

REVIEW

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

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Chronic hepatitis B (CHB) is an important public health problem worldwide and in the United States, with approximately 25% of patients infected as neonates dying prematurely from cirrhosis or liver cancer. A treatment algorithm for CHB previously developed and published by a panel of United States hepatologists was revised based on new developments in the understanding of CHB, the availability of more sensitive molecular diagnostic testing, the addition of new treatments, and better understanding of the advantages and disadvantages of approved therapies. This updated algorithm is based on available evidence using a systematic review of the scientific literature. Where data are lacking, the panel relied on clinical experience and consensus expert opinion. Serum HBV DNA can be detected at levels as low as 10 IU/mL using molecular assays and should be determined to establish a baseline level before treatment, monitor response to antiviral therapy, and survey for the development of drug resistance. The primary aim of antiviral therapy is durable suppression of serum HBV DNA to the lowest levels possible. The threshold level of HBV DNA for determination of candidacy for therapy is 20,000 IU/mL or more for patients with hepatitis B e antigen-positive CHB. A lower serum HBV DNA threshold of 2000 IU/mL or more is recommended for patients with hepatitis B e antigen-negative CHB, and 200 IU/mL or more for those with decompensated cirrhosis. Interferon alfa-2b, lamivudine, adefovir, entecavir, and peginterferon alfa-2a all are approved as initial therapy for CHB and have certain advantages and disadvantages. Issues for consideration include efficacy, safety, incidence of resistance, method of administration, and cost.

This hepatitis B virus (HBV) treatment algorithm was developed by a panel of US hepatologists and originally was published in 2004.¹ Since then 2 additional therapies, entecavir (Baraclude; Bristol-Myers

Squibb, Princeton, NJ) and peginterferon alfa-2a (Pegasys; Roche, Nutley, NJ), have been approved by the US Food and Drug Administration for the treatment of chronic hepatitis B (CHB). In light of the availability of these new agents and new knowledge regarding the natural history of CHB, the panel met again to reassess and revise its recommendations. The aim was to build on the previously published practical and comprehensive algorithm for the diagnosis, treatment, and monitoring of patients with chronic HBV infection in the United States. New data were identified for review by the panel based on independent research by panel members that was aided by a structured literature review and assessment of current treatment guidelines.²⁻⁴ The structured literature review included a comprehensive search of the PubMed computerized bibliographic database for English-language articles published between January 1, 2003 and July 28, 2005 that evaluated the treatment of CHB. In addition, hand searches of bibliographies from relevant articles and consultations with experts in the field yielded additional references. By using explicit inclusion and exclusion criteria developed to evaluate the acceptability of a publication, a total of 37 of 455 reports identified were accepted and abstracted. An additional 28 abstracts from the following conferences also were

Abbreviations used in this paper: AFP, α -fetoprotein; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; PCR, polymerase chain reaction; US, ultrasound; YMDD, tyrosine-methionine-aspartate-aspartate.

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accepted for inclusion in the evidence table: Digestive Disease Week 2004 and 2005, American Association for the Study of Liver Diseases Annual Meeting 2003 and 2004, and the European Association for the Study of the Liver Annual Meeting 2004 and 2005. Selected abstracts from the American Association for the Study of Liver Diseases Annual Meeting 2005 were added later.

Before the meeting, panel members evaluated the appropriateness of various treatment options in structured clinical scenarios corresponding to key decision points in the algorithm. A 9-point rating scale was used to highlight agreement or divergence of opinion with respect to appropriateness. This information was used to explore the reasons for any divergence and to help the group to reach consensus. Where possible, the panel's recommendations are based solidly on evidence, but where data are lacking panel members relied on their own clinical experience and expert opinion. The algorithm aims to assist the treating physician in answering the practical questions of what tests to order and how to interpret the results, which patients to treat, when and how long to treat, what the available treatment options are, and how to monitor patients. The cost of treatment has not been considered in reaching these recommendations because of the lack of cost-effectiveness data for all of the drugs licensed for treatment of CHB.

Burden of Disease

It is estimated that worldwide at least 350 million people are chronically infected with HBV.⁵ Although the prevalence of HBV infection in the United States is lower than in many other countries, an estimated 1.25 million individuals are infected with the virus.⁶ However, the prevalence of CHB in the United States is likely to be underestimated. The prevalence of HBV infection among foreign-born persons immigrating to the United States from Asia, the middle East, and Africa ranges from 5% to 15% and reflects the pattern of infection in the country of origin. The size of the Asian American population has increased significantly over the past decade, and currently is estimated to be approximately 10.5 million people.⁷ A recent cross-sectional survey of Chinese, Korean, and Vietnamese individuals conducted in several large US cities reported a hepatitis B surface antigen (HBsAg) seroprevalence rate of 10.4%,⁸ and a retrospective survey of the Asian American population in the city of New York found a remarkable 23% with detectable serum HBsAg.⁹ Despite a 67% decrease in the incidence of acute hepatitis B during 1990 to 2002, attributed in part to broader use of the hepatitis B vaccine,¹⁰ new infections with HBV remain

common. It is estimated by the Centers for Disease Control and Prevention that approximately 70,000 people in the United States become acutely infected each year.¹¹ Individuals with CHB are at increased risk for developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), and it is estimated that approximately 25% of patients infected as neonates die prematurely from cirrhosis or liver cancer.⁵ It is estimated that up to 5000 people die each year in the United States from these complications of HBV infection.¹²

Natural History and Terminology

After acute HBV infection, approximately 3%–5% of adults and up to 95% of children fail to produce an immune response adequate to clear the infection;^{5,13,14} in these persons, chronic HBV infection develops. The clinical terms used for the stages of chronic HBV infection and the criteria used in their diagnosis, adopted at the National Institutes of Health Workshop on Management of Hepatitis B,^{2,15} are summarized in Table 1. Other clinical terms relating to HBV infection are summarized in Table 2.

The onset of chronic HBV infection is marked by the continued presence of HBsAg, high levels of serum HBV DNA, and the presence of hepatitis B e antigen (HBeAg) in serum. In adult-acquired disease, the early phase of infection often is accompanied by marked disease activity, with increased alanine aminotransferase (ALT) levels, whereas in perinatally acquired disease, patients tend to have normal ALT levels (immune tolerant phase). The activity of disease can accelerate in the latter group, with increased ALT levels, but this usually does not occur until adulthood. HBeAg seroconversion (defined as loss of HBeAg and gain of antibody to HBeAg [anti-HBe], occurring either spontaneously or treatment-related) is most common in the phases when ALT levels are increased. Loss of HBeAg and seroconversion to anti-HBe usually are preceded by a marked decrease in serum HBV DNA levels to less than 20,000 IU/mL,¹⁶ and typically are followed by normalization of ALT levels. Thus, HBeAg seroconversion usually represents a transition from CHB to an inactive HBsAg carrier state in which there is little evidence of hepatitis clinically and lower levels of serum HBV DNA. Some patients also lose HBsAg, which is referred to as *resolution* of HBV infection. However, in the majority of patients CHB is controllable but not usually curable.

A proportion of patients who undergo HBeAg seroconversion have a return of high levels of HBV DNA and persistent or intermittent increases of ALT levels. These patients have a naturally occurring mutant form of HBV that abolishes or down-regulates HBeAg production,

Table 1. Definitions and Diagnostic Criteria Used in HBV Infection

Definitions	Diagnostic criteria
Chronic hepatitis B	
Chronic necroinflammatory disease of the liver caused by persistent infection with HBV	HBsAg-positive >6 mo Serum HBV DNA >20,000 IU/mL Persistent or intermittent increase of ALT/AST levels Liver biopsy specimen showing chronic hepatitis (necroinflammatory score ≥ 4) ^a
Chronic hepatitis B can be subdivided into: HBeAg-positive chronic hepatitis B HBeAg-negative chronic hepatitis B	HBeAg-positive, anti-HBe-negative HBeAg-negative, anti-HBe-positive ^b
Inactive HBsAg carrier state	
Persistent HBV infection of the liver without significant ongoing necroinflammatory disease	HBsAg-positive >6 mo HBeAg-negative, anti-HBe positive Serum HBV DNA <20,000 IU/mL Persistently normal ALT/AST levels Liver biopsy specimen showing absence of significant hepatitis (necroinflammatory score <4) ^a
Resolved hepatitis B	
Previous HBV infection without further virologic, biochemical, or histologic evidence of active virus infection or disease	Previous known history of acute or chronic hepatitis B or the presence of anti-HBc \pm anti-HBs HBsAg-negative Undetectable serum HBV DNA ^c Normal ALT levels

Adapted from Lok and McMahon.²

^aPerformance of liver biopsy optional.

^bMost of these patients have precore or core promoter mutations.

^cVery low levels may be detectable by PCR.

usually because of mutation in the precore or core promoter region. This form of chronic HBV infection is called *HBeAg-negative chronic hepatitis B*. Hence, CHB can be divided into 2 major forms: HBeAg-positive and HBeAg-negative. A study of 283 patients who experienced spontaneous HBeAg seroconversion showed that, after a median of 8.6 years of follow-up evaluation, HBeAg seroconversion was sustained in approximately two thirds of patients. Twenty-four percent of patients had ALT increases associated with HBV DNA detectability.¹⁷

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

Acute exacerbation or flare of hepatitis B
Intermittent increases of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B
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 less than 20,000 IU/mL
HBeAg reversion
Reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe positive

Adapted from Lok and McMahon.²

Spontaneous flares of disease activity can occur during the natural course of CHB,¹⁸ and repeated exacerbations may lead to progressive fibrosis and cirrhosis as well as carcinogenesis. As a result, older patients who present with high HBV DNA concentrations with normal ALT levels are more likely to have greater fibrosis on liver biopsy examination than younger patients with a similar HBV DNA and ALT profile. Untreated, fibrosis can progress at a significant rate in HBeAg-positive and HBeAg-negative patients with increased serum HBV DNA and ALT concentrations. Liver biopsy findings from 2 placebo-controlled studies showed that over 48 weeks between 21% and 36% of untreated patients experience progression of fibrosis.^{19,20} For patients with CHB, the mortality rate at 5 years is 16% for those with compensated cirrhosis^{21,22} and 65%–86% for those with decompensated cirrhosis (in the absence of liver transplantation).^{22,23} The presence of HBeAg and HBV DNA are associated with an increased risk for HCC. Men who are positive for both HBsAg and HBeAg have been calculated to have a relative risk of progression to HCC of 60.2 (9.6 for HBsAg alone) compared with those without HBsAg.²⁴ This study also showed that the likelihood of HCC in individuals with detectable serum HBV DNA by a branched-chain DNA assay (Quantiplex; Chiron, Emeryville, CA) is 3.9-fold that of those without detectable HBV DNA, and that the risk increases with increasing HBV DNA levels.²⁴

A recently published analysis from a long-term cohort study of 3653 patients with CHB, of whom 164 developed HCC, found that incidence rates of HCC increased across a biological gradient of serum HBV DNA levels in a dose-response relationship.²⁵ The cumulative incidence of HCC was 1.3% in persons with serum HBV DNA levels of less than 300 copies/mL and increased to an incidence of 14.9% for those with HBV DNA levels of 10⁶ or more copies/mL. This biological gradient remained significant after adjustment for age, sex, cigarette smoking, alcohol consumption, ALT levels, and HBeAg status.²⁵ A similar analysis in 3582 patients showed that the cumulative incidence of cirrhosis increased from 4.5% to 36.2% for patients with HBV DNA levels of less than 300 copies/mL and of 10⁶ or more copies/mL, respectively.²⁶ This relationship between serum HBV DNA level and cirrhosis was independent of HBeAg status and other variables, including ALT levels.

