a linear, broad dynamic range of quantification allowing the evaluation of viremia at both the lowest and highest concentrations. Hybridization assays (Digene Hybrid Capture 2 assay; Digene Corporation, Gaithersburg, MD) demonstrate the reliable quantification of HBV DNA but are limited by a narrow range of detection (10^3 – 10^7 IU/mL). PCR-based assays have increased the sensitivity, detecting HBV DNA at levels as low as 10^2 IU/mL; however, quantification is not as reliable at viral levels $>10^6$ IU/mL with many of the earlier PCR-based assays (Cobas and Amplicor; Roche Diagnostics, Basle, Switzerland). Real-time PCR-based assays (COBAS TaqMan; Roche Diagnostics and RealART HBV; Qiagen Inc, Valencia, CA and Abbott Real Time PCR; Abbott Molecular, Des Plaines, IL) have been introduced that demonstrate both sensitivity and a broad linear range of quantification (10 – 10^8 IU/mL).⁴⁹

The panel recommends real-time PCR assays as the preferred test for the initial evaluation of patients and, even more importantly, for monitoring both treated and untreated patients. However, clinicians might have little control over the method of HBV testing, which is often dictated by providers. Therefore, clinicians should be aware of the sensitivity and dynamic range of the test used for the quantification of serum HBV DNA levels. The same test should be specified each time when monitoring HBV DNA levels for a given patient in clinical practice to ensure consistency.

Hepatitis B Virus Genotype Testing

HBV genotypes appear to influence the progression of disease, the risk of HCC, and the response to therapy.⁵⁰⁻⁵⁵ Preliminary data suggest that HBV genotype might be related to clinical outcomes. Some studies in Asia suggest that genotype C is associated more frequently with HBV reactivation, severe liver disease, and HCC than is genotype B.^{13,53,56-58} Genotype B appears to be associated with seroconversion from HBeAg to anti-HBe at a younger age than genotype C.^{56,59,60} It is also possible that genotype C is responsible for more cases of perinatal transmission, given that HBeAg seroconversion occurs decades later than in other genotypes.⁶⁰ Genotype has not been shown to consistently influence the outcome of therapy with oral nucleoside and nucleotide analogs. However, genotype has been shown to affect response to interferon therapy, in that genotypes A and B appear to be associated with higher rates of antiviral response to interferon alfa-2b therapy than are genotypes D and C.⁶¹ In a study evaluating patients treated with peginterferon alfa-2a with or without lamivudine, HBV genotype, in addition to baseline ALT and HBV DNA levels, patient age, and gender, significantly influenced the attainment of combined response at 24 weeks after treatment.⁶² At 1 year after treatment, HBV genotype was significantly predictive of efficacy for patients treated with peginterferon alfa-2a with or without lamivudine.⁶² In addition, higher rates of HBeAg seroconversion after treatment with peginterferon alfa-2a have been reported in patients with genotype A than in patients with other genotypes when treated with this drug,^{6,63} and higher rates of HBeAg loss after treatment with peginterferon alfa-2b have been reported in patients with both genotypes A and B.⁵⁰

In light of these data, the panel recommends that genotyping be performed selectively to help identify patients who might be at greater risk for disease progression and routinely when there is consideration of peginterferon therapy to determine the most appropriate candidates for treatment. An informed discussion regarding the option of treatment with peginterferon versus an oral agent is enhanced by knowledge of the likelihood of response to peginterferon.

Commercial tests for HBV genotyping are now available through referral laboratories as part of the standard panel of tests for HBV infection. These tests differ from HBV phenotype tests conducted *in vitro* to determine the degree of resistance conferred by various mutations in the viral genome that arise during therapy (see the section on HBV resistance testing). The diagnostic tests currently available to determine genotype include sequencing-based assays, which are the gold standard for HBV genotyping, and a line probe assay (INNO-LiPA HBV genotype; Innogenetics NV, Ghent, Belgium).⁶⁴ Real-time PCR or multiplex PCR assays can also be used for genotype analysis if validated against the gold standard.

Other Screening

Fibrosis Screening

After initial serologic testing and HBV DNA quantification, it might also be helpful to establish the baseline liver histology before the initiation of therapy and to exclude other causes of liver disease. Liver biopsy is currently the gold standard for this assessment, but its use is limited because of its invasiveness, and it only samples a small portion of the liver; in addition, it has limited interobserver and intraobserver concor-

dance. Although significant progress has been made during the past few years in the development of noninvasive methods for assessing fibrosis and in the identification of potential serum markers of fibrosis, the panel does not believe that these methods have been validated fully; thus, they are not ready for routine clinical use in CHB, although they might be helpful on a case-by-case basis.⁶⁵⁻⁶⁹

Screening for Hepatocellular Carcinoma

The panel recommends following the standard approach for HCC screening as outlined in the American Association for the Study of Liver Diseases Practice Guideline.⁷⁰ Standard tools for HCC screening include alpha-fetoprotein (AFP) testing and ultrasound. Magnetic resonance imaging and computed tomography, although more expensive, generally are considered to be more sensitive than ultrasound and might be preferred by clinicians for some patients (eg, those with cirrhosis or obesity, in whom ultrasound has poor sensitivity). Screening should be performed every 6 months with AFP and ultrasound, particularly in patients at high risk of HCC, such as Asian men older than 40 years of age and Asian women older than age 50, persons with cirrhosis, Africans older than age 20, persons with a family history of HCC, and any carrier older than 40 years of age exhibiting persistent or intermittent ALT elevations, high HBV DNA levels (>2000 IU/mL), or both.⁸ The panel also recommends earlier screening (at 30-35 years of age or even younger) in Asian patients with presumed infection at the time of birth or in early childhood because of the higher risk for HCC in this patient population.

Candidates for Therapy

Although there is general agreement on the tests that should be ordered in the initial evaluation of patients with chronic HBV infection (Table 4), controversy remains regarding the identification of candidates for therapy and how to follow patients who are not initially considered for therapy, particularly HBeAg-positive patients with high HBV DNA levels and normal ALT levels.

Normal Versus Elevated Alanine Aminotransferase Levels

The serum ALT level has been commonly used for the assessment of liver disease and as an important criterion for defining which patients are candidates for therapy. The relevance of increased ALT levels to the decision to treat is based on its value in predicting a serologic response to antiviral therapy.⁷¹⁻⁷³ However, relying solely on the finding of increased ALT levels as a prerequisite to treatment candidacy has limitations. There is a lack of correlation between the extent of liver cell necrosis and the degree of increase in ALT, which means that ALT alone does not identify patients with necroinflammatory activity or fibrosis.⁷⁴ ALT activity also might be affected by other factors such as body mass index, gender, abnormal lipid and carbohydrate metabolism, fatty liver, and uremia.^{74,75} Elevations in ALT levels also might occur under various circumstances, such as during spontaneous HBeAg loss, in association with some antiviral therapies, and during infection with other viruses.⁷⁶

Moreover, data from clinical studies have shown that the true normal values of ALT are significantly lower than the

previously established limits, which were 40 IU/mL for men and 30 IU/mL for women, and are also significantly lower than the variously defined upper limit of normal (ULN) values used by commercial laboratories. Data from cohort studies involving first-time blood donors and healthy volunteers indicate that the ULNs for ALT and AST should be decreased to 30 IU/mL for men and 19 IU/mL for women.^{74,75} Clinical studies have shown that HBV-infected individuals with ALT values of <40–45 IU/mL are at risk for significant liver disease^{12,36} and mortality from liver complications, including ALT levels between 20 and 30 IU/mL.⁷⁷ Long-term follow-up of 3233 CHB patients from Hong Kong confirmed a relationship between ALT level and disease progression.⁷⁸ Thus, the panel recommends that serum ALT values of 30 IU/L for men and 19 IU/L for women be used as the ULN when making decisions regarding the initiation of therapy.

Patients with high HBV DNA and normal ALT levels generally have less fibrosis on liver biopsy and poor response to antiviral therapy. Accordingly, this patient population is generally not considered for treatment. However, emerging data from several clinical studies suggest that up to one third of patients with persistently normal ALT levels have histologic evidence of significant fibrosis or inflammation on biopsy, particularly patients 35–40 years of age or older.^{79–82} A retrospective study examined the relationship between ALT level and fibrosis in CHB patients.⁷⁹ This study involved 192 patients who were stratified by ALT levels into 3 groups: persistently normal ALT, ALT 1–1.5 × ULN, and ALT >1.5 × ULN. Factors predictive of fibrosis were increasing age (starting at age 40), higher ALT level, higher grade of inflammation on biopsy, and HBeAg positivity. Of the 59 patients with persistently normal ALT levels, 18% had stage 2 fibrosis, and 34% had grade 2 or 3 inflammation. Overall, 37% of patients with persistently normal ALT levels had significant fibrosis or inflammation. Subgroup analysis showed that the majority of patients with fibrosis had ALT levels in the high-normal range, and that only a minority who were young and immune tolerant had significant findings on biopsy.

Similar findings were reported in a second retrospective cohort study involving 129 patients with active CHB and normal ALT who underwent liver biopsy.⁸¹ Only 62% of the patients with normal ALT at evaluation had persistently normal ALT levels on follow-up. Of these, one third had histologic evidence of significant liver disease (ie, stage 2 fibrosis or grade 2 inflammation plus stage 1 fibrosis or higher). Multivariate analysis found older age (starting at age 35) and elevated ALT levels at follow-up to be predictive of significant histology.

These findings indicate that a normal ALT level alone might not be an adequate indicator of who should be treated. ALT levels should be considered in conjunction with the level of serum HBV DNA and the patient's age. Hence, in HBsAg-positive patients with HBV DNA levels $\geq 20,000$ IU/mL and normal ALT levels, a liver biopsy should be considered, particularly in patients older than 35–40 years of age, who are less likely to be in the immune tolerance phase of infection. If significant disease is found (ie, moderate fibrosis [stage 2] or greater, significant necroinflammation, or both), treatment should be considered. Patients with HBV DNA levels $\geq 20,000$ IU/mL and elevated ALT levels (1–2 × ULN) should definitely be treated, regardless of whether a liver biopsy is performed. The panel was split on recommendations for treatment of

patients with HBV DNA levels $\geq 20,000$ IU/mL and persistently normal ALT levels. Some panel members would treat these patients, whereas the majority thought that there were insufficient data at this time to support a mandate for treatment in this patient population, who, if young, are most often in the immune tolerance phase of chronic HBV infection. It was generally agreed that such patients should be monitored every 3–6 months, and a liver biopsy should be considered to determine the extent of liver fibrosis and the need for treatment. If significant disease is found (ie, moderate fibrosis [stage 2] or greater, significant necroinflammation, or both), the patient should be considered for treatment. For young patients (<30 years of age) with HBV DNA levels $\geq 20,000$ IU/mL and persistently normal ALT levels, a liver biopsy was considered to be optional, to be performed at the discretion of the clinician, because many of these patients are in the immune tolerance phase of infection. When a decision to treat HBeAg-positive patients with high HBV DNA and normal levels is considered, it must be recognized that long-term therapy is likely to be needed as a result of the low incidence of HBeAg seroconversion after 1 year in such patients.

Viral Threshold for Treatment

Although mounting data indicate that any level of HBV DNA >300 copies/mL is associated with an increased risk for disease progression,^{19,35} the diagnostic threshold for defining the presence of CHB and indication for therapy remains set at 20,000 IU/mL (10^5 copies/mL) for patients with HBeAg-positive disease and at 2000 IU/mL (10^4 copies/mL) for patients with HBeAg-negative disease.⁸³ However, some HBeAg-positive patients and many HBeAg-negative patients have fluctuating HBV DNA levels that decrease to <20,000 IU/mL and even <2000 IU/mL.^{84,85} In addition, low levels might not necessarily be an indicator of the absence of progressive liver disease; 15% of patients with HCC have HBV DNA levels < 10^3 copies/mL.⁸⁴ For these reasons, it is often difficult to set a single HBV DNA level as a cutoff between HBeAg-negative hepatitis and the inactive carrier state. Serial testing of serum HBV DNA with a sensitive real-time PCR-based assay is recommended to assist in making this distinction.^{8,86}

A lower HBV DNA level (3–5 \log_{10} IU/mL) might be associated with progressive liver disease, necessitating treatment, especially in patients who are HBeAg-negative or who are already cirrhotic.^{6,8,19,87} In the panel's experience, patients can have advanced liver disease even if they have serum HBV DNA levels persistently <20,000 IU/mL; thus, the significance of low HBV DNA levels is uncertain, and the decision to initiate treatment should be individualized.