Because HBeAg and HBV DNA are both markers of HBV replication, the findings of the earlier-described studies implicate viral replication in the progression of chronic HBV infection and provide a rationale for antiviral therapy to arrest progression of liver disease.

Hepatitis B Virus Mutants

HBV has a mutation rate approximately 10 times higher than that of other DNA viruses, and its reverse transcriptase lacks a proofreading function that is common to most other polymerases. Mutations may occur in any of the HBV genes; several viral mutants occur naturally or by selective pressure from antiviral therapy. Four forms of HBV are relevant in current clinical practice: wild-type HBV, precore mutants, core promoter mutants, and various treatment-induced mutants.

Precore and Core Promoter Mutants

HBeAg generally is regarded as a marker of HBV replication and, in the past, patients found to be HBeAg-negative were considered to have nonreplicative HBV infection. Patients with normal ALT levels often previously were referred to as *healthy carriers* in the past, but now are called *inactive HBsAg carriers*. A number of studies were conducted in HBV-infected patients with increased ALT levels in the absence of HBeAg to evaluate other possible causes of hepatitis. In the early 1980s, an increasing number of patients in the Mediterranean region were identified with active HBV replication despite absence of HBeAg.²⁷ In 1989, specific mutations were identified in the HBV genome that prevented HBeAg formation despite active HBV replication.²⁸ The most common mutation, a G to A substitution at nucleotide

1896 in the precore region, results in a stop codon, preventing HBeAg production, and is termed the *precore mutant*. A second dual mutation, the *double basic core promoter* mutant involving 2 nucleotide substitutions (A₁₇₆₂T and G₁₇₆₄A), leads to down-regulation of HBeAg production.²⁹

HBeAg-negative CHB is not typically acquired as a de novo infection, although there are reports of transmission of precore mutant HBV.³⁰ The precore mutant form most often emerges as the predominant species during the course of typical HBV infection with wild-type virus and is selected during the immune clearance phase (HBeAg seroconversion). The development of HBeAg-negative CHB can occur either close to HBeAg seroconversion or many years or even decades later.³¹ There are 2 main patterns of disease activity in HBeAg-negative CHB. Approximately 30%–40% of patients experience persistently increased ALT levels (3- to 4-fold increase), but 45%–65% of patients have an erratic pattern of ALT increases with frequent flares of disease activity.^{32,33} Serum HBV DNA levels also tend to be high, particularly before ALT increases.³¹ However, mean HBV DNA levels are lower in HBeAg-negative CHB compared with HBeAg-positive disease. Sustained spontaneous remission is uncommon in patients with HBeAg-negative CHB (6%–15%),^{32,33} and the long-term prognosis is reportedly poorer compared with HBeAg-positive patients, although this may in part reflect a later stage of HBV infection.³²

Treatment-Induced Mutants

The YMDD mutation is a specific mutation occurring in the tyrosine-methionine-aspartate-aspartate (abbreviated *YMDD*) portion of the HBV P gene associated with the active site of the DNA polymerase. The mutation is caused by selective pressure of L-nucleoside analogue antivirals, such as lamivudine and emtricitabine, and results in the production of a viral polymerase with an altered active site and confers resistance to certain antiviral agents.

More recently, other mutations in the reverse transcriptase associated with resistance to adefovir and entecavir have been identified. Resistance to adefovir is characterized by the emergence of 2 key mutations, A181V/T and/or N236T, in the B and D domain of the reverse transcriptase. Although no evidence of resistance to entecavir has been observed in nucleoside treatment-naïve patients, phenotypic resistance has been documented in patients with pre-existing lamivudine-resistant mutations (I169, T184, S202, and M250).³⁴ The emergence and clinical relevance of treatment-related mutants are described in more detail in a later section.

Hepatitis B Virus Genotypes

It now is possible to identify 8 HBV genotypes (A–H) based on DNA sequence differences of 4% in the S antigen and 8% in the entire genome, with a variable worldwide geographic distribution.^{35,36} Genotype A is found mainly in North America, Northern Europe, India, and Africa; genotypes B and C in Asia; genotype D in Southern Europe, the Middle East, and India; genotype E in West Africa and South Africa; genotype F in South America and Central America; and genotype G in the United States and Europe. A further genotype (H) recently was identified in persons from Central America and California.³⁵ HBeAg-negative (precore mutant) HBV is most common in genotypes B, C, and D, which explains why precore mutant HBV infection is more common in Asia and Southern Europe.

Preliminary data suggest that HBV genotype may be related to clinical outcomes. Some studies in Asia suggest that genotype C is associated more frequently with severe liver disease and HCC than is genotype B.^{37–39} Genotype B appears to be associated with seroconversion from HBeAg to anti-HBe at a younger age than genotype C.^{37,40} Genotype has not been shown to consistently influence the outcome of therapy with oral nucleoside and nucleotide therapies. However, genotype has been shown to affect response to interferon (IFN) therapy because genotypes A and B appear to have higher rates of antiviral response to IFN alfa-2b therapy than genotypes D and C, respectively.^{41,42} In addition, higher rates of HBeAg seroconversion after treatment with peginterferon alfa-2a have been reported in patients with genotype A,⁴³ and higher rates of HBeAg loss after treatment with peginterferon alfa-2b have been reported in patients with genotypes A and B.⁴⁴

In light of these emerging data, we recommend that patients routinely should be genotyped to help to identify those patients who may be at greater risk for disease progression, and in particular those who are the most appropriate candidates for treatment with peginterferon. An informed discussion regarding the option of treatment with peginterferon vs an oral agent is enhanced by knowledge of the likelihood or response. Commercial tests for HBV genotyping are now widely available through referral laboratories.

Diagnostic Markers in Hepatitis B Virus Infection

The diagnosis of chronic HBV infection typically is based on the evaluation of serologic and virologic markers of HBV infection in serum and the evaluation of biochemical and histologic markers of liver disease.

Serologic Markers

HBsAg is the first serologic marker to appear after infection. Its persistence for more than 6 months indicates chronic HBV infection. Antibody to HBsAg (anti-HBs) implies recovery and/or immunity to HBV. Anti-HBs also is detectable after immunity conferred by hepatitis B vaccination. Occasionally, anti-HBs and HBsAg both are detectable in patients with chronic infection, a finding of no known significance. The presence of HBeAg indicates active replication of HBV. However, its absence cannot be assumed to equate to absent viral replication because HBeAg is not detectable in patients with HBeAg-negative (precore or core promoter mutant) HBV infection. The presence of anti-HBe generally indicates HBeAg seroconversion, although it also is found in patients with precore or core promoter mutant HBV infection. HBeAg seroconversion (HBeAg loss and detection of anti-HBe) generally has been considered the end point for HBV therapy for the HBeAg-positive patient because it has been shown to be associated with a lower risk for disease progression,⁴⁵ although not protective against later development of HCC.

Virologic Markers

The amount of HBV DNA in serum is a measure of the level of viral replication. Previously, serum HBV DNA testing was performed using nonamplified hybridization assays. These assays have limited sensitivity with a lower limit of quantification of 10^5 to 10^6 copies/mL and should no longer be used in the routine management of patients with chronic HBV infection. The National Institutes of Health Workshop on Management of Hepatitis B recommended that treatment be considered for patients with detectable HBV DNA by nonamplified assays (ie, $>10^5$ copies/mL, or 20,000 IU/mL).¹⁵ However, some HBeAg-positive patients and many HBeAg-negative patients have fluctuating HBV DNA levels that decrease to less than 10^5 copies/mL.⁴⁶ Furthermore, the threshold HBV DNA level associated with progressive liver disease is unknown. In the panel's experience, patients can have advanced liver disease even if they have serum HBV DNA levels persistently less than 20,000 IU/mL; thus, the clinical significance of low HBV DNA levels is uncertain and should be individualized.

The ideal HBV DNA assay should have a linear large dynamic range of quantification allowing evaluation of viremia at both the lowest and highest concentrations. Currently, the Roche COBAS Taqman HBV DNA assay has both the lowest limit of detection and the broadest linear range of quantification (<50 to 10^9 copies/mL).⁴⁷ Real-time polymerase chain reaction (PCR) assays have

become more widely available and are preferred in the initial evaluation of patients and, even more importantly, in the monitoring of both treated and untreated patients. The current lack of standardization between assays, which makes it difficult to compare data from different laboratories, will be resolved with the introduction of an HBV DNA standard.⁴⁸ In the future all results should be reported in IU/mL (1 IU/mL equals approximately 5.6 genomes/mL).

Biochemical Markers

Increased serum ALT levels (ie, greater than the upper limit of the normal range) are an indicator of necroinflammatory activity. Hence, a normal ALT level often is considered predictive of histologic quiescence, and HBV-infected patients with persistently normal ALT levels generally have milder inflammation on liver biopsy specimens than patients with increased ALT levels. Moreover, patients with normal ALT levels tend to have a poor serologic response to antiviral therapy and often are not considered for treatment. However, some patients with normal ALT levels and increased HBV DNA levels do have significant inflammation and fibrosis on biopsy examination.⁴⁹ Three recent preliminary reports showed that 12%–43% of patients with chronic HBV infection and persistently normal ALT levels had stage 2 fibrosis or greater.^{50–52} In 2 of the studies,^{51,52} age older than 40–45 years was an independent predictor of significant histology. These studies in aggregate suggest that the management algorithm of patients with chronic HBV infection and normal ALT levels should include more liberal use of liver biopsy examination in those who are older than ages 40–45 because 12% to 43% will have stage 2 fibrosis or greater. In such patients, treatment may be indicated.

At many institutions, it is likely that the upper limit of normal for ALT levels is overestimated because of the use of populations that include patients with subclinical liver disease for the determination of normal reference ranges. In a large retrospective study involving a cohort of first-time blood donors who had been screened for the presence of liver disease, the upper limit of normal for serum ALT was found to be significantly lower than the previously established limits (ie, 30 IU/L for men and 19 IU/L for women).⁵³ Moreover, an interesting prospective cohort study of 95,533 men and 47,522 women aged 35 to 59 years showed that the relative risk of mortality from liver disease was increased in the individuals with slightly increased ALT levels based on these new criteria but that were still within the traditional normal range.⁵⁴ Compared with those individuals with an ALT of less than 20 IU/L, those with ALT levels of 20–29 had a

relative risk of mortality of 2.9, and those with an ALT level of 30–39 had a relative risk of mortality of 9.5. Thus, the panel of investigators recommended that an upper limit of normal of 30 IU/L for men and 19 IU/L for women be used for serum ALT levels when making decisions regarding initiation of therapy.

Histologic Markers

Histologic evaluation of liver biopsy specimens is a more sensitive and accurate indicator of liver disease than ALT levels. It is useful to establish the baseline status of liver histology at initial evaluation before initiation of therapy and to exclude other causes of liver disease. However, liver biopsy examination is not always used as a method of diagnosis and is resisted by some patients because of its invasive nature. Significant progress has been made in the development of noninvasive serum markers of fibrosis over the past few years.⁵⁵ Although these data are encouraging, these methods have not yet been validated fully and are not ready for routine clinical use.

Patient Evaluation

Table 3 summarizes the tests that should be performed at the initial evaluation of patients with chronic HBV infection, and the suggested follow-up evaluation

Table 3. Evaluation of Patients With Chronic HBV Infection

Initial evaluation
History and physical examination
Laboratory tests to assess liver function: complete blood count with platelets, hepatic panel, and prothrombin time
Tests for HBV replication: HBeAg/anti-HBe, HBV DNA
Test for HBV genotype
Tests to rule out other causes of liver disease: anti-HCV, antibody to hepatitis D virus (anti-HDV)
Test for hepatitis A immunity: antibody to hepatitis A virus (anti-HAV)
Test for human immunodeficiency infection, in at-risk patients: anti-HIV
Tests to screen for HCC in high-risk patients: AFP and US
Liver biopsy examination to grade and stage liver disease, if criteria for chronic hepatitis
Suggested follow-up evaluation for patients not considered for treatment
HBeAg-positive chronic hepatitis B with HBV DNA $\geq 10^4$ IU/mL and normal ALT
ALT every 3–6 mo
Consider liver biopsy examination and/or treatment when ALT levels become increased
Consider screening for HCC in relevant populations
Inactive HBsAg carrier state
ALT every 6–12 mo
If ALT levels become increased, check serum HBV DNA and exclude other causes of disease
Consider screening for HCC in relevant populations

Adapted from Lok and McMahon.²

for patients who are not considered for treatment. 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 co-infection, and alcohol use. Laboratory tests should include assessment of liver disease, markers of HBV replication, HBV genotype, and tests for co-infection with other viruses for those at risk. A liver biopsy examination also is recommended for patients with intermittent or persistent increases in ALT levels, but it is not mandatory. Screening for HCC should be considered in high-risk individuals (next section). Patients also should be counseled on precautions to prevent transmission of HBV infection and vaccination of sexual and household contacts. All patients should be discouraged from heavy alcohol use, and counseled that there is no proven safe level of alcohol use. Abstinence from alcohol is recommended for those with cirrhosis. All individuals with chronic HBV infection who are not immune to hepatitis A should be vaccinated according to Centers for Disease Control and Prevention recommendations (ie, 2 doses of hepatitis A vaccine, with an initial injection at baseline and a booster injection at 6–18 mo).

Screening for Hepatocellular Carcinoma

HBV carriers are at increased risk for development of HCC.^{56,57} In most patients, HCC generally begins as an encapsulated single tumor. The doubling time of HCC ranges from 2 to 12 months (median, 4 mo).^{58,59} HCC can be detected early with periodic α -fetoprotein (AFP) and ultrasound (US) screening. Periodic screening studies using AFP and US, respectively, in HBV-infected subjects detected small tumors (<5 cm) in 64% and 83% of persons with HCC.^{60,61} The combination of AFP and US appears superior to either modality alone. Data suggest that screening every 6 months with AFP and US is more effective than annual screening in detecting HCC, but there appears to be no difference between screening every 3 or 6 months.^{60–65}

The standard approach for HCC screening is outlined in the American Association for the Study of Liver Diseases Practice Guideline² and in the European Association for the Study of the Liver HBV Consensus Guideline,⁴ and recently was updated.⁶⁶ HCC screening should be performed for HBV carriers at high risk for HCC (ie, Asian men older than age 40, Asian women older than age 50, Africans older than age 20, persons with cirrhosis, patients with a family history of HCC, and those with high HBV DNA levels and/or active hepatic inflammatory activity).⁶⁶ Many clinicians, including the panel of investigators, prefer to institute screening earlier (eg, 30–35 years of age or even younger) in Asian

patients with presumed infection at the time of birth or in early childhood. It is important to be aware that, in hepatitis B patients, HCC can occur in the absence of cirrhosis.^{56,57} Screening should be performed every 6 months using AFP and US. Magnetic resonance imaging and computed tomography, although more expensive, generally are considered to be more sensitive than US and may be preferred by clinicians for some patients (eg, those with cirrhosis or obesity, resulting in poor US sensitivity). Although AFP is less sensitive than US, it has a high negative predictive value (99%).^{60,67} Periodic screening for HCC, using AFP, should be considered in low-risk individuals from endemic areas.²

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 3), there are some controversial issues on how these should be used to identify candidates for therapy.

Normal Versus Increased Alanine Aminotransferase Levels

ALT level is used commonly as an assessment of liver disease and has been important in defining which patients are candidates for therapy. However, reliance on increased ALT levels as a prerequisite to treatment candidacy has limitations. The extent of liver cell necrosis and degree of increased ALT levels do not always correlate, and ALT measurements may fail to identify patients with necroinflammatory activity or fibrosis, as has been seen in hepatitis C.^{53,68} In addition, ALT activity may be related independently to body mass index, sex, abnormal lipid and carbohydrate metabolism, and whether a patient is receiving dialysis.⁵³ Moreover, ALT increases occur in different circumstances, such as during spontaneous HBeAg loss, in association with some antiviral therapies, or with infection with other viruses.¹⁸

The ALT level has been an important influence on the decision to treat because of its value in predicting a serologic response (HBeAg loss or seroconversion) to lamivudine,^{69,70} IFN,^{71,72} peginterferon alfa-2a,⁴³ and adefovir.⁷³ The predictive value of ALT levels has been reinforced by the observation that, despite the generally lower response rates seen in Asian patients, those with increased ALT levels respond as well as Caucasian patients with equivalent degrees of ALT increase to lamivudine and IFN.^{70,72}

Geographic origin and genotype also affect the usefulness of ALT as a determinant for treatment. The majority of Asian patients have normal ALT levels, but up to one third have CHB.⁷² Asian and other patients from pop-

ulations where HBV infection is acquired at an early age often are identified during the immune-tolerant phase of the disease, which is characterized by an absence of necroinflammatory activity and normal ALT levels despite active replication. Genotypes B and C found in patients from Asia and elsewhere predispose to HBeAg-negative (precore and core promoter) mutants. These patients have the ability to significantly replicate HBV in the presence of anti-HBe, even when ALT levels are normal.

The use of ALT levels to define CHB patients who are candidates for treatment derives from the historic experience with IFN therapy and helps to define a cohort more likely to respond to that medication, not a disease state appropriately in need of effective therapy. A treatment algorithm should, on the basis of the natural history of the disease, define the patient disease state that requires treatment and then identify the drug treatment options. Although it is helpful to know a patient's ALT level, a normal ALT level does not always help to determine who should be treated. A patient's ALT level needs to be considered in conjunction with his or her level of serum HBV DNA and age. Hence, in patients with detectable HBV DNA ($\geq 10^4$ IU/mL) and normal ALT levels, a liver biopsy examination should be considered, particularly in individuals older than 35 to 40 years of age who are less likely to be immune tolerant. If significant disease is found (ie, moderate fibrosis [stage 2] or greater and/or significant necroinflammation), the patient should be considered for treatment. Patients with HBV DNA levels of 10^4 IU/mL or higher and increased ALT levels generally should be treated, regardless of whether or not a liver biopsy examination is performed.

Viral Threshold

Historically, the presence (ie, levels greater than assay limit of detection) or absence (ie, levels less than assay limit) of HBV DNA by hybridization techniques was a major determinant of treatment candidacy. This was chosen because, in most patients who have undergone HBeAg seroconversion, HBV DNA levels decrease to less than the detection limit of unamplified hybridization assays ($< 10^5$ copies/mL), ALT levels normalize, and necroinflammation decreases.^{74,75} However, patients with CHB have fluctuating HBV DNA levels that may at times decrease to less than that level. In addition, the threshold HBV DNA level that is associated with progressive liver disease is unknown. Undetectable HBV DNA levels by hybridization techniques has in the past been considered clinically insignificant; however, HBV DNA levels less than 20,000 IU/mL are associated with significant intrahepatic HBV DNA and covalently closed

circular DNA levels.⁷⁶ Furthermore, HBV DNA has been detected by PCR in the serum and liver of patients with cirrhosis and HCC who have been found to have undetectable HBV DNA by hybridization (and negative HBsAg).^{77,78} Sensitive real-time target amplification assays such as the Roche Taqman PCR assay can detect levels as low as 10 IU/mL (50 copies/mL).⁴⁷ Although the clinical significance of low levels of HBV DNA is unclear, patients with fewer than 10^5 copies/mL have been shown to be at risk for progression to cirrhosis or HCC.^{25,26}

With the advent of sensitive real-time PCR, serum HBV DNA has become the most useful measurement for the follow-up evaluation of patients with CHB. A review of 26 prospective studies found significant correlations between viral load level or viral load change and various accepted markers of disease activity (histologic grading and biochemical and serologic response).⁷⁹ To determine whether there is a clinically significant threshold for HBV DNA, Chu et al⁴⁶ analyzed sequential samples (by PCR) from 165 Chinese patients with different stages of CHB. Serum HBV DNA levels decreased by a mean of 3 \log_{10} in patients who had spontaneous or IFN-related HBeAg loss, but no threshold HBV DNA level was associated with HBeAg loss. Also, serum HBV DNA at the time of HBeAg loss was not a predictor of the durability of HBeAg loss. HBeAg-positive patients tended to have higher HBV DNA levels (10^5 to 10^8 copies/mL) than HBeAg-negative patients, but levels as high as 10^8 copies/mL were detected in some HBeAg-negative patients. Moreover, approximately one third of HBeAg-negative patients had HBV DNA levels persistently higher than 10^5 copies/mL. Interestingly, two thirds of HBeAg-negative patients and all inactive carriers had levels persistently lower than 10^5 copies/mL, indicating that it is not possible to define a single cut-off HBV DNA value to distinguish inactive carriers from patients with HBeAg-negative chronic hepatitis B. Repeated measurements of HBV DNA and ALT levels or liver biopsy results can be used to differentiate among these patients, although the latter is not used routinely. In another study, Manesis et al⁸⁰ found that a viral load of 30,000 copies/mL, measured by a sensitive quantitative PCR assay, was an appropriate level to distinguish between patients with HBeAg-negative CHB and the inactive HBsAg carrier state. However, because serum HBV DNA levels fluctuate in HBeAg-negative CHB, they also suggest that patients with normal ALT levels and low serum HBV DNA be evaluated at several time points to assess whether they are an inactive carrier or have HBeAg-negative CHB.