Goals of Therapy

The goal of therapy for CHB is to eliminate or significantly suppress the replication of HBV and prevent the progression of liver disease to cirrhosis, with culmination in liver failure, or HCC, eventually leading to death or transplantation. Hence, the primary aim of treatment should be to reduce and maintain serum HBV DNA at the lowest possible levels (ie, achieve durable HBV DNA suppression). This, in turn, will promote the other aims of therapy, including histologic improvement and ALT normalization. In patients who are HBeAg-positive before therapy, an additional goal of treatment is loss

of HBeAg with seroconversion to anti-HBe. The latter is preferable, because attainment of complete HBeAg seroconversion indicates a high likelihood that the benefit will persist once the patient is off therapy, enabling the clinician to discontinue treatment at some point after the seroconversion. Loss of HBsAg, although highly desirable, is rarely achieved with short-term antiviral therapy and, hence, is not a realistic goal for antiviral trials.

Hepatitis B Therapies

Currently, 7 drugs are available for the management of chronic HBV infection in the United States: interferon alfa-2b, lamivudine, adefovir, entecavir, peginterferon alfa-2a, telbivudine, and tenofovir. At present, the preferred first-line treatment choices are entecavir, peginterferon alfa-2a, and tenofovir because of their superior efficacy, tolerability, and favorable resistance profiles in HBeAg-positive (Table 5) and HBeAg-negative (Table 6) CHB over comparable drugs in pivotal clinical trials. Standard interferon alfa-2b has largely been replaced by peginterferon alfa-2a in routine practice.^{6,8,88} Lamivudine has been removed from the list of preferred first-line drugs because of its known high rate of resistance and because of evidence from pivotal trials showing the superiority of entecavir and telbivudine to lamivudine.^{6,89–92} Tenofovir should replace adefovir as a first-line drug in previously untreated patients with HBeAg-positive and HBeAg-negative disease, on the basis of pivotal phase III studies showing the superiority of tenofovir over adefovir.^{93,94} In addition, tenofovir has demonstrated potent antiviral activity against HBV in patients coinfecting with HBV and HIV.^{95–99} Although telbivudine demonstrates superior efficacy over lamivudine and adefovir in clinical trials, it is associated with an intermediate rate of resistance compared with these agents.^{89,100} Telbivudine might be a potential treatment option for patients if treatment results in undetectable serum HBV DNA levels at week 24; this is predictive of a very low rate of resistance and continued efficacy, indicated by undetectable virus at week 52.⁸⁹ Other new antiviral agents and immunomodulatory therapies are under investigation but are not yet available commercially. A brief summary of current data for the preferred first-line agents and treatment recommendations follows. It is important to comment that many patients have been successfully treated with lamivudine and adefovir long-term, with persistently undetectable serum HBV DNA over many years. The risk of subsequent antiviral resistance is very low in these patients, and there is general agreement that they do not require a change in their therapy. However, treatment-naïve patients who are beginning therapy for the first time should be treated with entecavir, peginterferon alfa-2a, or tenofovir on the basis of their superior potency and low rate of antiviral drug resistance.

Treatment and Management of Chronic Hepatitis B

Hepatitis B e Antigen–Positive Patients

Peginterferon alfa-2a. The efficacy of peginterferon alfa-2a has been demonstrated in a large phase III randomized study that compared peginterferon alfa-2a 180 $\mu\text{g}/\text{wk}$, lamivudine 100 mg/day, and both drugs in combination for 48 weeks in patients with HBeAg-positive CHB.⁶³ At the end of treat-

ment, therapy with peginterferon alfa-2a, with or without lamivudine, resulted in significantly greater rates of HBeAg seroconversion, HBV DNA undetectability, and ALT normalization, compared with treatment with lamivudine alone (Table 5). At 24 weeks after the end of treatment, the HBeAg seroconversion rate was 32% in the peginterferon alfa-2a arm, compared with 27% in the peginterferon alfa-2a plus lamivudine arm and 19% in the lamivudine monotherapy arm. Although the combination of peginterferon alfa-2a and lamivudine resulted in a greater degree of viral load reduction, the rate of HBeAg seroconversion was not different from treatment with peginterferon alfa-2a monotherapy. Higher rates of HBeAg seroconversion were observed in patients who were HBV genotype A, had low baseline HBV DNA concentrations, or had increased baseline serum ALT levels. These findings suggest that peginterferon alfa-2a might be a reasonable choice as first-line therapy in patients with genotype A or B who are young, lack significant comorbidities, and have HBV DNA levels $<10^9$ copies/mL and ALT levels $\geq 2\text{--}3 \times \text{ULN}$.¹⁰¹

Similar findings have been reported in clinical trials evaluating the efficacy of peginterferon alfa-2b in patients with CHB.^{50,102,103} On the basis of findings from these clinical trials, peginterferon alfa-2b might be an option for the treatment of CHB in countries where it is available. Although the efficacy of peginterferon alfa-2b and peginterferon alfa-2a has not been compared in prospective randomized clinical studies of CHB, data from a small retrospective study comparing the efficacy of agents in 53 HBeAg-positive Chinese patients found a higher rate of sustained virologic response in patients treated with peginterferon alfa-2a for 48 weeks (34.5%), compared with patients treated with peginterferon alfa-2b for 24 weeks.¹⁰⁴ This study is limited by small numbers and different treatment durations with the 2 peginterferons. The side effect profile of peginterferon alfa is similar to that of standard interferon, with the most common side effect being influenza-like illness characterized by fever, chills, headache, malaise, and myalgia as well as psychological side effects. Patients require careful monitoring for the potential development of all of these side effects.

Entecavir. Entecavir is a cyclopentyl guanosine analog that inhibits both the priming and elongation steps of viral replication. It is a highly potent inhibitor of HBV polymerase. In vitro, entecavir demonstrates greater antiviral potency than lamivudine or adefovir and is active against lamivudine-resistant HBV mutants. In a phase III randomized study involving 715 patients with compensated liver disease, entecavir 0.5 mg/day demonstrated superior benefit to lamivudine 100 mg/day at 48 weeks in nucleoside-naïve patients with HBeAg-positive CHB.⁹⁰ At 48 weeks, the entecavir-treated patients had higher rates of histologic improvement (72% vs 62%), HBV DNA reduction (-6.9 vs $-5.4 \log_{10}$), HBV DNA undetectability (<300 copies/mL) (67% vs 36%), and ALT normalization ($\leq 1 \times \text{ULN}$) (68% vs 60%) (Table 5).⁹⁰ Although entecavir is the most potent licensed oral agent in terms of its effect on serum HBV DNA, in this study there was no difference in the rate of HBeAg loss or seroconversion between entecavir and lamivudine after 1 year of therapy. The safety profile of entecavir during a period of 48 weeks was similar to that observed with lamivudine.

A recent report showed continued efficacy of entecavir after 96 weeks of therapy that was superior to that observed with lamivudine.¹⁰⁵ In the follow-up to the study described above, 709 HBeAg-positive CHB patients were randomized to entecavir

Table 5. Comparison of Currently Approved Treatment Options in Patients With HBeAg-Positive CHB

| Parameter ^a | Interferon (vs untreated), ^b 12–24 wk | Peginterferon alfa-2 (vs lamivudine), ^b 48 wk | Lamivudine (vs placebo), ^b 48–52 wk | Adefovir (vs placebo), ^b 48 wk | Entecavir, 48 wk | Telbivudine, 52 wk | Tenofovir, 48 wk |
|--|---|--|--|--|--|---------------------------------------|---------------------------------------|
| HBV DNA loss ^c | 37% (17%) | 25% (40%) | 44% (16%) | 21% (0%) | 67% | 60% | 76% |
| HBV DNA log ₁₀ reduction | Not reported | 4.5 log ₁₀ (5.8) | 5.39 log ₁₀ | 3.52 log ₁₀ (0.55) | 6.86 log ₁₀ | 6.45 log ₁₀ | N/A |
| HBeAg loss | 33% (12%) | 30% (22%) at wk 48, 34% (21%) at wk 72 | 17%–32% (6%–11%) | 24% (11%), 46% at 96 wk, 53% at 144 wk | 22% | 26% | 22% |
| HBeAg seroconversion | 18% | 27% (20%) at wk 48, 32% (19%) at wk 72 | 16%–18% (4%–6%), 50% at 5 y | 12% (6%), 33% at 96 wk, 46% at 144 wk | 21% | 22% | 21% |
| HBsAg loss | 11%–25% at 5 y in white patients | 3% (0%) at wk 72 (HBsAg seroconversion) | <1% (0%) | 0% (0%) | 2% | <1% | 3% |
| ALT normalization | 23% | 39% (62%) | 41%–75% (7%–24%) | 48% (16%) | 68% | 77% | 69% |
| Histologic improvement | N/A | 38% (34%) at wk 72 | 49%–56% (23%– 25%) | 53% (25%) | 72% | 65% | 74% |
| Durability of response | 80%–90% | N/A | 50%–80% | 90% | 69% | 80% | N/A |
| Resistance | No | No | 15%, increasing to 69% at 5 y | N/A | 0.20% at 1 y, 0.5% at 2 y, 1.2% at 3 y, 1.2% at 4 y, 1.2% at 5 y | 5% at 1 y, 25% at 2 y | 0 |
| Defined treatment course | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Unclear |
| Side effects | Many | Better than interferon | Minimal | Minimal | Minimal | Minimal | Minimal |
| Adult dosing regimen | 5–10 MU ^d tiw for 16–24 wk (injection) | 180 µg/wk for 24– 48 wk (injection) | 100 mg qd ^e (oral); minimum of 48 wk | 10 mg qd (oral); minimum of 48 wk | 0.5 mg qd (oral); minimum of 48 wk | 600 mg qd (oral); minimum of 48 wk | 300 mg qd (oral); minimum of 48 wk |
| Cost/year | +++ | ++++ | + | ++ | +++ | ++ | ++ |

Adapted from Keeffe et al.⁶^aAll data are at 1 y unless otherwise stated.^bControl arm.^cInterferon and lamivudine: hybridization assay with lower limit of detection = 10⁵ copies/mL; adefovir: PCR assay (Roche Amplicor Monitor) with lower limit of detection = 400 copies/mL; peginterferon alfa-2a: PCR assay (Roche Cobas) undetectable is < 400 copies/mL; entecavir, telbivudine, tenofovir: PCR assay undetectable is <300 copies/mL.^dMU = million units.^eqd = once daily.

Table 6. Comparison of Currently Approved Treatment Options in Patients With HBeAg-Negative CHB

| Parameter ^a | Interferon (vs untreated), ^b 12–24 wk | Peginterferon alpha-2 (vs lamivudine), ^c 48 wk | Lamivudine (vs placebo), ^d 52 wk | Adefovir (vs placebo), ^e 48 wk | Entecavir, 48 wk | Telbivudine, 52 wk | Tenofovir, 48 wk |
|-------------------------------------|---|--|--|--|---|------------------------------------|------------------------------------|
| HBV DNA loss ^c | 10%–47% (0%) | 63% (73%) | 63% (6%) at week 24 | 51% (0%) | 90% | 88% | 93% |
| HBV DNA log ₁₀ reduction | Not reported | 4.1 log ₁₀ (4.2) | 3.0–4.0 log ₁₀ (1.5) | 3.91 log ₁₀ (1.35) | 5.0 log ₁₀ | 5.23 log ₁₀ | N/A |
| HBeAg loss | 5.6% after 1 y | 3% (0%) at wk 72 | 0% (1.5%) at wk 24 | Not reported | <1% | <1% | N/A |
| ALT normalization | 10%–47% (0%) | 38% (73%) | 63% (6%) at week 24 ^b | 72% (29%) | 78% | 74% | 77% |
| Histologic improvement | Poor data | 59% (58%) at wk 72 | 60% | 64% (33%) | 70% | 67% | N/A |
| Resistance | No | No | 14%, increasing to 70% at 4 y | 0% at 1 y, 3% at 2 y, 11% at 3 y, 18% at 4 y, 29% at 5 y | 0.2% at 1 y, 0.5% at 2 y, 1.2% at 3 y, 1.2% at 4 y, 1.2% at 5 y | 2.2 at 1 y, 11% at 2 y | 0% |
| Defined treatment course | Yes | Yes | Unclear | Minimal | Unclear | Unclear | Unclear |
| Side effects | Many | Better than interferon | Minimal | Minimal | Minimal | Minimal | Minimal |
| Adult dosing regimen | 5–10 MU tiw for 12 mo (injection) | 180 µg/wk for 48 wk (injection) | 100 mg qd (oral); minimum of 48 wk | 10 mg qd (oral); minimum of 48 wk | 0.5 mg qd (oral); minimum of 48 wk | 600 mg qd (oral); minimum of 48 wk | 300 mg qd (oral); minimum of 48 wk |
| Cost/year | +++ | +++++ | + | ++ | ++++ | ++ | ++ |

Adapted from Keeffe et al.⁶

^aAll data are at 1 y unless otherwise stated.

^bControl arm.

^cInterferon and lamivudine: hybridization assay with lower limit of detection = 10⁵ copies/mL; adefovir (Roche Amplior Monitor) with lower limit of detection = 400 copies/mL; peginterferon alpha-2a: PCR assay (Roche Cobas) undetectable is <400 copies/mL; entecavir, telbivudine, tenofovir: PCR assay undetectable is <300 copies/mL.

0.5 mg or lamivudine 100 mg once daily.¹⁰⁵ At week 52, protocol-defined virologic responders (HBV DNA <0.7 mEq/mL, but positive for HBeAg) could continue blinded treatment for up to 96 weeks. At year 2, a greater proportion of entecavir-treated than lamivudine-treated patients achieved HBV DNA <300 copies/mL (74% vs 37%) and ALT normalization (79% vs 68%). Similar proportions of entecavir-treated and lamivudine-treated patients achieved HBeAg seroconversion (11% vs 12%). Significantly higher proportions of entecavir-treated than lamivudine-treated patients achieved cumulative, confirmed HBV DNA levels <300 copies/mL (80% vs 39%) and ALT normalization (87% vs 79%) through 96 weeks.¹⁰⁵ Cumulative, confirmed HBeAg seroconversion occurred in 31% of entecavir-treated and 25% of lamivudine-treated patients. The safety profile was comparable in both groups. Long-term resistance data for entecavir indicate a low resistance rate (1.2%) in nucleoside-naïve patients (HBsAg-positive or -negative) treated for up to 5 years.^{106–108} Higher rates of resistance (51% at 5 years) have been reported in patients with lamivudine-resistant CHB.^{107,108}

The antiviral activity of entecavir is greater than that of adefovir in patients with HBeAg-positive CHB who are treatment-naïve.¹⁰⁹ Results from the E.A.R.L.Y. study, a randomized, open-label study that compared entecavir (0.5 mg) with adefovir (10 mg) in such patients, showed a significantly greater mean reduction in viral load from baseline levels among the entecavir-treated patients than among the adefovir-treated patients after 12 weeks of therapy (–6.23 vs –4.42 log₁₀ copies/mL).¹⁰⁹ The difference in mean HBV DNA change from baseline was significantly higher for entecavir as early as day 10, and this difference was maintained through week 96. At week 48, a higher proportion of entecavir-treated than adefovir-treated patients achieved HBV DNA levels <300 copies/mL (58% vs 19%). Suppression of HBV DNA levels remained greater for entecavir through the extended dosing phase of the study. At week 96, 79% of entecavir-treated patients and 50% of adefovir-treated patients achieved HBV DNA levels <300 copies/mL.¹¹⁰ Rates of ALT normalization (97% vs 85%) and HBeAg seroconversion (24% vs 25%) were similar for both treatment groups.¹¹⁰

Telbivudine. Telbivudine, an L-nucleoside analog of thymidine, is a potent and specific inhibitor of HBV DNA polymerase that preferentially inhibits HBV second-strand (DNA-dependent) DNA synthesis.¹¹¹ In phase I/II studies, telbivudine demonstrated potent antiviral activity in patients with CHB when compared with lamivudine monotherapy.¹¹² In a phase III trial involving 921 HBeAg-positive patients, virologic and biochemical responses associated with telbivudine were superior to those with lamivudine after 1 and 2 years of treatment.^{89,113} A higher proportion of patients treated with telbivudine than treated with lamivudine had undetectable HBV DNA by PCR assay (60% vs 40% at 1 year and 56% vs 39% at 2 years) and ALT normalization (77% vs 75% at 1 year and 70% vs 62% at 2 years) (Table 5). The rate of HBeAg loss and HBeAg seroconversion at the end of 1 year was similar between the treatment groups but was higher among patients treated with telbivudine at the end of 2 years (Table 5). Telbivudine was associated with a lower rate of resistance than was lamivudine. At 1 and 2 years, resistance rates were 5% and 25% for telbivudine, respectively, in HBeAg-positive patients.^{89,114} Patients who achieved undetectable HBV DNA levels (<300 copies/mL) at 24 weeks had a lower rate of resistance at 1 year than did patients who had HBV DNA levels of ≥4 log₁₀ copies/mL (1% vs 11%).⁸⁹

The frequency of adverse events was similar for patients receiving telbivudine and lamivudine, and serious adverse events were reported in 2.6% of patients receiving telbivudine and 4.8% receiving lamivudine.⁸⁹ Of note, elevations in creatine kinase levels more than 7 times the ULN were more common in patients receiving telbivudine than lamivudine (7.5% vs 3.1%) but decreased spontaneously during continued drug therapy. Muscle-related symptoms correlated poorly with elevations in creatine kinase levels.⁸⁹

Analyses of the 1-year and 2-year data from the phase III study showed that early virologic response at week 24 is predictive of clinical outcomes.^{89,113,115} Early maximal reduction in HBV DNA levels at 24 weeks correlated with improved clinical outcomes at 1 and 2 years, as measured by rates of HBeAg seroconversion, ALT normalization, HBV DNA undetectability, and resistance.^{89,113}

Telbivudine also has shown superiority over adefovir in HBeAg-positive CHB patients. Several randomized studies reported rapid and marked reductions in serum HBV DNA levels at 24 weeks of therapy in patients who had initially been treated with telbivudine or who had been switched from adefovir to telbivudine.¹⁰⁰ This early viral response was associated with the highest rates of achieving efficacy outcomes at 1 year (HBeAg seroconversion, ALT normalization, and undetectable HBV DNA levels on PCR assay).

Tenofovir. Tenofovir, an acyclic nucleotide analog with a molecular structure related to that of adefovir, is approved for the treatment of HIV infection and for HBV infection and was known before licensure for the treatment of CHB to have potent activity against HBV.^{96,97} Data from several small studies suggest that tenofovir might be more potent than adefovir in inducing the early and rapid suppression of HBV DNA in both HBeAg-positive and -negative patients.^{96,97,116} Limited clinical data suggest its efficacy in treating lamivudine-resistant patients.^{96,97,116} In a small study that compared the antiviral activity of tenofovir with that of adefovir in lamivudine-resistant patients, the tenofovir group achieved potent and rapid suppression of HBV DNA within weeks of treatment initiation as compared with a less consistent pattern of suppression in patients treated with adefovir.⁹⁷ At 48 weeks, significantly more patients treated with tenofovir had a reduction of HBV DNA levels to $<10^5$ copies/mL than did patients treated with adefovir (100% vs 44%). A follow-up study confirmed the superiority of tenofovir over adefovir in this setting.⁹⁶

Preliminary results from a multicenter, randomized, phase III trial comparing the safety and efficacy of tenofovir and adefovir in patients with HBeAg-positive CHB have been reported (Table 5).⁹⁸ A total of 266 patients were randomized in a 2:1 ratio to receive tenofovir 300 mg or adefovir 10 mg for 48 weeks. The primary end point of this study was complete response at week 48, defined as HBV DNA levels of <400 copies/mL and histologic improvement, defined as a ≥ 2 -point reduction in Knodell inflammatory score without worsening of fibrosis. At 48 weeks, 67% of patients in the tenofovir arm achieved a complete response, compared with 12% of patients in the adefovir arm ($P < .001$). A higher proportion of patients in the tenofovir arm than in the adefovir arm achieved undetectable HBV DNA levels at week 48 (<400 copies/mL: 76% vs 13%). The respective rates for ALT normalization were 69% vs 54% and for HBeAg seroconversion were 21% vs 18%. A higher proportion of patients treated with tenofovir had HBsAg loss

(3.2% vs 0%) and HBsAg seroconversion (1.3% vs 0%). The incidence of grade 2–4 adverse events was similar in the tenofovir and adefovir arms. No patients taking tenofovir experienced a 0.5-mg increase in serum creatinine levels or creatinine clearance of <50 mL/min (possible indicators of renal toxicity, which has been associated with tenofovir in some studies of patients with HIV infection), compared with 1% of patients taking adefovir. As with adefovir therapy, new onset or worsening renal impairment might occur, and it is recommended that baseline calculated creatinine clearance be obtained and creatinine clearance and serum phosphorus be monitored in patients at risk during therapy. The incidence of grade 3 or 4 ALT flares $2\times$ the baseline values were greater in the tenofovir arm than in the adefovir arm (11% vs 4%). All patients taking tenofovir who did not achieve HBV DNA levels of <400 copies/mL by week 48 or who experienced viral breakthrough while receiving treatment underwent genotypic resistance testing. The clinical benefits of tenofovir with respect to suppression of serum HBV DNA levels below the level of detection (79%) and ALT normalization (77%) were maintained through 72 weeks of treatment.¹¹⁷ The rate of HBsAg loss and seroconversion increased from 3% to 5% and from 1% to 2%, respectively, at weeks 48 and 64 in patients in the tenofovir arm, whereas no increase in HBsAg loss was observed among patients in the adefovir arm. No mutations associated with tenofovir resistance were identified at weeks 48 or 72.