The optimal management of CHB requires the use of sensitive real-time PCR assays to establish an accurate baseline HBV DNA level, and then continued use of sensitive assays during antiviral therapy to measure most accurately the response to therapy and viral rebound associated with resistance. The use of non-PCR assays may allow significant viral replication to go undetected, with potentially injurious clinical consequences, both in the pretreatment and on-treatment settings.

Patient Populations

The majority of chronic HBV infections result from perinatal transmission in Asia. In these patients, persistence of HBeAg is lengthier (immune-tolerant phase), ALT levels tend to be normal, and serum HBV DNA levels may be high.^{81,82} The majority of patients do not clear HBeAg or seroconvert until the third or fourth decade of infection. Those who remain HBeAg-positive can either remain immune tolerant or subsequently can develop a Western pattern of hepatitis and experience either persistent or intermittent increases of ALT levels.^{83–85} Even patients who clear HBeAg are at high risk for HBeAg-negative hepatitis B, which has serious implications.

Asians tend to develop complications of CHB (eg, HCC) in their sixth to seventh decade of infection, often after HBeAg seroconversion.²⁴ Although Asian patients with increased ALT levels respond to IFN⁷² and lamivudine⁷⁰ as well as Caucasian patients, many Asian patients have normal ALT levels at presentation and thus lower response rates to therapy. IFN rarely results in a permanent clearance of HBV in Asian patients. A recent study that followed-up a cohort of Chinese patients after treatment with IFN showed that even after HBeAg seroconversion, 91% of patients had detectable HBV DNA by PCR.⁸⁶ Furthermore, these patients still had a high incidence of cirrhosis and HCC. In contrast, in Caucasians, IFN increased the chance of HBsAg loss after clearance of HBeAg, which was associated with a better clinical and survival outcome.⁴⁵

A second serologic pattern of hepatitis is seen in Africa, Mediterranean countries, and Alaska, where transmission of HBV tends to be person-to-person during childhood.^{12,84,87} Most HBeAg-positive children have increased ALT levels, and seroconversion tends to occur in late childhood or in the teenage years. The natural history of this population is intermediate between that of Asian and Western populations. The third pattern of hepatitis, seen in individuals in Western developed countries, is quite different from that in the Asian population. HBV is acquired during adulthood and transmission is via sexual exposure, intravenous drug use, or transfusion. The risk of chronicity is lowest in this

group at less than 5%.¹³ Western chronic hepatitis B patients tend to have higher ALT and HBV DNA levels and overall respond better to antiviral treatment.

Goals of Therapy

The goal of therapy of chronic hepatitis B is to eliminate or significantly suppress replication of HBV and to prevent progression of liver disease to cirrhosis that may result in liver failure or HCC 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, durable HBV DNA suppression). This, in turn, will lead to 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 that antiviral therapy may be stopped, and the likelihood is high that the benefit will persist off-therapy. Loss of HBsAg, although highly desirable, rarely is achieved with short-term antiviral therapy and, hence, is not a common goal for antiviral trials.

Approved Hepatitis B Virus Therapies

Currently, there are 5 drugs that have been approved for treatment of chronic HBV infection in the United States from 1992 to 2005—IFN alfa-2b, lamivudine, adefovir, entecavir, and peginterferon alfa-2a. The role of IFN alfa-2b has been supplanted with the availability of peginterferon alfa-2a and, therefore, will not be included as an option in our treatment recommendations. Several new antiviral agents and immunomodulatory therapies are under investigation but are not yet available commercially; these agents are not discussed.

Treatment and Management of Chronic Hepatitis B

HBeAg-Positive Patients

Adefovir, entecavir, IFN alfa-2b, lamivudine, and peginterferon alfa-2a all are approved for first-line therapy in patients with HBeAg-positive chronic HBV infection.

Summary of key clinical data.

Adefovir dipivoxil. One year of adefovir 10 mg once daily resulted in histologic improvement, reduced serum HBV DNA and ALT levels, and increased rates of HBeAg seroconversion (Table 4).¹⁹ Patients treated be-

Table 4. Comparison of IFN, Peginterferon alfa-2a, Lamivudine, Entecavir, and Adefovir Dipivoxil in HBeAg-Positive CHB

Parameter ^a	IFN (untreated) ^b 12–24 wk	Peginterferon alfa-2a (lamivudine) ^b 48 wk	Lamivudine (placebo) ^b 52 wk	Adefovir dipivoxil (placebo) ^b 48 wk	Entecavir (lamivudine) ^b 48 wk
Serum HBV DNA loss ^c	37% (17%)	25% (40%)	44% (16%)	21% (0)	67% (36%)
Serum HBV DNA log ₁₀ reduction	Not available	4.5 log ₁₀ (5.8)	Not available	3.52 log (0.55)	6.9 (5.4)
HBeAg loss	33% (12%)	30% (22%) at week 48 34% (21%) at week 72	32% (11%)	24% (11%) 46% at 96 weeks, 53% at 144 weeks	22% (20%)
HBeAg seroconversion	18%	27% (20%) at week 48 32% (19%) at week 72	16%–18% (4%–6%) 50% at 5 y	12% (6%) 33% at 96 weeks, 46% at 144 weeks	21% (18%)
HBeAg loss	11%–25% at 5 years in white patients	3% (0%) at week 72 (HBsAg seroconversion)	Insufficient data	Insufficient data	2% (1%)
ALT normalization	23%	39% (62%)	41%–72% (7%–24%)	48% (16%)	68% (60%)
Histologic improvement	Poor data	38% (34%) at week 72	49%–56% (23%–25%)	53% (25%)	72% (62%)
Development of resistance	No	No	14% increasing to 69% at 5 y	0% at year 1, 2% at 2 years, 15% at 4 years	0% at year 1 and 2
Durability of response after HBeAg seroconversion	80%–90% at 4–8 y	Not available	77% at 37 mo	91% at 55 weeks	82% at 24 weeks
Defined treatment course	Yes	Yes	Unclear	Unclear	Unclear
Safety	Poor	Similar to IFN	Same as placebo	Same as placebo	Same as lamivudine
Tolerability	Poorly tolerated	Better than IFN	Well tolerated	Well tolerated	Similar to lamivudine
Dosing regimen	5 MU daily or 10 MU 3 times weekly for at least 16 wk (injection)	180 µg weekly for 48 wk (injection)	100 mg, once daily (oral)	10 mg, once daily (oral)	.5 mg, once daily (oral)
Cost/year ^d	\$6515–7600 ^e	\$16,170	\$2240	\$6038	\$7203

^aAll data are at 1 year unless otherwise stated.^bControl arm.^cIFN 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: PCR assay (Roche Cobas) undetectable is <300 copies/mL.^dAverage wholesale price, September 2005.^e16 weeks.

yond 48 weeks derived additional virologic, serologic, and clinical benefit. By week 144, 53% had HBeAg loss, 46% had HBeAg seroconversion, 48% had HBV DNA undetectability, and 80% had ALT normalization.⁸⁸ A recent preliminary report showed that long-term adefovir over 4–5 years in an open-label extension of the original randomized, controlled, prospective cohort study of HBeAg-negative patients showed continued improvement in hepatic fibrosis.⁸⁹ After 4 and 5 years of treatment, ALT level was normal in 70% and 69%, respectively, and HBV DNA level was less than 3 log₁₀ copies in 65% and 67%, respectively. Six (5%) patients had loss of HBsAg, with 5 patients developing anti-HBs. There also was continued histologic improvement.

The safety profile of adefovir was similar to that of placebo. No patients in the 10-mg group had serum creatinine level increases of .5 mg/dL or more, as has been described with higher doses of adefovir (8% of patients in the 30-mg group).¹⁹ Beyond 1 year there is no comparator, but the incidence of abnormalities in serum creatinine level was not different from the first year.⁸⁹ Renal toxicity was seen at higher doses of adefovir in the early drug discovery phase.

In contrast to lamivudine, no adefovir resistance mutations have been observed after 1 year of treatment. Recent resistance surveillance data from the 4- to 5-year follow-up study have shown the emergence of adefovir resistance (N236T and A181V/T mutations) in 3% of patients at year 2, 11% at year 3, 18% at year 4, and 29% at year 5.⁸⁹ Patients with increased HBV DNA levels after 48 weeks of treatment with adefovir have been identified as being at highest risk for developing resistance.⁹⁰ The N236T mutation has been shown to be susceptible to lamivudine and entecavir in vitro. However, the A181V mutation has reduced susceptibility to both lamivudine and entecavir in vitro, but remains sensitive to tenofovir.⁹⁰ Adefovir resistance associated with a rebound in serum HBV DNA and ALT levels has been shown to respond to lamivudine therapy.⁹¹ There are insufficient data on the impact of adefovir resistance on other clinical end points.