Hepatitis B e Antigen–Negative Patients

Peginterferon alfa-2a. Forty-eight weeks of therapy with peginterferon alfa-2a, with or without lamivudine, resulted in a significantly greater percentage of patients with ALT normalization and HBV DNA undetectability (<400 copies/mL) 24 weeks after the end of treatment (Table 6).¹¹⁸ The combination of peginterferon alfa-2a plus lamivudine appeared to offer no advantages over treatment with peginterferon alfa-2a alone. HBsAg seroconversion was reported in 3% of patients treated with peginterferon alfa-2a, 2% of patients treated with peginterferon alfa-2a plus lamivudine, and no patients treated with lamivudine alone. The rate of emergence of lamivudine-resistant mutations was reduced markedly in the combination therapy arm. The safety profile of peginterferon alfa-2a was judged to compare favorably with previous experience with conventional interferon. A recent follow-up study of patients with HBeAg-negative CHB treated with peginterferon alfa-2a or lamivudine monotherapy reported significantly higher rates of ALT normalization, HBV DNA suppression, HBsAg loss, and HBsAg seroconversion in the peginterferon alfa-2a-treated patients.¹¹⁹ At 4 years after treatment, virologic response rates in the peginterferon alfa-2a arms were 24% for both HBV DNA <4000 IU/mL (20,000 copies/mL) and HBV DNA <2000 IU/mL (10,000 copies/mL) levels. Among patients who received peginterferon alfa-2a, 17% had HBV DNA levels <400 copies/mL, compared with 7% of patients who received lamivudine alone. ALT normalization, defined as ALT levels of ≤ 30 U/L, was reported in 27% of patients who had received peginterferon alfa-2a, compared with 16% of patients who had received lamivudine alone. The rate of HBsAg clearance increased during follow-up for peginterferon alfa-2a-treated patients, reaching 11% at 4 years.¹¹⁹ In contrast, only 2% of lamivudine-treated patients (2/85) experienced HBsAg loss.¹¹⁹

Entecavir. A phase III clinical trial compared the safety and efficacy of entecavir and lamivudine in patients with HBeAg-negative compensated liver disease.⁹² A total of 648 patients were randomized to receive either entecavir 0.5 mg/day or lamivudine 100 mg/day for 48 weeks. Treatment with entecavir, compared with lamivudine, resulted in a significantly higher rate of histologic improvement, HBV DNA reduction, and HBV DNA undetectability (<300 copies/mL) (Table 6). This high rate of undetectable HBV DNA (90%) shows the remarkable potency of this agent. ALT normalization was also observed more frequently with entecavir than with lamivudine (78% vs 71%), but there was no difference in improvement in fibrosis compared with lamivudine. The safety profile of entecavir during a period of 48 weeks was similar to that observed with lamivudine. A low resistance rate (1.2%) has been observed in nucleoside-naïve HBeAg-negative patients treated with entecavir for up to 5 years.^{107,108}

Telbivudine. A phase III trial involving 466 HBeAg-negative patients showed that virologic response for telbivudine was superior to that for lamivudine after 1 and 2 years of treatment.^{89,113} A higher proportion of patients treated with telbivudine than lamivudine achieved undetectable HBV DNA levels (88% vs 71% at 1 year and 82% vs 57% at 2 years) (Table 6). No difference was observed in the proportion of patients with ALT normalization at 1 year (74% vs 79%), although a higher proportion of telbivudine-treated patients achieved ALT normalization after 2 years of treatment (78% vs 70%). Telbivudine was associated with a lower rate of resistance than was lamivudine. Resistance data at 1 and 2 years for telbivudine showed resistance rates of 2.3% and 11.0%, respectively, in HBeAg-negative patients.^{89,114} As observed in HBeAg-positive patients, lower rates of resistance at 1 year were observed in HBeAg-negative patients who had undetectable HBV DNA levels at week 24, compared with patients whose HBV DNA levels were $\geq 4 \log_{10}$ copies/mL (0% vs 30%).⁸⁹

Tenofovir. Preliminary data are available from a randomized phase III study comparing tenofovir and adefovir in patients with HBeAg-negative CHB.⁹⁹ The primary end point of this study was complete response at week 48, defined as HBV DNA levels <400 copies/mL and histologic improvement (defined as a ≥ 2 -point reduction in Knodell inflammatory score without worsening of fibrosis). In this study, 375 patients were randomized in a 2:1 ratio to receive tenofovir 300 mg ($n = 250$) or adefovir 10 mg ($n = 125$) for 48 weeks. At week 48, a significantly higher proportion of patients treated with tenofovir achieved the primary end point, compared with patients treated with adefovir (71% vs 49%) (Table 6). At the end of treatment, 93% of the patients in the tenofovir group had HBV DNA levels of <400 copies/mL, compared with 63% of patients in the adefovir group. The rates of ALT normalization were similar in both treatment groups (Table 6). No patients treated with tenofovir had a confirmed 0.5 mg increase in serum creatinine level or creatinine clearance of <50 mL/min. The incidence of ALT flare ($>10 \times$ ULN and $2 \times$ baseline) was low and similar in the 2 treatment groups (1.2% vs 0.8%). The clinical benefit of tenofovir with respect to the achievement of HBV DNA levels of <400 copies/mL (98%) and ALT normalization (79%) was maintained through week 72 with continuous tenofovir therapy.¹²⁰ The resistance rate was 0% for tenofovir at weeks 48 and 72.

Combination Therapy

De novo combination. Current limitations of monotherapy with respect to the achievement of sustained response and clinical end points (ie, HBeAg seroconversion, HBsAg loss) have sparked interest in the development of combination regimens for CHB to optimize responses and minimize problems with resistance. Preclinical studies suggest a benefit from the combination of nucleosides and nucleotides. Enhanced anti-HBV activity has been observed with the addition of tenofovir to lamivudine, emtricitabine, telbivudine, or entecavir.¹²¹ In vitro data indicate that adding tenofovir to nucleoside agents produces additive to slightly synergistic anti-HBV activity, without any observed cytotoxic effects. Data on the efficacy of de novo combination therapy is limited, and the results from these studies vary on the basis of the agents used and the study design. Initial clinical studies comparing combination antiviral therapy and monotherapy failed to demonstrate clinical benefit with regard to traditional clinical end points with combination therapy.^{63,112,118,122}

In large randomized phase III studies comparing lamivudine and peginterferon monotherapy and the combination of peginterferon and lamivudine in HBeAg-positive and -negative patients, combination therapy was associated with a more profound decrease in viral load, compared with either monotherapy.^{63,118} However, no significant difference was observed in treatment end points such as viral suppression, HBeAg seroconversion, and HBsAg clearance between peginterferon monotherapy and combination therapy. The study design of these trials required the discontinuation of lamivudine, like peginterferon, after 1 year, which is not performed routinely in practice. More recently, preliminary data from several studies have illuminated the potential advantages of combination therapy in patients with CHB.¹²³⁻¹²⁶ Preliminary results of a multicenter, randomized, controlled trial in which HBeAg-negative CHB patients were treated with peginterferon alfa-2a alone or in combination with adefovir showed that significantly more patients in the combination treatment group achieved undetectable HBV DNA levels at 24 weeks than in the group treated with peginterferon alone (71% vs 41%); in addition, there was a significant difference in the reduction in mean viral load (-4.3 vs $-3.0 \log_{10}$).¹²³ Another study evaluated changes in intrahepatic cccDNA levels in patients with HBeAg-positive CHB who were treated with the combination of peginterferon alfa-2a and adefovir.¹²⁴ This study found that after 48 weeks of therapy, the combination regimen was associated with marked decreases from baseline in levels of serum HBV DNA and intrahepatic cccDNA levels, which, in turn, were significantly correlated with reduced HBsAg.

Preliminary data from studies evaluating oral combination therapy have also been reported.^{125,126} Sung et al¹²⁵ compared the efficacy of lamivudine monotherapy ($n = 57$) and lamivudine plus adefovir ($n = 54$) in patients with HBsAg-positive CHB. Reductions in HBV DNA levels were comparable between the 2 treatment arms at week 16 (the primary study end point) and during the first 52 weeks, but after 104 weeks median HBV DNA reductions were -3.41 and $-5.22 \log$, respectively. Similarly, HBV DNA levels were <200 copies/mL in 41% and 40%, respectively, of patients in the 2 arms at 52 weeks but 14% and 26% at 104 weeks. The difference in virologic outcome was associated with a higher rate of viral breakthrough in the

monotherapy group than in the combination therapy group (44% vs 19%). In the lamivudine monotherapy group, the M204V/I mutation was detected in 20% and 43% of patients at weeks 52 and 104, respectively, compared with 9% and 15% of patients at the same time points in the combination therapy group. The N236T mutation was noted in only 1 adefovir recipient. Notably, the rate of HBeAg seroconversion was identical, 35%, in each group.

A second study by Hui et al¹²⁶ compared adefovir alone ($n = 16$) with a combination of adefovir plus emtricitabine ($n = 14$), a nucleoside analog with activity and a resistance profile similar to that of lamivudine, in HBeAg-positive patients for 96 weeks. Despite the small number of patients in the study, a significant advantage for combination therapy was noted, with median HBV DNA declines of -3.98 and -5.30 \log_{10} copies/mL for monotherapy and combination therapy, respectively, at 96 weeks and HBV DNA levels of <300 copies/mL in 37.5% and 78.5% of patients, respectively. No difference was observed in the incidence of HBeAg seroconversion. The design of this small trial makes it difficult to assess the degree to which the greater suppression of HBV DNA with the combination regimen was attributable to a contributory effect of adefovir, or whether it simply represented the efficacy of the more potent drug, emtricitabine.

Although these studies demonstrate potent antiviral effects of de novo combination therapy, they nonetheless fall short of establishing a definitive role for routine combination therapy in all patients, particularly when potent monotherapies with robust long-term resistance profiles are available. In addition, several issues need to be addressed before considering combination treatment with nucleosides and nucleotides for CHB. These include the resistance profiles of the agents, the previous therapies that the patient has received, the potential for negative drug-drug interactions among the agents, especially with long-term use, and cost considerations.¹⁸ Larger clinical trials of combination therapy with appropriate end points are needed before the adoption of de novo combination therapy with currently available anti-HBV agents.

Combination versus switching. Evidence from several recent clinical studies suggests that combining lamivudine with adefovir, compared with sequential monotherapy, is associated with an improvement in virologic response and a lower rate of resistance, particularly in the setting of lamivudine resistance.¹²⁷⁻¹³¹ In one study among patients who had received more than 6 months of adefovir therapy, 50% failed to achieve an initial virologic response to adefovir.¹³⁰ The patients who developed adefovir resistance were more likely to have been switched from lamivudine to adefovir monotherapy. In a second study involving 95 HBeAg-positive patients treated with adefovir for 48 weeks, the emergence of adefovir resistance was more common in patients with lamivudine resistance than in the patients who were treatment-naïve.¹²⁷ These findings suggest that switching from lamivudine to adefovir is associated with an increased risk of adefovir resistance, compared with the addition of adefovir to existing lamivudine therapy.

The addition of adefovir to lamivudine has been shown to be superior to switching to adefovir monotherapy in HBeAg-negative patients who have lamivudine resistance.^{127,128,131,132} In one study evaluating these strategies, both were comparable in terms of the proportion of patients achieving suppression of serum HBV DNA to undetectable levels and normalization of

ALT at 12 months.¹²⁸ However, significantly more patients who had been switched to adefovir experienced virologic and biochemical breakthroughs as a result of adefovir resistance mutations at 15-18 months from treatment initiation (21% for switched therapy vs 0% for combination; $P = .01$). In another study that compared the efficacy of combining adefovir with lamivudine and switching from lamivudine to adefovir monotherapy in 82 patients with HBeAg-negative CHB, the rate of virologic breakthrough as a result of the emergence of adefovir resistance mutations was higher among patients who were switched from lamivudine to adefovir than among patients who received combination therapy (22% vs 0%).¹³²

These findings have been confirmed by recent data demonstrating excellent suppression with virtually no long-term resistance to adefovir when that drug is added to lamivudine in patients with lamivudine resistance.¹³³ In a study involving 145 lamivudine-resistant patients with CHB treated with adefovir 10 mg in addition to lamivudine 100 mg for 42 months (range, 12-74 months), 116 patients (80%) cleared serum HBV DNA, 67 patients (84%) had normalized ALT levels, and 145 patients (100%) remained free of virologic and clinical breakthroughs, independent of the degree of HBV suppression. The 1-, 2-, 3-, and 4-year cumulative rates of de novo rtA181T were 1%, 2%, 4%, and 4%, respectively. None of the cirrhotic patients clinically decompensated, but 11 (12%) developed HCC.¹³³

The above findings are in accordance with results of a large retrospective/prospective cohort study of patients with lamivudine-resistant HBeAg-negative CHB who received either adefovir monotherapy or combination adefovir plus lamivudine.¹³¹ This study analyzed 588 patients with lamivudine-resistant CHB at 31 centers in Italy who received add-on therapy with adefovir 10 mg or were switched from lamivudine 100 mg/day to adefovir monotherapy. Virologic and biochemical response rates at 33 months of follow-up were similar between the 2 treatment groups. However, patients who were switched from lamivudine to adefovir monotherapy had a higher incidence of virologic breakthrough than did patients who had adefovir added to lamivudine (24% vs 5%), as well as higher rates of adefovir resistance (11% vs 0%). The overall 3-year cumulative probability of virologic breakthrough (30% vs 6%) and adefovir resistance (16% vs 0%) was higher among patients who were switched from lamivudine than among patients who received add-on adefovir therapy. A significantly greater proportion of patients in the combination therapy group experienced 3-year overall rates of maintained virologic response (74% vs 59%). The switch to combination therapy optimally should be made as soon as possible after lamivudine resistance has been detected. Adding adefovir to maintenance lamivudine therapy has been associated with poorer control of viral replication when lamivudine resistance is well-established (HBV DNA >6 \log_{10} copies and elevated ALT levels).¹³⁴

The efficacy of switching to entecavir therapy in patients with CHB and persistently high levels of viral replication after 1 year of adefovir therapy has also been evaluated.¹³⁵ In this study, 12 patients with HBV DNA levels >5 \log_{10} copies/mL after 48 weeks of adefovir were switched to entecavir 1 mg/day for 24 weeks. Of the 12 patients, 3 had adefovir-resistance substitutions at baseline, and 6 had a history of lamivudine resistance. At 24 weeks, the median decrease of HBV DNA (3.8 \log_{10} copies/mL) was suboptimal for the entecavir-switched patients, none of whom achieved undetectable HBV DNA levels.