Entecavir. Forty-eight weeks of treatment with entecavir .5 mg/day, compared with lamivudine 100 mg/day, resulted in a significantly higher rate of histologic improvement (72% vs 62%), HBV DNA reduction (−6.9 vs −5.4 log₁₀), HBV DNA undetectability <300 copies/mL (67% vs 36%), and ALT normalization defined as ALT of 1 or less × upper limit of normal (68% vs 60%). Although entecavir is the most potent licensed oral agent in terms of effect on serum HBV DNA, there was no difference in HBeAg loss or seroconversion be-

tween entecavir and lamivudine after 1 year of therapy (Table 4).⁹² The safety profile of entecavir over 48 weeks was similar to that observed with lamivudine.

A recent preliminary report shows continued efficacy of entecavir after 96 weeks of therapy compared with lamivudine.⁹³ Virologic-only responders (HBV DNA < .7 megaequivalents (MEq)/mL but positive for HBeAg) after 48 weeks of therapy received continued entecavir or lamivudine. Two years of therapy with entecavir, compared with lamivudine, resulted in a significantly higher rate of undetectable serum HBV DNA (80% vs 39%, $P < .0001$) and a higher rate of HBeAg seroconversion (31% vs 25%, NS). No HBV DNA polymerase mutations were detected at weeks 48 or 96.^{34,92–94} This high rate of potency and absence of resistance after 2 years of therapy makes entecavir an excellent choice for the treatment of CHB.⁹⁵

Interferon. A meta-analysis of data from 15 trials showed HBeAg loss and HBeAg seroconversion in treated patients (Table 4).⁹⁶ Increased ALT levels and low serum HBV DNA levels are the best predictors of a response to treatment.⁹⁷ Most Asian patients with chronic HBV infection have normal ALT levels even in the presence of high levels of HBV DNA⁷² and thus respond poorly to IFN.⁷¹ In European studies, HBsAg loss has been observed in 5%–10% of patients within 1 year of the start of IFN treatment; among sustained responders, this increases to 11%–25% by 5 years.^{45,98,99} This has not been observed in Asian studies. IFN is administered by subcutaneous injection, and therapy is associated with many adverse effects such as flu-like symptoms, fatigue, anorexia, depression, and leukopenia.¹⁰⁰ For patients opting for IFN-based therapy, peginterferon likely will supplant the use of standard IFN.

Lamivudine. One year of lamivudine therapy results in histologic improvement, HBeAg seroconversion, suppression of serum HBV DNA, and ALT normalization (Table 4).^{49,101,102} If therapy is stopped before HBeAg seroconversion, viral replication returns; hence, long-term therapy is required in most patients. HBeAg seroconversion increases with duration of lamivudine treatment from 17% at year 1 to 27%, 40%, 47%, and 50% at years 2, 3, 4, and 5, respectively.^{49,103–106} HBeAg seroconversion rates also increase with increasing pretreatment ALT levels.^{69,70} In an analysis of 4 lamivudine trials, HBeAg loss occurred in 56% of patients with pretreatment ALT levels greater than 5 times the upper limit of normal.⁷⁰ Unfortunately, the incidence of lamivudine resistance increases with duration of therapy from 14% at 1 year to 69% at 5 years.¹⁰⁷ In

patients who develop lamivudine-resistant HBV, their HBV DNA and ALT levels tend to rebound toward pretreatment levels. More recent data have shown that some patients experience reversion of their initial histologic improvement.^{104,108} Furthermore, in some patients, development of lamivudine-resistant HBV has been associated with severe ALT flares and even rapid decompensation.¹⁰⁹ Lamivudine is well tolerated and has an excellent safety profile.

Peginterferon alfa-2a. Forty-eight weeks of 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 4).⁴³ 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 and lamivudine arm and 19% in the lamivudine arm. Although the combination of peginterferon alfa-2a and lamivudine resulted in a greater degree of viral load reduction, it appeared to offer no advantages over treatment with peginterferon alfa-2a alone in terms of HBeAg seroconversion. Higher rates of HBeAg seroconversion were observed in patients who were genotype A, had low baseline HBV DNA concentrations, or who had increased baseline serum ALT levels. The safety profile of peginterferon alfa-2a was judged to compare favorably with the previous experience with conventional interferon alfa although there were notably more adverse events reported than in the lamivudine arm.

Combination therapy. Some trials suggest that there is some additive benefit of lamivudine/IFN combination therapy,^{102,110} but large well-designed studies are needed to confirm these initial observations. Recent data from the peginterferon alfa-2a studies in HBeAg-negative and HBeAg-positive patients show that there was no additional benefit from treatment with the combination of peginterferon alfa-2a and lamivudine compared with peginterferon alfa-2a alone after 1 year of therapy.^{43,111} A small, double-blind, single-center study of 30 patients randomized to receive either adefovir or adefovir plus emtricitabine showed that the combination therapy arm achieved a significantly greater degree of HBV DNA suppression after 48 weeks of treatment (5.44 log₁₀ vs 3.40 copies/mL).¹¹² However, no benefit was seen in a similar study comparing lamivudine and adefovir with lamivudine alone.¹¹³ Prevention of resistance may be a greater benefit of combination therapy than enhanced potency, but large well-designed studies will need to be conducted to confirm this concept.

Durability of response. HBeAg loss induced by IFN treatment has been found to be durable in 80%–90% of patients after 4–8 years of follow-up evaluation.^{2,114–118} Data on the durability of response after lamivudine treatment are limited. In a follow-up study of patients who had HBeAg seroconverted during lamivudine treatment, seroconversion was durable in 77% (30/39) of patients after a median follow-up period of 37 months (range, 5–46 mo).¹¹⁹ Most clinicians consider HBeAg seroconversion preferable to HBeAg loss alone, but it still remains uncertain if the durability of treatment response to lamivudine is affected by this distinction. The durability of lamivudine-induced HBeAg seroconversion may be affected by the duration of treatment after HBeAg seroconversion. In a study from Korea, patients who received lamivudine for at least 4 months after seroconversion had a lower rate of relapse at 2 years (32%) compared with those who received only up to 2 months treatment after seroconversion (74%).¹²⁰ These data support the continuation of treatment for at least 6 months after HBeAg seroconversion. In a recent study of 61 patients whose serum HBeAg and HBV DNA (solution hybridization) had been persistently negative for at least 24 months of lamivudine therapy, the cumulative reappearance rates of serum HBV DNA after cessation of lamivudine therapy were 15%, 21%, and 31% at 6 months, 1 year, and 2 years, respectively.¹²¹ Cumulative reappearance rates for serum HBeAg were 11%, 13%, and 16%, respectively, suggesting that long-term additional administration of lamivudine might enhance the durability of HBeAg seroconversion.

The durability of HBeAg seroconversion after adefovir therapy was estimated to be 91% in a cohort of patients observed for a median of 55 weeks after completion of treatment.¹²² Patients in whom HBeAg seroconversion was maintained had been treated for a longer duration after seroconversion than those in whom it was not (48 vs 23 wk, respectively). The durability of HBeAg seroconversion after entecavir therapy was 82% at 24 weeks off treatment.¹²³ In summary, the durability of HBeAg seroconversion after completion of treatment is approximately 80%–90% with INF alfa-2b, ranges widely from 50% to 80% with lamivudine, is 91% with adefovir, and is 82% with entecavir after 6 months of follow-up evaluation.

Predictors of response. A number of clinical, biochemical, and serologic factors have been identified as predictive of a good response to IFN. However, the best predictors are high pretreatment ALT and low HBV DNA levels.^{97,100,124} These parameters also are associated with a higher rate of spontaneous HBeAg serocon-

Table 5. Recommendations for Treatment: HBeAg-Positive Patients

HBeAg status	HBV DNA ^a	ALT ^b	Treatment strategy
Positive	<20,000	Normal	No treatment Monitor every 6–12 mo ^c
Positive	≥20,000	Normal	Consider therapy in patients with known significant histologic disease even if low-level replication Low rate of HBeAg seroconversion for all treatments Younger patients often immune tolerant Consider liver biopsy examination, particularly if older than age 35–40 years; treat if disease; in the absence of biopsy examination, observe for increase in ALT levels If treated, adefovir, entecavir, or peginterferon alfa-2a preferred ^d
Positive	≥20,000	Elevated	Adefovir, entecavir, or peginterferon alfa-2a are preferred first-line options ^{d,e} If high HBV DNA; adefovir or entecavir preferred over peginterferon alfa-2a

^aValues shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL).

^bThe upper limit of normal for serum ALT concentrations for men and women are 30 IU/L and 19 IU/L, respectively.

^cOn initial diagnosis, every 3 months for 1 year to ensure stability.

^dGenotyping may be useful to help decide between treating with peginterferon alfa-2a rather than with adefovir or entecavir (ie, peginterferon has been shown to be more effective in patients with genotype A vs D).

^ePeginterferon alfa-2a and entecavir are preferred over lamivudine because they have been shown to be superior in randomized clinical trials, and lamivudine is limited by high rates of resistance.

version. Recent studies have shown that HBV genotype may influence IFN response.^{37,41,42} High pretreatment ALT is also the best predictor of a favorable response to lamivudine and adefovir treatment.^{69,70,73}

Treatment recommendations: HBeAg-positive patients. The recommendations for treatment of HBeAg-positive patients are summarized in Table 5. The panel recommends 20,000 IU/mL or higher as a reasonable threshold for determining candidates for treatment in HBeAg-positive patients. Patients with less than 20,000 IU/mL are not recommended routinely for treatment because the majority of these individuals are inactive HBsAg carriers and at low risk for disease. However, because these individuals may 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 may be performed and therapy considered when there is histologic evidence of significant liver disease. Patients who are not treated should be monitored initially every 3 months for 1 year to ensure stability of HBV DNA and ALT levels, and then if stable monitored every 6–12 months.

HBeAg-positive patients with a serum HBV DNA level of 20,000 IU/mL or higher should be considered for treatment, depending on their ALT levels. Patients with normal ALT levels appear to experience viral suppression at a rate similar to that of patients with increased ALT levels, but with lower rates of loss of HBeAg. However, because patients with normal ALT levels may have significant liver disease and viral suppression is associated with histologic response, biopsy examination should be considered, particularly in individuals older than 35–40 years of age, and the patient 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 20,000 IU/mL or higher and normal ALT levels. For patients with serum HBV DNA levels of 20,000 IU/mL or higher and with elevated ALT levels, lamivudine, adefovir, entecavir, or peginterferon alfa-2a all may be considered as first-line options; however, adefovir or entecavir would be preferred for patients with high levels of serum HBV DNA and/or with normal ALT levels because response to IFN-based therapy is low, and lamivudine is associated with a high rate of resistance. Genotyping may be useful to help decide whether treatment with peginterferon alfa-2a is warranted because it has been shown to be most effective in patients with genotype A. Because both peginterferon alfa-2a and entecavir have been shown to be superior to lamivudine in randomized clinical trials and lamivudine is associated with high rates of resistance, lamivudine is not recommended as a first-line therapy in HBeAg-positive patients. Although serum HBV DNA can be suppressed effectively with oral nucleoside/nucleotide analogs in patients with normal ALT levels, which may confer benefit, HBeAg seroconversion is infrequent.