The majority of these patients had HBV DNA levels $>3 \log_{10}$ copies/mL at the end of the 24-week period.

A retrospective study involving 121 patients with CHB evaluated the efficacy of switching to tenofovir monotherapy in nucleoside- and nucleotide-experienced patients with CHB.¹³⁶ Eligible patients included those with HBV DNA $>10^5$ copies/mL and prior treatment with lamivudine or lamivudine with consecutive adefovir therapy as a result of lamivudine resistance. Patients with genotypic resistance to adefovir ($n = 14$) were excluded. At week 48, 91% and 78% of the patients had undetectable HBV DNA levels and ALT normalization, respectively. HBeAg seroconversion occurred in 23% of patients after an average of 9 months. HBsAg loss was observed in 4% of patients after an average of 13 months.

However, another study of a small cohort of patients with lamivudine-resistant CHB who were switched to adefovir monotherapy showed limited efficacy with subsequent tenofovir monotherapy.¹³⁷ These patients had all developed genotypic resistance to adefovir after receiving an average of 24 months of adefovir monotherapy. The patients treated with tenofovir still had detectable HBV DNA and elevated ALT levels at week 24, week 48, and the end of observation. In a retrospective analysis of antiviral response to tenofovir therapy in 127 patients with prior nucleoside analog experience with lamivudine, adefovir, or both, patients with genotypic adefovir resistance had a significantly slower decrease of HBV DNA levels at month 12 than did patients without adefovir resistance.¹³⁸ Similar findings were reported in a study investigating virologic response to tenofovir alone and in combination with emtricitabine in patients with adefovir-resistant CHB therapy. Combination therapy resulted in a greater reduction in HBV DNA levels than did tenofovir monotherapy in patients with virologic breakthrough or a sub-optimal response to adefovir.¹³⁹ All patients who received combination therapy had undetectable HBV DNA levels within 3–12 months, including 2 patients who had adefovir resistance at baseline. Despite findings indicating that tenofovir has antiviral efficacy in patients with genotypic adefovir resistance, the suppression of HBV DNA replication with tenofovir occurs at a much slower rate, and the complete suppression of HBV DNA replication occurs in only a minority of patients. Moreover, the selection of adefovir resistance mutations is not prevented. Thus, as observed with entecavir, tenofovir might have less activity in patients with genotypic resistance to adefovir than in treatment-naïve patients.

No evidence to date supports combining lamivudine with telbivudine, as might be expected, because these drugs are cross-resistant. One multicenter randomized study showed similar efficacy (reduction in HBV DNA levels, normalization of ALT levels) between telbivudine alone and telbivudine in combination with lamivudine.¹¹² A long-term concern with this approach is that cross-resistance for lamivudine and telbivudine has been demonstrated at codon 204 (rtM204I).¹⁴⁰ Moreover, HBV harboring M204V and L180M mutations is resistant to telbivudine, even if M204V mutations in isolation do not confer telbivudine resistance.

Treatment Recommendations

Hepatitis B e Antigen–Positive Patients

The recommendations for the treatment of HBeAg-positive patients are summarized in Table 7. The panel recom-

Table 7. Recommendations for Treatment: HBeAg-Positive CHB

| HBV DNA ^a | ALT ^b | Treatment strategy |
|----------------------|------------------|--|
| $<20,000$ | Normal | <ul style="list-style-type: none"> • No treatment • Monitor every 6–12 mo^c • Consider therapy in patients with known significant histologic disease, even if low-level replication |
| $\geq 20,000$ | Normal | <ul style="list-style-type: none"> • Low rate of HBeAg seroconversion for all treatments • Younger patients often immune tolerant • Consider liver biopsy examination, particularly if patient is >35–40 y; treat if disease; in the absence of biopsy examination, observe for increase in ALT levels • If treated, entecavir, tenofovir, or peginterferon alfa-2a preferred^d |
| $\geq 20,000$ | Elevated | <ul style="list-style-type: none"> • Entecavir, tenofovir, or peginterferon alfa-2a preferred^d |

^aIU/mL (1 IU/mL is equivalent to approximately 5–6 copies/mL).

^bULN for serum ALT concentrations for men and women are 30 and 19 IU/L, respectively.

^cOn initial diagnosis, then every 3 mo for 1 y to ensure stability.

^dLamivudine is not considered a reasonable treatment option because of the high risk of resistance with long-term therapy and its proven inferiority to entecavir and telbivudine in randomized clinical trials. Telbivudine is associated with moderate rate of resistance unless serum HBV DNA levels are undetectable at wk 24. Tenofovir is superior to adefovir in pivotal randomized controlled trials and should replace adefovir as initial therapy. Standard interferon alfa-2b has been replaced by peginterferon alfa-2a in practice.

mends an HBV DNA level of $\geq 20,000$ IU/mL as a reasonable threshold for determining candidates for treatment, in combination with elevated ALT levels. HBeAg-positive patients who have HBV DNA levels of $<20,000$ IU/mL are atypical and are not recommended routinely for treatment because the majority of these individuals have inactive disease. However, because these individuals might be at risk for biochemical, histologic, and clinical progression of disease, they should be monitored actively by a sensitive HBV DNA assay. On a case-by-case basis, liver biopsy examination might be performed and therapy considered when there is histologic evidence of significant liver disease. Patients who are not treated should initially be monitored every 3 months for 1 year to ensure stability of HBV DNA and ALT levels. Then, if the levels remain stable, the patient should be monitored every 6–12 months.

HBeAg-positive patients with a serum HBV DNA level of $\geq 20,000$ IU/mL should be considered for treatment, depending on their ALT levels. However, patients with normal ALT levels might have significant liver disease, and because viral suppression is associated with histologic response, biopsy examination should be considered, particularly in individuals older than 35–40 years of age. Such patients should be treated if disease is found. Further studies are required to investigate the efficacy of antiviral therapy in patients with HBV DNA levels of $\geq 20,000$ IU/mL and normal ALT levels, especially in the younger individuals, who are typically in the immune tolerance phase of infection.

For patients with serum HBV DNA levels of $\geq 20,000$ IU/mL and elevated ALT levels, entecavir, tenofovir, or peginterferon

alfa-2a might be considered as first-line options; however, entecavir or tenofovir would be preferred for patients with high levels of serum HBV DNA and/or normal levels of ALT, given that response to interferon-based therapy is low in this population. Lamivudine is not recommended as a first-line therapy in HBeAg-positive patients because entecavir and telbivudine have been shown to be superior to lamivudine in randomized clinical trials, and lamivudine is associated with high rates of resistance. Telbivudine is associated with a moderate rate of resistance, although low rates of resistance and sustained suppression can be achieved with telbivudine if HBV DNA levels are undetectable by week 24. However, the panel did not include telbivudine as a preferred agent because of the high rate of resistance compared with entecavir and tenofovir and lack of long-term resistance surveillance in telbivudine-treated patients. A therapeutic change is advisable if there is detectable HBV DNA at week 24 of telbivudine therapy. In addition, both telbivudine and tenofovir have been shown to be superior to adefovir in clinical trials; therefore, adefovir is not recommended as a first-line therapy in HBeAg-positive patients.

Duration of therapy. The panel recommends that HBeAg-positive patients continue to be treated after HBeAg seroconversion as long as HBV DNA levels are decreasing and until the HBV DNA levels are undetectable by PCR. Treatment then should be continued for an additional 12 months. In patients who undergo HBeAg seroconversion but who still have detectable but stable HBV DNA levels, treatment should be continued for 6 months; seroconversion should be documented again, and then consideration should be given to stopping treatment in patients without cirrhosis. Patients who relapse can be re-treated. HBeAg-positive patients who fail to lose HBeAg should be treated long-term because the chance of HBeAg seroconversion increases with time, and there is a high risk of recurring viremia if therapy is stopped in the absence of HBeAg seroconversion.

Hepatitis B e Antigen–Negative Patients

The end point of therapy for HBeAg-negative patients with chronic HBV infection is more difficult to assess than that for HBeAg-positive patients because HBeAg-negative disease does not allow for HBeAg seroconversion. Thus, HBV DNA suppression and ALT normalization are the only practical measures of response to therapy, and long-term therapy is most often required to maintain these responses.

Recommendations for the treatment of HBeAg-negative patients are shown in Table 8. Because HBeAg-negative patients tend to have lower levels of serum HBV DNA than do HBeAg-positive patients but still might have active disease, the panel recommends treating patients who have serum HBV DNA levels of ≥ 2000 IU/mL. Otherwise, the recommendations are similar to those for HBeAg-positive patients. Entecavir, tenofovir, and peginterferon alfa-2a can be considered first-line options. Because long-term treatment is required in most cases (unless HBsAg seroconversion occurs, which is unlikely), lamivudine is not recommended because of the high risk for the development of resistance,¹⁴¹ and tenofovir is preferred over adefovir because of evidence of its superiority.^{98,99} As in patients with HBeAg-positive CHB, telbivudine was not recommended as a first-line option on the basis of the intermediate rate of resistance with use of this drug.

Table 8. Recommendations for Treatment: HBeAg-Negative CHB

| HBV DNA ^a | ALT ^b | Treatment strategy |
|----------------------|------------------|--|
| <2000 | Normal | <ul style="list-style-type: none"> • No treatment; majority are inactive HBsAg carriers • Monitor every 6–12 mo^c • Consider therapy in patients with known significant histologic disease, even if low-level replication |
| ≥ 2000 | Normal | <ul style="list-style-type: none"> • Consider biopsy; treat if disease present. In the absence of biopsy, observe for rise in serum ALT levels. • If treated, entecavir, tenofovir, or peginterferon alfa-2a preferred^d |
| ≥ 2000 | Elevated | <ul style="list-style-type: none"> • Entecavir, tenofovir, or peginterferon alfa-2 preferred^d • Long-term treatment required for oral agents |

^aIU/mL (1 IU/mL is equivalent to approximately 5–6 copies/mL).

^bULN for serum ALT concentrations for men and women are 30 and 19 IU/L, respectively.

^cOn initial diagnosis, then every 3 mo for 1 y to ensure stability.

^dLamivudine is not considered a reasonable treatment option because of the high risk of resistance with long-term therapy and its proven inferiority to entecavir and telbivudine in randomized clinical trials. Telbivudine is associated with moderate rate of resistance unless serum HBV DNA levels are undetectable at wk 24. Tenofovir is superior to adefovir in pivotal randomized controlled trials and should replace adefovir as initial therapy. Standard interferon alfa-2b has been replaced by peginterferon alfa-2a in practice.