Duration of therapy and on-treatment monitoring. Patients should be monitored at least every 6 months while on therapy with either entecavir or adefovir. Patients should be monitored more frequently while on lamivudine therapy to facilitate early detection of resistance. Taking into account the available data,^{120–122} the panel recommends that patients should be treated after HBeAg seroconversion as long as HBV DNA levels are decreasing until the HBV DNA levels are undetectable by PCR. Treatment then should be continued for an additional 6–12 months. In patients who have HBeAg seroconversion but in whom HBV DNA levels are detectable and stable, treatment should be continued for 6 months;

seroconversion should be documented again, then consideration should be given to stopping treatment (in the noncirrhotic patient). 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.

HBeAg-Negative Patients

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

Summary of key clinical data.

Adefovir dipivoxil. One year of therapy with adefovir resulted in histologic improvement in 64% of patients compared with 33% of placebo patients.²⁰ Serum HBV DNA levels were reduced by a median of 3.91 log₁₀ copies/mL compared with 1.35 for placebo, and HBV DNA was less than 400 copies/mL in 51% of treated patients and in none of the placebo patients. ALT normalized in 72% of treated patients compared with 29% of placebo patients. Recent data showed that treatment for 144 weeks resulted in long-term virologic and biochemical suppression. At week 144, 79% of patients had undetectable HBV DNA levels (<1000 copies/mL), and 69% had normal ALT levels.¹²⁵ Further histologic improvement was observed in a small cohort of patients who consented to an additional liver biopsy examination at week 144. In addition, 4-year and 5-year data showed continued histologic improvement.⁸⁹ Adefovir was well tolerated and had a safety profile similar to that of placebo. Four patients (3%) had confirmed increases in serum creatinine level of .5 mg/dL or more. No adefovir-resistant mutations were observed at up to 48 weeks of therapy. However, the N236T and A181V/T adefovir-resistance mutations subsequently were observed in 3% of patients at year 2, in 11% of patients at year 3, in 18% at year 4, and in 29% at year 5.⁸⁹

Entecavir. Forty-eight weeks of treatment with entecavir, compared with lamivudine, resulted in a significantly higher rate of histologic improvement (70% vs 61%), HBV DNA reduction (−5.0 vs −4.5 log₁₀), and HBV DNA undetectability less than 300 copies/mL (90% vs 72%). This high rate of undetectable HBV DNA shows the remarkable potency of this agent. ALT normalization (ALT ≤1 × upper limit of normal) was more frequent with entecavir compared with lamivudine (78% vs 71%), but there was no difference in improvement in fibrosis compared with lamivudine.¹²⁶ The

safety profile of entecavir over 48 weeks was similar to that observed with lamivudine. No HBV DNA polymerase mutations were detected at weeks 48 or 96.^{34,94}

Interferon. IFN treatment of HBeAg-negative patients has resulted in end-of-treatment responses ranging from 40% to 90%,¹⁵ but relapse rates are high at 30%–90%.³⁰ Overall, sustained virologic response rates range from 15% to 25%.¹⁵ Responses appear to be more durable in patients who receive treatment for more than 12 months.¹²⁷ Also, up to 32% of patients who achieve a sustained virologic response go on to clear HBsAg. IFN-treated patients with a sustained virologic response seem to have significantly better and complication-free survival than nonresponders or untreated patients.^{128,129}

Lamivudine. Overall, approximately two thirds of patients have a biochemical and virologic response after 6–12 months of lamivudine therapy,^{130–132} with necroinflammation improving in a similar proportion. However, most patients relapse once therapy is stopped, and the majority relapse once lamivudine resistance develops.^{131,132} However, 1 recent study suggested that lamivudine could be stopped after 2 years in patients with persistently undetectable HBV DNA levels, with lower rates of relapse than reported in prior studies, although these results need to be confirmed.¹³³ Longer treatment durations can maintain normal ALT levels and undetectable HBV DNA, but biochemical and virologic breakthroughs occur as a result of the emergence of lamivudine-resistant YMDD mutant HBV. A study of long-term lamivudine therapy showed that although ALT and HBV DNA responses were seen in 96% and 68% of patients, respectively, at 12 months, responses then steadily decreased with duration of therapy. Only about 40% of patients maintained normal ALT and undetectable HBV DNA at more than 30 months.¹³² The incidence of lamivudine resistance increases with time; 19%–27% of patients have YMDD mutant HBV at 1 year,^{130,134} increasing to 44% at 2 years¹³⁰ and 60% at 4 years.^{31,132} The emergence of YMDD mutants in this population can be associated with clinically significant hepatitis,¹³² which significantly limits the role of lamivudine in treating HBeAg-negative chronic HBV infection.

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.¹¹¹ In the peginterferon alfa-2a-treated patients, 59% and 19% had normal ALT and undetectable HBV DNA concentrations, respectively, compared with 60% and 20% in the peginterferon alfa-2a and lamivu-

Table 6. Recommendations for Treatment: HBeAg-Negative Patients

HBeAg status	HBV DNA ^a	ALT ^b	Treatment strategy
Negative	<2000	Normal	No treatment; majority inactive HBsAg carriers Monitor every 6–12 mo ^c
Negative	≥2000	Normal	Consider therapy in patients with known significant histologic disease even if low-level replication Consider liver biopsy examination; treat if disease present; in the absence of biopsy examination, observe for increase in serum ALT levels If treated, adefovir, entecavir, or peginterferon alfa-2a are preferred ^d
Negative	≥2000	Elevated	Adefovir, entecavir, or peginterferon alfa-2a are preferred first-line options ^d Long-term treatment required for oral agents

^aValues shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL).

^bThe upper limit of normal for serum ALT concentrations for men and women are 30 IU/L and 19 IU/L, respectively.

^cOn initial diagnosis, every 3 months for 1 year to ensure stability.

^dLamivudine is not considered a reasonable treatment option because of the high risk for resistance with long-term therapy, and proven inferiority to peginterferon alfa-2a and entecavir in randomized clinical trials.

dine arm, and 44% and 7% in the lamivudine arm, with end points measured 24 weeks after cessation of treatment. The combination of peginterferon alfa-2a and lamivudine appeared to offer no advantages over treatment with peginterferon alfa-2a alone. HBsAg seroconversion was reported in 3% of those treated with peginterferon alfa-2a, 2% of those treated with peginterferon alfa-2a and lamivudine, and in no patients treated with lamivudine alone. The rate of emergence of lamivudine-resistant mutations was reduced markedly in the combination arm. The safety profile of peginterferon alfa-2a was judged to compare favorably with previous experience with conventional IFN alfa, although there were notably more adverse events reported than in the lamivudine arm.

Treatment recommendations: HBeAg-negative patients. The recommendations for treatment of HBeAg-negative patients are shown in Table 6. Chu et al.⁴⁶ showed that approximately half of HBeAg-negative patients had serum HBV DNA levels persistently less than 10⁵ copies/mL on initial testing at the time of presentation. Because HBeAg-negative patients tend to have lower levels of serum HBV DNA than HBeAg-positive patients but still may have disease, the panel recommends treating patients who have serum HBV DNA levels of 2000 IU/mL or higher. Otherwise, the recommendations are similar to those for HBeAg-positive patients. Adefovir, entecavir, and peginterferon alfa-2a all 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.

Duration of therapy and on-treatment monitoring. Patients on therapy should be monitored every 6 months. The duration of therapy for IFN remains unclear, although longer treatment duration (12 mo) appears to be more beneficial in terms of sustained virologic response off treatment than shorter periods of treatment (4–6

mo). The panel believed that peginterferon alfa-2a will replace standard IFN alfa-2b. Tolerability compared with oral agents is clearly an issue for patients with interferon-based therapy. Entecavir and adefovir need to be given long term; however, there are currently no long-term data available for entecavir beyond 2 years. On-treatment monitoring of serum HBV DNA by PCR assay and ALT levels should be performed every 6 months.

Patients With Antiviral Drug Resistance

The recent advances in antiviral therapy of CHB with the oral agents have been associated with the emergence of antiviral-resistant HBV mutants. The incidence of resistance with the oral agents is summarized in Table 7, and the nomenclature, prevention strategies, and potential management of antiviral resistance are outlined in Table 8.¹³⁵

Development of resistance is associated with loss of initial response with HBV DNA rebound, followed by ALT increase and eventual reversion of histologic improvement and, in some cases, progressive liver disease associated with severe exacerbations.^{103,104,108,109,132,135}

Table 7. Incidence of Resistance in Patients Treated With Lamivudine, Adefovir, or Entecavir

	Year 1	Year 2	Year 3	Year 4	Year 5
Lamivudine ^a	24%	42%	53%	70%	NA
Adefovir ^b	0%	3%	11%	18%	29%
Entecavir (treatment-naive patients) ^c	0%	0%	NA	NA	NA
Entecavir (lamivudine-refractory patients) ^c	7%	9%	NA	NA	NA

NA, not available.

^aData from Liaw et al.¹⁰³

^bData from Hadziyannis et al.⁸⁹

^cData from Colonno et al.⁹⁴

Table 8. Nomenclature, Prevention, and Potential Management of Antiviral Resistance

Nomenclature	
Genotypic resistance	Detection of HBV polymerase mutation(s) by direct sequencing of PCR products
Phenotypic resistance	In vitro confirmation by cell culture-based or enzymatic assays that mutation confers resistance
Virologic breakthrough	Increase in HBV DNA by >1 log ₁₀ greater than nadir while receiving continuous treatment
Biochemical breakthrough	Increase in ALT while receiving treatment after achieving initial response
Prevention	
Use potent agents with high genetic barrier to resistance	
Switch therapy if early response suboptimal	
Avoid sequential monotherapy	
Use combination therapy when possible; greater use likely in future	
Management	
Lamivudine-resistance	Add adefovir (may be preferred over switch to adefovir) Switch to entecavir (risk for subsequent entecavir resistance) Potential future management: add tenofovir or switch to emtricitabine/tenofovir
Adefovir resistance ^a	Add lamivudine (may be preferred over switch to lamivudine) Switch to entecavir (if no prior lamivudine resistance) Potential future therapy: switch to emtricitabine/tenofovir
Entecavir resistance ^a	Add or switch to adefovir or tenofovir

Adapted from Locarnini et al.¹³⁵^aLimited in vivo data.

Lamivudine resistance has been described in all patient groups, including compensated and decompensated patients, transplant recipients, and human immunodeficiency virus (HIV) co-infected patients. In cirrhotic patients, the development of resistance is associated with increased ALT levels, which can be severe, and a decrease in liver synthetic function, leading to decompensation of liver disease.¹³⁶ Predictors of lamivudine resistance include high pretreatment HBV DNA levels, non-Asian ethnicity, male sex, and high body mass index.¹³⁷ Resistance accurately can be diagnosed clinically by an increase in serum HBV DNA in a patient on prolonged antiviral therapy who experienced an early decrease in viral levels after initiation of therapy. This increase in HBV DNA typically is associated with liver damage (increase in serum ALT level). There is a strong correlation between this clinical diagnosis of resistance and genotypic markers of polymerase mutations, making di-

rect sequencing of HBV to confirm resistance unnecessary.

Resistance mutations to adefovir have been observed in HBeAg-positive and HBeAg-negative patients treated for more than 48 weeks. There are some data to suggest that patients who are treated with the combination of lamivudine and adefovir are unlikely to develop adefovir-related resistance mutations, and may develop a lower incidence of lamivudine resistance.⁹⁰

Resistance has not been detected in nucleoside-naïve patients treated with entecavir for up to 96 weeks. However, resistance to entecavir has been observed in lamivudine-refractory patients who had pre-existing YMDD mutations (Table 7).³⁴

Summary of key clinical data: lamivudine-resistant hepatitis B virus.

Adefovir dipivoxil. Several studies have evaluated the use of adefovir in lamivudine-resistant HBV. Two studies that included patients with compensated and decompensated lamivudine-resistant HBV and a study in HBV/HIV co-infected patients are covered in later sections (Patients With Cirrhosis [Including End-Stage Liver Disease] and Patients coinfecting with HIV/HBV and HCV/HBV).

Another study measured the independent contribution of adefovir monotherapy for patients with compensated lamivudine-resistant HBV.¹³⁸ Adefovir monotherapy and adefovir in combination with continued lamivudine resulted in similar reductions in serum HBV DNA in contrast to continued lamivudine, which did not reduce HBV DNA levels. No patients experienced clinically significant ALT increases when they were switched from lamivudine to adefovir monotherapy. Combination therapy was well tolerated. Two recent studies showed a higher rate of emergence of adefovir mutations when switching from lamivudine to adefovir treatment in patients with lamivudine resistance, compared with naïve patients undergoing adefovir therapy (15% and 19% vs 3% after 2 years of therapy).^{139,140} Another recent study of patients with and without prior lamivudine therapy showed that the combination of adefovir plus lamivudine therapy provided more potent and consistent inhibition of HBV DNA levels than adefovir alone.¹⁴¹ The combination treatment group had greater HBV DNA suppression compared with the monotherapy group (6.2 log₁₀ vs 4.2 log₁₀ suppression, respectively). However, the proportion achieving undetectable HBV DNA was similar between the 2 groups, and biochemical and histologic responses also were similar. These studies suggest that combination therapy should be considered to prevent sequential antiviral resistance. Because there is particular

concern about the clinical consequences associated with the development of adefovir resistance in patients with advanced liver disease switched to adefovir, continuation of lamivudine plus adefovir in patients with cirrhosis may be prudent.

Entecavir. A study evaluating higher doses of entecavir (1.0 mg/day), compared with continuation of lamivudine 100 mg/day, in HBeAg-positive lamivudine-refractory patients resulted in a higher percentage of patients with histologic improvement (55% vs 28%), HBV DNA reduction (-5.14 vs $-.48$ log₁₀), HBV DNA undetectability less than 400 copies/mL (21% vs 1%), HBeAg loss (10% vs 3%), and ALT normalization defined as less than $1.25 \times$ upper limit of normal (75% vs 23%).¹⁴² However, these responses to entecavir were lower across all end points than those observed in treatment-naïve patients receiving entecavir. In addition, after 1 year of therapy, novel mutations developed in 7% of patients, with 1.6% experiencing breakthrough with an increase of serum HBV DNA levels. With 2-year follow-up evaluation, 9% of patients developed resistance and experienced virologic breakthrough (Table 7).⁹⁴

Treatment recommendations: patients with lamivudine-resistant hepatitis B virus. Management options for patients who develop HBV antiviral resistance are summarized in Table 8. Adefovir and entecavir are both acceptable alternatives for the treatment of patients with lamivudine resistance. However, adefovir may be preferred over entecavir for treatment of lamivudine-resistant HBV based on the currently available data. Whether adefovir is given as monotherapy or in combination with continued lamivudine depends on the status of the patient's liver disease. Data in compensated patients showed mild increases in ALT levels in some patients when switching from lamivudine to adefovir, but no patient experienced clinically significant ALT increases.¹³⁸ These observations suggest that switching patients from lamivudine to adefovir may be a safe strategy in many patients. Because the consequences of returning wild-type HBV are potentially more hazardous in patients with advanced liver disease and switching to adefovir is associated with a 15%–19% rate of adefovir resistance after 2 years,^{139,140} addition of adefovir to continued lamivudine therapy is preferred in patients with cirrhosis. Pending the availability of future data from studies underway, the addition of adefovir to lamivudine may be preferred to switching to adefovir in all patients with lamivudine resistance. Entecavir results in a 5-log₁₀ reduction in serum HBV DNA levels in lamivudine-refractory patients, and this potency needs to be weighed against the development of novel genotypic mutations in 7% and 9% of patients with 1 and 2 years, respectively, of entecavir therapy. Potential future

therapy of lamivudine resistance is to add tenofovir or switch to the combination of emtricitabine and tenofovir.

Duration of therapy and on-treatment monitoring. The recommendation for duration of therapy with adefovir and monitoring also depend on the status of the patient. Generally, compensated HBeAg-positive patients should be treated until HBeAg seroconversion and undetectable HBV DNA levels by PCR assay, then treated for an additional 6 months. (Refer to the section Treatment recommendations: HBeAg-positive patients.)

Summary of key clinical data: adefovir-resistant hepatitis B virus. There have been no formal studies evaluating the treatment of patients who have developed resistance to adefovir. Clinical data from individual case studies show that treatment of patients with the N236T or A181V/T mutations with lamivudine resulted in an antiviral response.⁹⁰ Another potential strategy is to switch to entecavir, if there is not prior lamivudine resistance. A potential future therapy is to switch to the combination of emtricitabine and tenofovir (Table 8).

Patients With Cirrhosis (Including End-Stage Liver Disease)

Before the advent of effective antiviral therapy, the 5-year survival rate was 84% for compensated cirrhosis and 14%–35% for decompensated cirrhosis.^{21–23} Various clinical parameters, such as bilirubin level and older age, were shown to predict survival. In addition, in compensated cirrhosis, patients who had lost HBeAg had 97% survival at 5 years compared with 72% in HBeAg-positive patients, implicating viral replication in adverse outcomes.²⁰

Summary of key clinical data.

Adefovir dipivoxil. A compassionate-use study of adefovir 10 mg/day included chronic hepatitis B patients with either compensated or decompensated cirrhosis and clinical evidence of lamivudine resistance, who either were listed for liver transplantation ($n = 226$) or were posttransplant patients ($n = 241$).^{143,144} In posttransplant patients, serum HBV DNA was undetectable (<1000 copies/mL) in 78%, and ALT normalized in 58% of patients after 144 weeks of treatment. In pretransplant patients, in whom there was a shorter duration of follow-up evaluation, serum HBV DNA was undetectable in 76%, and ALT normalized in 84% of patients after 96 weeks of treatment. Markers of synthetic liver function improved in the majority of patients, and Child–Turcotte–Pugh scores remained stable or improved in the majority of patients. Survival was more than 80% and more than 90% after 2 years of treatment in pretransplant and posttransplant patients, respectively. The safety profile of adefovir was consistent with

the stage of liver disease and comorbidities of this population. Serum creatinine level increases of .5 mg/dL or greater were observed in approximately 21% of patients.

Another study in patients with compensated or decompensated lamivudine-resistant HBV infection showed similar results. The addition of adefovir to lamivudine resulted in significant reductions in serum HBV DNA ($\sim 4\text{--}5 \log_{10}$ copies/mL after 48 weeks of therapy).¹⁴⁵ Decompensated patients showed significant improvement in biochemical parameters and hepatic functional status.

Interferon. IFN has been problematic to use in patients with clinically decompensated cirrhosis. Although patients have shown posttreatment responses to IFN therapy with some clearing HBsAg, their disease tends to deteriorate during therapy and it may take months for liver chemistries to return to normal after completion of therapy. In addition, there is a high risk for serious complications, including serious bacterial infections and exacerbations of hepatitis.¹⁴⁶ Among decompensated patients, response appears to be better in those with Child–Turcotte–Pugh class A (100%) compared with classes B (33%) and C (0%).¹⁴⁷ The occurrence of bacterial infections, even at low doses, in non-class A cirrhotic patients suggests that IFN should not be used for these patients.¹⁴⁷ IFN appears to be safe and effective for patients with compensated cirrhosis, although there is a risk of hepatic decompensation with prolonged therapy. Peginterferon has not been evaluated in randomized clinical trials in these patient populations.

Lamivudine. Treatment with lamivudine has been shown to delay clinical progression of disease in patients with advanced fibrosis or cirrhosis. In a large, randomized, placebo-controlled study, 7.8% of patients treated with lamivudine for a median of 32 months reached a clinical end point compared with 17.7% of patients who received placebo.¹⁴⁸ In addition, there was also a significant reduction in the incidence of HCC (3.9% vs 7.4% in the lamivudine and placebo groups, respectively). Although 49% of lamivudine-treated patients developed YMDD mutations, there were fewer clinical complications in these patients despite the development of resistance as compared with placebo. Thus, lamivudine appears to improve treatment outcomes considerably for patients with decompensated cirrhosis. Several other studies support this conclusion. In 27 nontransplanted patients treated for a median of 869 days with lamivudine, there was a rapid decrease in serum HBV DNA levels and normalization of ALT levels, with some patients clearing HBeAg.¹⁴⁹ Serum albumin and bilirubin levels also were improved. In a similar study by Ville-neuve et al,¹⁵⁰ improvement was seen in treated patients

beyond approximately 9 months of therapy. Serum HBV DNA levels decreased, aspartate aminotransferase and ALT levels normalized, and there were improvements in albumin, prothrombin time, and Child–Turcotte–Pugh score. Both of these studies also showed that survival was improved with treatment compared with historical controls. However, YMDD mutant HBV emerges after 6–12 months of therapy, indicated by increases in HBV DNA and ALT.¹⁴⁹ In decompensated cirrhotic patients, YMDD mutant HBV has been associated with biochemical dysfunction and a reduction in efficacy. Some cirrhotic patients cannot tolerate the development of YMDD mutant HBV and may deteriorate very rapidly once YMDD develops.¹⁰⁹ These studies support the theoretic benefit of lamivudine, or possibly entecavir, plus adefovir in the treatment of patients with decompensated cirrhosis secondary to HBV infection.