Duration of therapy. HBeAg-negative patients who are receiving therapy should be monitored every 6 months. The duration of therapy with peginterferon remains unclear, although longer treatment (12 months) appears to be more beneficial in terms of sustained virologic response off treatment than do shorter periods of treatment (4–6 months). Tolerability is clearly an issue for patients undergoing interferon-based therapy, as compared with therapy involving oral agents. Entecavir, tenofovir, and telbivudine need to be given for the long-term; however, there are currently no long-term data on sustained virologic response available beyond 1 year (tenofovir), 2 years (telbivudine), and 5 years (entecavir). Special monitoring guidelines might be needed for HBeAg-negative patients to determine when treatment might safely be stopped. Despite the prolonged negativity of serum HBV DNA levels, relapse is common in patients with HBeAg-negative CHB.¹⁴² Serum HBsAg concentrations appear to decline rapidly during therapy with peginterferon but not lamivudine.¹⁴³ The slope of decline for HBsAg concentration during extended peginterferon therapy might provide a clue that sustained virologic response is likely to occur.¹⁴⁴ Prolonged therapy with nucleoside and nucleotide analogs after HBV undetectability is associated with lower rates of relapse in patients with HBeAg-negative CHB. Increasing relapse rates as a result of rebound in viremia have been reported after stopping prolonged therapy with either lamivudine¹⁴² or adefovir¹⁴⁵. The probability of clinical and virologic relapse 6, 12, and 18 months after treatment withdrawal were 12% and 30%, 18% and 50%, and 30% and 50%, respectively.¹⁴² In a 5-year follow-up study of adefovir therapy in patients with HBeAg-negative CHB, approximately 25% of patients had long-term

HBV DNA negativity after stopping therapy.¹⁴⁵ Future trials are needed to better understand the optimal duration of therapy in HBeAg-negative patients.

Monitoring Virologic Response and Management of Resistance to Oral Antiviral Therapy

Prolonged antiviral therapy with the oral nucleosides and nucleotides is associated with the development of antiviral resistance.¹⁴⁶ The rate of resistance depends on a number of factors, including pretreatment HBV DNA levels, potency of the antiviral agent, prior exposure to oral nucleoside or nucleotide antiviral therapy, duration of treatment, and the degree of genetic barriers to resistance to the individual drug. The long-term rates of resistance are highest for lamivudine (65%–70% at 4–5 years),¹⁴⁷ intermediate for telbivudine (25% in HBeAg-positive patients and 11% in HBeAg-negative patients at 2 years),¹¹⁴ lower for adefovir (29% at 5 years),¹⁴⁵ and lowest for entecavir in the absence of prior lamivudine resistance (1.2% at 5 years)¹⁰⁷ and for tenofovir in treatment-naïve patients (0% at 1 year).^{98,99} Patients with lamivudine resistance have a 51% rate of novel mutations after 5 years of entecavir therapy.¹⁰⁷ The development of resistance is associated with loss of initial response and HBV DNA rebound, which is followed by biochemical breakthrough and eventual reversion of histologic improvement; in some cases, resistance leads to progressive liver disease associated with severe exacerbations.³⁹ Thus, when possible, it is most beneficial to use the most potent nucleosides and nucleotides that possess the lowest risk of genotypic resistance as initial therapy for patients with nucleoside-naïve disease.

Antiviral Resistance Testing

The detection of antiviral resistance before virologic and biochemical breakthrough can prevent more serious liver-related complications and the development of cross-resistance to other nucleoside or nucleotide analog therapies, which might limit future treatment options.¹⁴⁶ Standardized nomenclature and definitions of terms used to define resistance are indicated in Table 9.¹⁴⁸ Clinically, antiviral resistance manifests as virologic breakthrough, which is defined as a $\geq 1 \log_{10}$ IU/mL

Table 9. Definitions of Terms Relating to Antiviral Resistance to Nucleoside and Nucleotide Analog Treatment

| |
|--|
| Genotypic resistance: detection of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV genome that have been shown to confer resistance to antiviral drugs in phenotypic assays during antiviral therapy. These mutations are usually detected in patients with virologic breakthrough but can also be present in patients with persistent viremia and no virologic breakthrough |
| Virologic breakthrough: increase in serum HBV DNA level by $>1 \log_{10}$ copies/mL above nadir after achieving a virologic response during continued therapy |
| Viral rebound: increase in serum HBV DNA level to $>20,000$ IU/mL or above pretreatment level after achieving virologic response during continued therapy |
| Biochemical breakthrough: increase in ALT level above the ULN after achieving normalization during continued therapy |

Adapted from Lok et al.¹⁴⁸

Table 10. Methods to Detect Resistance

| | |
|--|--|
| Commercially available | |
| Standard population-based sequencing | INNO-LiPA |
| <ul style="list-style-type: none"> • Less sensitive • Detects variants present at 25% of viral population • Needed to detect “new” substitutions not previously described | <ul style="list-style-type: none"> • More sensitive • Detects variants present at 5% of viral population • Detects only known mutations |
| Research | |
| Restriction fragment length polymorphism analysis | Allele-specific PCR |
| <ul style="list-style-type: none"> • Detects variants present at 1% of viral population • Like INNO-LiPA, only detects known mutations | |

increase in serum HBV DNA levels from nadir in 2 consecutive samples taken 1 month apart in patients who have responded and been adherent to therapy with antiviral medications.¹⁴⁸

When virologic breakthrough occurs in a patient who has adhered to antiviral therapy, the presence of mutations directly associated with drug resistance should be confirmed by using an *in vitro* assay. There are 2 types of HBV resistance analyses, genotypic and phenotypic. Genotypic resistance testing can be used to monitor treatment responses and diagnose primary and secondary treatment failures. Genotypic resistance assays identify the mutations in HBV polymerase that confer resistance by the direct sequencing of PCR products. Information from genotypic resistance testing can aid in the selection of appropriate add-on or alternative antiviral therapy. In clinical practice, genotypic resistance testing is recommended when virologic breakthrough occurs to confirm the presence of mutations directly associated with drug resistance to a particular nucleoside or nucleotide analog.¹⁴⁸ In contrast, *in vitro* phenotypic resistance analyses can be used to confirm, by cell culture–based or enzymatic assays, that a mutation confers resistance and the level of susceptibility or resistance conferred by a specific mutation. Phenotypic assays are typically reserved for research studies.

Baseline genotypic testing for resistance is not recommended for routine use at this time because of the low sensitivity of the tests and the low incidence of drug resistance mutations at baseline as reported in clinical studies, although such testing might provide useful information regarding the potential for resistance to specific agents. For instance, in large clinical trials of entecavir involving nucleoside-naïve patients with CHB, the incidence of drug resistance mutations at baseline was 0.6%.^{149,150} A 3-year follow-up study of patients with lamivudine resistance, who were being treated with lamivudine plus adefovir or lamivudine monotherapy, reported a 4% incidence of adefovir-resistant strains (rtA181V/T) at baseline, which was not found to influence the antiviral response rates.¹²⁹

Methods for resistance testing are shown in Table 10. Direct sequencing–based assays are the gold standard for genotypic HBV resistance testing because all mutations that confer resistance can be detected. Other methods available that identify resistance mutations by sequence include real-time PCR analysis with specific probes, hybridization methods (line probe assay), restriction fragment length polymorphism analysis, and allele-specific PCR analysis.^{151,152} The most commonly used

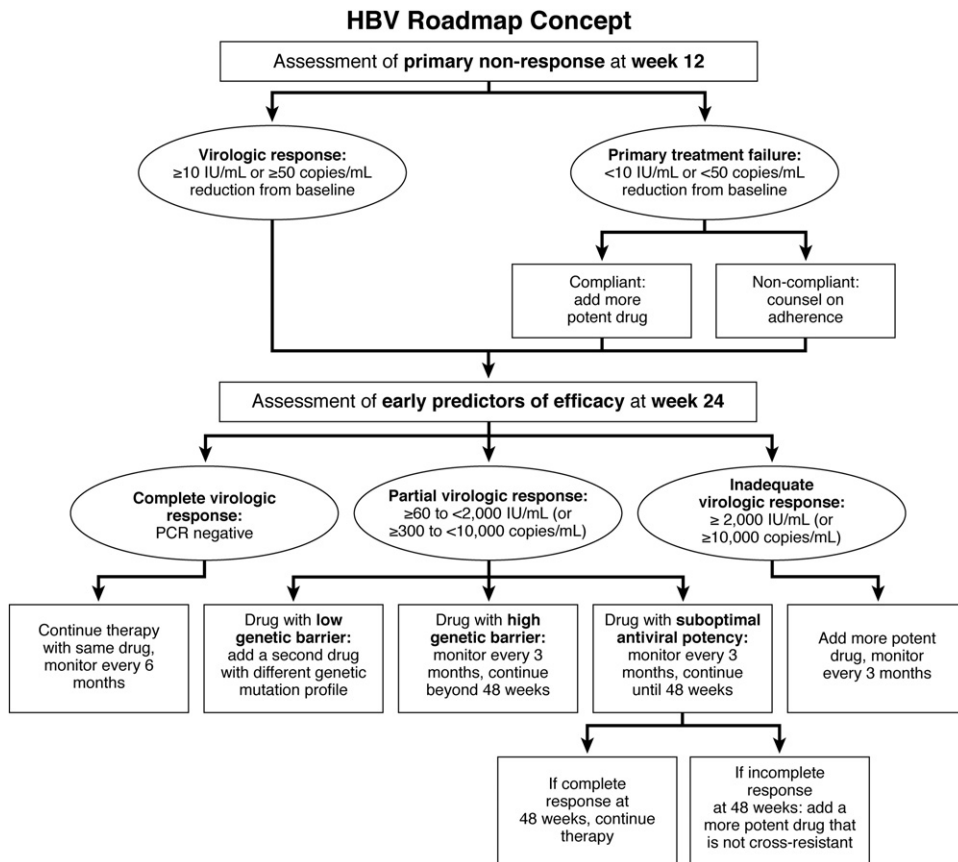


Figure 1. Algorithm for on-treatment monitoring of serum HBV DNA levels during therapy with oral nucleoside or nucleotide analogs.

methods in clinical practice include direct sequencing and line probe assays. Direct PCR sequencing allows the identification of mutations that comprise $\geq 20\%$ of the total viral population. More sensitive assays involving hybridization and real-time PCR methods can detect emerging viral resistance when the HBV DNA encoding the resistance mutations comprises 5% of the total viral population.^{148,153} Although more sensitive tests enable the early identification of patients who harbor HBV encoding resistance mutations at baseline, before the definition of clinical resistance is met, their use is currently restricted to clinical research and high-risk populations because of the expense involved and the complicated nature of performing the tests.

On-Treatment Monitoring

Appropriate treatment strategies are needed for drug-resistant patients that will not potentiate the risk for further resistance. Although current guidelines for the management of CHB stress the goals of therapy and describe the criteria for patient selection, the indications for initial therapy, and the advantages and disadvantages of available antiviral agents, they provide little information regarding on-treatment monitoring. Also lacking are criteria for determining patient response to treatment and for modifying the treatment regimen to attain optimal outcomes.

Recently an on-treatment strategy for patients receiving oral nucleotide therapy has been proposed.⁷ On the basis of this strategy of on-treatment monitoring, serum HBV DNA levels should be monitored at 12 weeks to determine primary treatment failure (HBV DNA decline of $<1 \log_{10}$ IU/mL) and at 24 weeks to confirm adequate virologic suppression by antiviral therapy. At 24 weeks, virologic response should be categorized

as complete, partial, or inadequate, according to the following definitions: complete, HBV DNA level <60 IU/mL; partial, HBV DNA level 60 to <2000 IU/mL; and inadequate, HBV DNA level ≥ 2000 IU/mL. Monitoring of HBV DNA levels should occur every 3–6 months to confirm adequate viral suppression and detect viral breakthrough. Management strategies are then based on the nature of the virologic response at week 24 (Figure 1).⁷ The recommendation for all cases of HBV resistance is to use add-on therapy with a drug in another class, while continuing therapy with the original drug, or to switch to another drug within that

Table 11. Potential Management of Hepatitis B Antiviral Drug Resistance

| | |
|------------------------|--|
| Lamivudine resistance | <ul style="list-style-type: none"> Continue lamivudine and add adefovir or tenofovir^a |
| Adefovir resistance | <ul style="list-style-type: none"> Switch to emtricitabine/tenofovir Continue adefovir and add lamivudine or telbivudine |
| Entecavir resistance | <ul style="list-style-type: none"> Switch to or add entecavir (if no prior lamivudine resistance) Switch to emtricitabine/tenofovir |
| Telbivudine resistance | <ul style="list-style-type: none"> Switch to or add adefovir or tenofovir Switch to emtricitabine/tenofovir Continue telbivudine and add adefovir or tenofovir^a Switch to emtricitabine/tenofovir |

Updated from Lok and McMahon.⁸

^aTenofovir might be preferred over adefovir as the add-on agent.

Table 12. Recommendations for Treatment: Patients With Cirrhosis (HBeAg-Positive or HBeAg-Negative)

| HBV DNA ^a | Cirrhosis | Treatment strategy |
|----------------------|---------------|---|
| <2000 | Compensated | <ul style="list-style-type: none"> • Might choose to treat or observe • Entecavir or tenofovir preferred^b |
| ≥2000 | Compensated | <ul style="list-style-type: none"> • Entecavir or tenofovir are first-line options • Long-term treatment required, and combination therapy might be preferred^c |
| Any detectable | Decompensated | <ul style="list-style-type: none"> • Combination with lamivudine, or possibly entecavir, plus tenofovir preferred^{c,d} • Long-term treatment required, and combination therapy might be preferred^c • Wait list for liver transplantation |

^aIU/mL (1 IU/mL is equivalent to approximately 5–6 copies/mL).

^bAlthough there are no data available for peginterferon alfa-2a, it might be an option in patients with early, well-compensated cirrhosis. No data are available for telbivudine, whose intermediate risk of resistance is a liability in patients with cirrhosis.

^cCombination therapy with lamivudine, or possibly entecavir, plus tenofovir has a theoretical advantage of a lower likelihood of the development of resistance.

^dLimited data are available for entecavir, no data are available for tenofovir, and no data are available for telbivudine, whose intermediate rate of resistance is a liability in patients with cirrhosis. Peginterferon alfa-2a is contraindicated.

same class but one that is more potent. For patients with lamivudine resistance, adefovir add-on therapy represents a new paradigm that is highly effective at restoring viral suppression and preventing the emergence of resistance. Add-on therapy with tenofovir might represent another, even more attractive, option for these patients. Patients with genotypic adefovir resistance should receive combination treatment with tenofovir plus lamivudine, telbivudine, entecavir, or emtricitabine.^{135,137,139} Table 11 lists proposed treatment strategies for patients who develop antiviral drug resistance.^{5,6,8,154}

Special Patient Populations

Patients With Cirrhosis

Before the advent of effective antiviral therapy, the 5-year survival rate was 84% for patients with compensated cirrhosis and 14%–35% for patients with decompensated cirrhosis.^{38,155,156} Various clinical parameters such as bilirubin level and older age were shown to predict survival. In addition, patients with compensated cirrhosis who lost HBeAg had 97% survival at 5 years, compared with 72% in HBeAg-positive patients; such findings implicated viral replication in adverse outcomes.^{38,40,157} The recommendations for treating HBeAg-positive or HBeAg-negative patients with cirrhosis (compensated or decompensated) are shown in Table 12.

The approach to patients with compensated cirrhosis and with serum HBV DNA levels <2000 IU/mL is to either monitor

or treat them with entecavir or tenofovir. However, the panel believes that in the absence of currently available data to guide this choice, the potential for clinical improvement with treatment outweighs the low risk for drug toxicity and cost considerations in patients with significant, albeit compensated, liver disease. In patients with HBV DNA levels of ≥2000 IU/mL, entecavir and tenofovir are first-line options because of their known efficacy and good tolerability, with low rates of resistance. The panel believes that although interferon is contraindicated because of the potential for decompensation, including disease flare induced by interferon, there might be a role for peginterferon alfa-2a in patients with well-compensated cirrhosis. Entecavir and tenofovir are preferred over lamivudine for long-term treatment because of the high risk for resistance to lamivudine, which could result in clinical decompensation. Combination therapy with tenofovir plus lamivudine, or possibly entecavir or tenofovir monotherapy, has the theoretical benefit of reducing the development of resistance to either or both of the drugs.

All patients with decompensated cirrhosis, regardless of their serum HBV DNA level, should be considered for treatment. Combination therapy with tenofovir and lamivudine, or possibly entecavir or tenofovir monotherapy, is the preferred first-line option in these patients. The aim in decompensated patients is to improve their status such that they eventually might be removed from the transplantation list. Combination therapy might decrease or delay the incidence of drug resistance; hence, the combination of tenofovir plus lamivudine, or possibly entecavir or tenofovir, as the first-line treatment option for patients with decompensated liver function is recommended. Studies to evaluate the combination of tenofovir plus lamivudine, adefovir plus entecavir, or other combinations in patients with decompensated cirrhosis are warranted.

Duration of therapy and on-treatment monitoring. The panel believes that therapy in patients with cirrhosis should be long-term. Although there are no data on the benefit of continuation of treatment in patients with compensated cirrhosis after HBeAg seroconversion, data from China show that patients who undergo HBeAg seroconversion still might develop HCC or have progression of their liver disease.¹⁵⁸ This might be caused by persistent low levels of HBV or by events in oncogenesis that are initiated and propagated despite the suppression of viral replication. In the absence of data on benefit and given the excellent safety profile of nucleoside and nucleotide analogs, therapy should be continued until the patient becomes HBV DNA-negative and has lost HBeAg. On-treatment monitoring should be performed every 3 months. Monitoring of renal function before and during therapy is particularly important in patients who have multiple risk factors for renal impairment. Adjustments to the dosing frequency of entecavir, tenofovir, and lamivudine should be made as recommended by the manufacturers.

Human Immunodeficiency Virus–Hepatitis B Virus Coinfection

Coinfection with HIV is a common result of shared routes of transmission. In the United States and the European Union, approximately 10% of all patients who are HIV-positive are coinfecting with HBV.¹⁵⁹ Coinfected individuals are more likely to develop chronic infection than are individuals with HBV mono-infection (23% vs 4%). HIV-HBV coinfection is asso-

ciated with higher HBeAg positivity rates and HBV DNA levels, longer duration of viremia, lower aminotransferase values, milder necroinflammation, and more rapid progression to cirrhosis compared with HBV monoinfection. Data from large cohort studies showed that liver-related mortality in HIV-HBV coinfecting patients is 14-fold higher than that in patients with either virus alone.^{160,161}

The general principles of diagnosis are not different for HBV-infected persons with or without HIV infection. However, HIV-HBV coinfection is often associated with atypical patterns of serologic markers of HBV infection, which hinder an appropriate diagnosis. The presence of occult hepatitis B, defined as the presence of HBV DNA without circulating HBsAg, might also complicate the diagnosis and management of HIV-HBV-coinfecting individuals.¹⁶²⁻¹⁶⁴ Patients should be monitored for liver disease, particularly when HIV infection is not going to be treated immediately, because of the increased risk for cirrhosis and liver-related mortality.^{160,165} The impact of HIV on the risk of HCC is unknown, and thus the current recommendations for HCC surveillance in patients with CHB should be followed.

The criteria for HBV therapy in persons with concomitant HIV infection are the same as for patients with HBV monoinfection.¹⁶⁶⁻¹⁶⁸ Individuals who have fluctuating, mildly elevated ($1-2 \times$ ULN) ALT levels or normal ALT values, and elevated HBV DNA levels ($>20,000$ IU/mL in HBeAg-positive individuals and >2000 IU/mL in HBeAg-negative individuals) should undergo liver biopsy and be considered for treatment if liver biopsy shows necroinflammation or significant fibrosis. Treatment generally is not recommended for HIV-infected patients (either HBeAg-positive or HBeAg-negative) if they have persistently normal ALT levels, low HBV DNA levels (a precise cutoff for "low" is not well-defined, but <2000 IU/mL is reasonable), and no fibrosis on a liver biopsy specimen.

Management of HBV infection in HIV coinfection is complicated by several factors. Current treatment options for treating the HBV infection in HIV-coinfecting patients include interferon and nucleoside or nucleotide analogs.¹⁶⁶ However, many of the nucleoside or nucleotide analogs, including lamivudine, tenofovir, emtricitabine, and entecavir, possess dual activity against HBV and HIV.¹⁶⁹ Of greatest concern is the potential for the development of resistance, which could compromise the future management of either virus. The rate of lamivudine resistance is higher in HIV-HBV coinfecting patients, reaching 90% at 4 years.¹⁷⁰ Moreover, prolonged treatment with lamivudine has been shown to be associated with the development of vaccine mutations to HBV, which might have important public health implications for transmission of the virus.¹⁷¹ Thus, the primary consideration in initiating treatment under conditions of HIV-HBV coinfection is to determine which virus requires treatment. The chosen therapy must be designed to avoid the development of drug-resistant HBV or HIV.

Recommendations for the treatment of HIV-HBV coinfection have recently been published by the U.S. Department of Health and Human Services.¹⁷² In HIV-infected patients, if therapy for either HIV or HBV infection is indicated, initiation of a fully suppressive antiretroviral regimen that includes tenofovir and either lamivudine or emtricitabine is recommended to prevent the development of antiretroviral drug resistance. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with

anti-HBV activity should be used in combination with lamivudine or emtricitabine for the management of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression. If antiretroviral therapy is not initiated, HBV therapy should include only agents that have the least potential of selecting HIV resistance mutations.

In instances when HIV treatment is not an option or is not desirable, peginterferon alfa-2a or alfa-2b, adefovir, and telbivudine are potential options. Telbivudine is not known to be active against HIV, and one drawback to its use is that resistance might develop rapidly when it is used as monotherapy.¹¹⁴ Adefovir at a low dose (10 mg) is not active against HIV, although higher doses of adefovir do demonstrate activity. Adefovir is also the least potent of these choices. Although clinical data supporting the use of interferons in the HIV setting are limited, the advantage of peginterferons is that they do not select for drug-resistant HIV. Patients who are more likely to respond to this treatment are those who are young and immunocompetent and have low HBV DNA levels and high ALT levels; they must also not be harboring any known drug-resistant HBV. Individuals with HBeAg-negative CHB do not typically respond well to peginterferons, so in the setting of HIV infection these agents are not a first-line choice.

Antiviral agents that inhibit both HIV reverse transcriptase and HBV DNA polymerase include tenofovir, adefovir at doses of >10 mg, lamivudine, emtricitabine, and entecavir. Exposure to these antiviral agents without a fully active HIV regimen could potentially compromise future HIV care. Accordingly, these agents should not be used without concomitant HIV therapy for the treatment of HBV in coinfecting patients. Lamivudine and emtricitabine should also be avoided as the only anti-HBV active agent in the initial treatment of HBV infection in HIV-coinfecting patients because of the high incidence of resistance in this population.^{171,173}

For patients who require treatment for HIV alone or both HIV and HBV, tenofovir plus emtricitabine (Truvada; Gilead Sciences, Foster City, CA) is recommended, along with other classes of antiretroviral agents, to form a potent anti-HIV regimen. The combination of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir 300 mg (coformulated as Atripla; Bristol-Myers Squibb Company, Princeton, NJ, and Gilead Sciences, Foster City, CA) is available for the management of HIV infection and is a reasonable choice in a patient naïve to therapy. If tenofovir cannot be used, an alternative HIV regimen along with entecavir might be considered. If both viruses need to be treated but the patient has lamivudine-resistant HBV, the best option is still to include both tenofovir and emtricitabine or lamivudine as part of the anti-HIV regimen. The combination is advocated, because it might reduce the rate of development of tenofovir-resistant HBV.¹⁷⁴

Chemotherapy and Immunosuppressed Patients

Reactivation of HBV replication, as indicated by increased serum HBV DNA and ALT levels, is a well-recognized complication in HBV-infected individuals undergoing cancer chemotherapy or immunosuppression.^{175,176} Although more rare, reactivation also might occur in patients with resolved infection who are HBsAg-negative, anti-HBs-positive, and anti-HBc-positive. In some cases, hepatitis flares associated with the

reactivation of HBV are asymptomatic; however, HBV reactivation might lead to severe, even life-threatening, hepatitis flares that must be recognized and treated promptly.

Reactivation of HBV infection was studied in 626 patients with cancer who received cytotoxic chemotherapy during a 12-month period.¹⁷⁵ Before chemotherapy, all of the patients had inactive HBV infection. Of the 78 patients who were HBsAg-positive, 34 (44%) developed elevated ALT levels during their course of chemotherapy, and 15 of those experienced reactivation of HBV infection. Reactivation was more likely to develop in patients who were male, of younger age, HBeAg-seropositive, and diagnosed with lymphoma. A recent study showed an association between the presence of non-Hodgkin's lymphoma and reactivation of HBV infection.¹⁷⁷ The use of prophylactic lamivudine, as compared with no lamivudine, significantly decreased the incidence of HBV reactivation (13% vs 38%; $P = .02$) and disruption to chemotherapy (43% vs 4%; $P = .02$). Reactivation of HBV infection has also been observed in patients receiving immunomodulatory agents for the treatment of rheumatic diseases.¹⁷⁸⁻¹⁸⁰

Current guidelines recommend HBsAg testing for patients at high risk for HBV infection before the initiation of chemotherapy or immunosuppressive therapy.⁸ Patients who are anti-HBc-positive should be monitored closely during and after the administration of cytotoxic chemotherapy for signs of HBV reactivation, and patients who are HBeAg-positive should be treated.¹⁸¹

The panel recommends the administration of prophylactic oral nucleoside or nucleotide antiviral therapy to HBsAg-positive individuals several weeks before the onset of chemotherapy or immunosuppressive therapy.^{6,8} Prophylactic therapy with lamivudine reduces the rate of HBV reactivation, the severity of associated hepatitis flares, and mortality when compared with historical controls.^{175,176,182-184} Antiviral therapy should be maintained for 6 months after completion of the chemotherapy or immunosuppressive therapy in patients with HBV DNA levels of <2000 IU/mL. However, discontinuation of anti-HBV therapy after 6 months might not be sufficient for patients with high HBV DNA levels. Reactivation after withdrawal of anti-HBV therapy has been reported in patients with high baseline HBV DNA levels. In a study of 46 HBsAg-positive patients with hematologic malignancies receiving lamivudine prophylaxis before the initiation of cytotoxic chemotherapy, a higher proportion of the patients with high pre-chemotherapy HBV DNA levels ($\geq 10^4$ copies/mL) than with low pre-chemotherapy HBV DNA levels ($< 10^4$ copies/mL) developed HBV reactivation (50% vs 10%, respectively; $P < .001$).¹⁸⁵ A high pre-chemotherapy HBV DNA level of $\geq 10^4$ copies/mL was the most important risk factor for HBV reactivation after the withdrawal of preemptive lamivudine. On the basis of these findings, treatment guidelines recommend that patients with HBV DNA levels of >2000 IU/mL continue antiviral therapy until HBV DNA is undetectable, and ALT levels are normalized.

Evidence supporting the use of prophylactic antiviral therapy for individuals who require long-term immunosuppressive therapy (ie, renal transplantation recipients) is limited.¹⁸⁶ These patients should be monitored and therapy initiated when signs of reactivation appear (ie, an increase in HBV DNA or ALT levels). The use of lamivudine and telbivudine should be avoided because of the progressive risk of resistance associated with these agents. In situations in which therapy is to be given

for >6 months, the use of entecavir or tenofovir might be advisable. Adefovir is a less suitable choice in the renal transplantation setting because of its risk of nephrotoxicity. Therapy with interferon or peginterferon should be avoided because of the associated bone marrow suppression.

A final group of individuals with chronic HBV infection who warrant consideration of antiviral prophylaxis are HBsAg-positive patients undergoing therapy with anti-tumor necrosis factor- α agents for treatment of conditions such as rheumatoid arthritis or inflammatory bowel disease. These patients have also experienced reactivation of hepatitis B and should be considered for prophylaxis with an oral antiviral agent during therapy with these agents.¹⁸

Pregnancy

Perinatal transmission of HBV is the most common cause of chronic HBV infection in regions of high HBV endemicity, and it remains a serious problem, despite the implementation of immunization programs.¹⁸⁷ A high proportion (80%–90%) of infants born to HBsAg/HBeAg-positive mothers become chronically infected with HBV.¹⁸⁸ With appropriate, timely immunoprophylaxis, $>90\%$ of these perinatal infections can be prevented.¹⁸⁹⁻¹⁹² HBV-related complications occur more frequently in pregnant women and are associated with a higher mortality.¹⁹³

Of the currently available oral nucleoside and nucleotide analogs, only telbivudine and tenofovir are classified as pregnancy category B (ie, not teratogenic) for the treatment of CHB. Lamivudine, entecavir, and adefovir are classified as category C; therefore, standard category C recommendations should be followed. All drugs might be continued during pregnancy. However, there is extensive experience with the safety of lamivudine used for treatment of HIV infection during pregnancy. The use of lamivudine in the last month of pregnancy might prevent mother-to-infant transmission of HBV in women with high HBV DNA levels; it might also be an effective and safe measure to reduce the risk of viral breakthrough in the child during vaccination.^{194,195} However, lamivudine might not prevent the perinatal transmission of precore mutant HBV.¹⁹⁶ Because of this experience, lamivudine is the most commonly used antiviral agent for the treatment of pregnant women with CHB.

Decisions about initiating or continuing antiviral therapy in pregnant women should depend on the stage of the mother's liver disease and the potential benefit to her versus the small risk to the fetus. Because treatment mostly concerns young women who are likely to have only mild liver disease, postponement of therapy until after pregnancy might be prudent.⁶ However, data from clinical studies indicate that women with CHB who have HBV DNA levels $>10^7$ copies/mL and elevated ALT levels, or who already have had an HBsAg-positive child, are candidates for antiviral therapy because of the increased risk for transmission to the newborn. For these individuals, antiviral therapy with lamivudine, telbivudine, or tenofovir during the third trimester is recommended. Although lamivudine and telbivudine are potential treatment options for women who require treatment during pregnancy, caution is advised when using lamivudine for those who require long-term therapy because of the increased risk for resistance. For women who are immune tolerant (ie, have high HBV DNA and normal ALT levels) and wish to become pregnant, a biopsy is recommended.

Peginterferon can be considered for patients who have significant fibrosis on biopsy because of the limited course of therapy. Women with CHB who become pregnant while receiving antiviral therapy might continue treatment or stop therapy and restart after pregnancy. This poses a small risk to the fetus that must be weighed against the stage of the mother's liver disease, the potential benefit of therapy, and the risk of reactivation of HBV if the therapy is abruptly discontinued. If possible, it might be advisable to switch to an antiviral agent with pregnancy category B status (telbivudine, tenofovir) or known safety experience (ie, lamivudine, tenofovir) during pregnancy and then resume the original treatment regimen after delivery.

Conclusion

For patients with chronic HBV infection, the primary goal of treatment is to prevent progression of liver disease to liver failure or HCC and prevent premature death or need for transplantation. On the basis of clinical and epidemiologic data, durable HBV DNA suppression is now considered the primary determinant of treatment outcomes, along with avoidance of resistance. The threshold level of HBV DNA for initiation of therapy remains unchanged at $\geq 20,000$ IU/mL for patients with HBeAg-positive CHB. Patients also should have increased ALT levels (with revised definitions), evidence of hepatitis on liver biopsy examination, or both. For viremic patients who have normal ALT levels, the decision to obtain a liver biopsy examination and initiate therapy should be individualized. Further studies of this population of HBV-infected patients are needed because approximately 20%–25% have significant fibrosis. A lower serum HBV DNA threshold of 2000 IU/mL is sufficient as an indication for treatment for patients with HBeAg-negative CHB and also for patients with compensated cirrhosis. Patients with decompensated cirrhosis are candidates for treatment regardless of their serum HBV DNA levels. Patients with HBeAg-negative CHB and patients with cirrhosis require long-term antiviral therapy.

The currently available agents recommended as first-line treatment are effective in yielding the treatment goals. Interferon, lamivudine, adefovir, peginterferon alfa-2a, entecavir, telbivudine, and tenofovir are approved as initial therapy for CHB. In choosing a therapy, however, consideration should be given to the advantages and disadvantages of the 7 therapies. The issues to consider are efficacy, safety, resistance, and method of administration. Entecavir, tenofovir, and telbivudine are the most potent oral agents and have shown superiority to comparable agents in randomized clinical trials. In addition, a rate of resistance of 1.2% has been shown after 5 years of therapy with entecavir in treatment-naïve patients, and no resistance has been reported after 1.5 years of therapy with tenofovir in treatment-naïve patients. Although moderate rates of resistance have been observed with telbivudine at 2 years, patients who achieve undetectable HBV DNA levels by week 24 have low rates of resistance. However, long-term efficacy and resistance data are not available beyond 2 years with telbivudine. For patients initiated on telbivudine, the panel considers it a viable ongoing choice only if HBV DNA is negative at week 24. Although interferon and peginterferon alfa-2a have the advantages of a finite duration of treatment, durable response (in patients who respond), and lack of resistance, they are expensive, require administration by injection, and are associated with many side effects. In current practice, peginterferon alfa-2a has supplanted

standard interferon. Lamivudine is well-tolerated, with an excellent safety profile and good efficacy, but its long-term use is limited by the development of resistance. Therefore, the panel does not recommend lamivudine for first-line use except in special circumstances, such as for patients receiving short-term antiviral prophylaxis during chemotherapy or pregnancy, as part of an HIV regimen in patients with HIV-HBV coinfection, or in combination with adefovir or tenofovir in patients with hepatic decompensation. Similarly, the panel does not recommend adefovir as a first-line drug because it has proved inferior in antiviral efficacy to tenofovir in large phase III trials reported recently. Patients requiring therapy for >1 year probably are best treated with entecavir or tenofovir, which have much lower rates of resistance. Many patients have been successfully treated long-term in the past with lamivudine and adefovir, with persistently undetectable serum HBV DNA for many years. The risk of subsequent antiviral resistance appears to be very low in these patients, and there is general agreement that these patients do not require a change in their therapy. However, treatment-naïve patients beginning antiviral therapy for the first time should receive one of the first-line drugs, ie, entecavir, peginterferon alfa-2a, or tenofovir, on the basis of their superior potency and low rates of resistance.

Active, on-treatment monitoring of patients receiving oral therapy has recently been proposed to help clinicians individualize therapy and modify the treatment plan according to the patient's response. Combination therapy might prove to be more effective than monotherapy in suppressing viral replication, and it very likely will decrease the incidence of drug resistance or delay its development. The universal application of combination therapy to all patients undergoing treatment for CHB requires a firmer foundation in comparative trials with potent agents used as monotherapy before it can be adopted into routine clinical practice. However, limited evidence from recent trials suggests that oral combination therapy might be useful in selected situations, including the treatment of patients with cirrhosis who can least afford the emergence of resistance or patients who have established resistance to an anti-HBV drug or experienced suboptimal response to initial monotherapy at a specified time point (eg, 24 weeks with a drug with a low genetic barrier to resistance or 1 year with an agent with a high barrier), and in the setting of HIV-HBV coinfection. Several large studies are exploring the use of 2 nucleoside or nucleotide antiviral agents together or the combination of an oral antiviral agent plus peginterferon in patients with compensated cirrhosis. Combination therapy with oral agents could be of particular value in patients with decompensated cirrhosis, but a study comparing combination therapy with adefovir plus lamivudine against monotherapy in this patient group clearly is needed. Until more definitive studies are completed, the recommendations in the updated treatment algorithm will allow clinicians to manage patients with CHB on the basis of the most current understanding of this disease.

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