There currently are limited data available for entecavir in patients with advanced liver disease. Patients with cirrhosis in the phase III entecavir study were analyzed retrospectively for their response to therapy, and the results showed that entecavir was well tolerated and superior to lamivudine for the end points of histologic improvement, ALT normalization, and undetectable serum HBV DNA.¹⁵¹ There are no data on the use of peginterferon alfa-2a in patients with advanced liver disease, but the experience with IFN in this population suggests that peginterferon should be avoided.

Treatment recommendations: patients with cirrhosis. The recommendations for treatment for compensated and decompensated HBeAg-positive or HBeAg-negative cirrhotic patients are shown in Tables 9 and 10. The approach to patients with compensated cirrhosis and with serum HBV DNA levels less than 2000 IU/mL is either to monitor or to treat the patient with either entecavir or adefovir. The panel believed that in the absence of currently available data to guide this choice, the upside potential for clinical improvement with treatment outweighed the low downside risk for drug toxicity and cost in patients with significant liver disease—albeit compensated. In patients with HBV DNA levels of 2000 IU/mL or higher, entecavir or adefovir are first-line options because of their proven efficacy and good tolerability. The panel believed that although IFN is contraindicated because of the potential for decompensation with a flare of disease induced by IFN, there is likely a role for using peginterferon alfa-2a in patients with compensated cirrhosis. Entecavir and adefovir 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 ad-

Table 9. Recommendations for Treatment: Compensated Cirrhotic Patients

HBeAg status	HBV DNA ^a	Cirrhosis	Treatment strategy
Positive or negative	<2000	Compensated	May choose to treat or observe Adefovir or entecavir preferred ^b
Positive or negative	≥2000	Compensated	Adefovir or entecavir are first-line options Long-term treatment required, and combination therapy may be preferred ^c

^aValues shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL).

^bAlthough there are no data available for peginterferon alfa-2a, it may be an option in patients with early, well-compensated cirrhosis.

^cCombination therapy with lamivudine, or possibly entecavir, and adefovir has a theoretic advantage owing to the lower likelihood of the development of resistance.

efovir plus lamivudine, or possibly entecavir, has the theoretic benefit of reducing the development of resistance to either and/or both drugs.

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

Duration of therapy and on-treatment monitoring. The panel believed that therapy in cirrhotic patients should be long-term and indefinite. Although there are no data on the benefit of continuation of treatment in compensated cirrhotic patients after HBeAg seroconversion, data from China show that patients who undergo HBeAg seroconversion still may develop HCC or have progression of their liver disease.¹⁵² This may be caused by persistent low levels of HBV and/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/nucleotide analogs, therapy should be continued

until the patient becomes HBV DNA negative and has lost HBsAg. 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 adefovir, entecavir, and lamivudine should be made as recommended by the manufacturers.

Patients co-infected with HIV/HBV and HCV/HBV.

Human immunodeficiency virus/hepatitis B virus co-infected patients. In the United States and Europe, approximately 10% of all HIV patients are co-infected with HBV.¹⁵³ Data from the Multicenter AIDS Cohort Study, which include data on patients in care before and after the availability of highly active antiretroviral therapy, showed that the liver-related mortality in HIV/HBV co-infected patients is 14-fold higher than that for patients with either virus alone.¹⁵⁴ A high percentage of HIV-positive patients are treated with lamivudine, tenofovir, and/or emtricitabine, which also have activity against HBV.

Summary of key clinical data.

Adefovir dipivoxil. Adefovir 10 mg/day has been shown to be effective in HIV/HBV co-infected patients with lamivudine-resistant HBV, resulting in a 5.45-log₁₀ decrease in HBV DNA and ALT normalization in 64% by 144 weeks.^{155,156} No adefovir-resistant reverse-transcriptase mutations developed in any of the patients tested up to week 96. Because adefovir at the 10-mg dose is not effective against HIV, adefovir has the benefit of being unlikely to select adefovir- or tenofovir-resistant

Table 10. Recommendations for Treatment: Decompensated Cirrhotic Patients

HBeAg status	HBV DNA ^a	Cirrhosis	Treatment strategy
Positive or negative	<200 or ≥200	Decompensated	Combination with lamivudine, or possibly entecavir, plus adefovir preferred ^{b,c} Long-term treatment required Waiting list for liver transplantation

^aValues shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL).

^bNo data available for entecavir; peginterferon alfa-2a contraindicated.

^cCombination therapy with lamivudine, or possibly entecavir, and adefovir has a theoretic advantage owing to the lower likelihood of the development of resistance.

HIV mutants. Serum creatinine level increases of .5 mg/dL or higher without changes in serum phosphorus were seen in 2 patients.¹⁵⁶ Both resolved and were considered unrelated to adefovir.

Entecavir. A recent study has shown that entecavir is effective for treating co-infected patients. Treatment of HIV-HBV co-infected patients with entecavir in a placebo-controlled study has been shown to result in a 3.66- \log_{10} reduction in HBV after 24 weeks of therapy.¹⁵⁷

Lamivudine. Lamivudine has been shown to be effective and well tolerated in patients co-infected with HBV and HIV,¹⁵⁸ resulting in significant reductions in serum HBV DNA. The rate of emergence of lamivudine-resistant HBV is higher in co-infected patients than in those with HBV infection alone, reaching 90% at 4 years.¹⁵⁹

Tenofovir. Several studies have confirmed that tenofovir is effective against both HIV and HBV. A study by Cooper et al¹⁶⁰ showed that tenofovir results in a .6- \log decrease in HIV and a 5- \log decrease from baseline for HBV. Similarly, another co-infection study showed a 4- \log decrease in HBV DNA by week 24 and an increase of around 80 CD4 cells.¹⁶¹ A small 48-week, open-label, nonrandomized study of lamivudine-resistant patients, some of whom were HIV infected, treated with either tenofovir or adefovir, showed a higher degree of viral load reduction (-5.5 vs -2.8 \log_{10} copies/mL) and HBV DNA undetectability (100% vs 44%) with tenofovir compared with adefovir.¹⁶² However, there have been reports of renal toxicity and hyperphosphatemia associated with tenofovir therapy.^{163,164}

Treatment recommendations. Therapy for HIV/HBV co-infected patients needs to be individualized according to the status of the patient. Tenofovir, entecavir, and adefovir are potent against HBV, but adefovir and entecavir have no activity against HIV. This lack of activity provides a theoretic advantage for adefovir and entecavir if a patient's HIV is not being treated because unnecessary exposure to tenofovir or lamivudine monotherapy would compromise the patient's HIV care. If a patient is being treated for HIV, highly active antiretroviral therapy regimens containing tenofovir, tenofovir/lamivudine, or tenofovir/emtricitabine combinations are options. For patients who are on a stable HIV regimen, it may be preferred to add adefovir or entecavir rather than switch to tenofovir to cover both viruses.

Hepatitis C virus/hepatitis B virus co-infected patients. Injecting drug users often are co-infected with HBV and hepatitis C virus (HCV).¹⁶⁵ Various studies have shown that the outcome of combined infection is more severe than infection with either virus alone.^{166,167} In most

patients, one infection tends to predominate and the other is dormant. In a situation in which HCV is the dominant disease, HCV RNA is detectable and HBV DNA is not. The converse is true for HBV-dominant disease. Many HBV/HCV co-infected patients tend to be HBeAg-negative and to have low levels of HBV DNA, with HCV infection being dominant.

Treatment recommendations. No standard of care has been established for patients who are co-infected with HBV and HCV. Patients should be assessed to determine which virus appears to be dominant, and then treated accordingly. Hence, patients with HBV DNA of 10^4 IU/mL or higher and undetectable HCV RNA should be treated for HBV. However, because most tend to have low levels of HBV DNA and detectable HCV RNA, the panel recommends that HCV/HBV co-infected patients with detectable HCV RNA and high levels of HBV DNA should be treated for 3 months with peginterferon and ribavirin in standard doses. If HBV DNA does not begin to respond or increases on therapy, entecavir or adefovir may be added. A recent study showed that patients with HCV/HBV co-infection treated for predominant HCV infection respond as well as patients with chronic HCV infection alone; only a few patients have activation of HBV infection during therapy.^{166,167}

Chemotherapy

Reactivation of HBV replication with increase in serum HBV DNA and ALT levels has been reported in 20%–50% of HBsAg carriers undergoing immunosuppressive or cancer chemotherapies.¹⁶⁸ In most cases, the hepatitis flares are asymptomatic, but icteric flares, and even hepatic decompensation and death have been observed. Uncontrolled studies showed that prophylactic therapy with lamivudine can reduce the rate of HBV reactivation, severity of associated hepatitis flares, and mortality compared with historical controls.¹⁶⁸ A study of pre-emptive lamivudine therapy vs initiation of lamivudine after demonstration of HBV reactivation during chemotherapy showed less clinical hepatitis in the group randomized to pre-emptive therapy.¹⁶⁹ Although there are limitations with these studies, it seems prudent to administer prophylactic antiviral therapy to HBsAg carriers at the onset of chemotherapy or immunosuppressive therapy, and to maintain antiviral therapy for approximately 3 months afterward. The benefit vs risk of prophylactic antiviral therapy in HBsAg carriers who require life-long immunosuppressive therapy, such as renal transplant recipients, is less certain. One approach would be to monitor these patients and initiate antiviral therapy when there is a significant increase in serum HBV DNA or ALT levels. Studies to date have focused on lamivudine, although adefovir or entecavir may

be used as alternative drugs. Because prophylaxis is generally short-term therapy, lamivudine resistance is of less concern. However, if therapy is likely to be required for longer than 6 months, the panel recommends that either adefovir or entecavir be used in place of lamivudine. Although HBV reactivation can occur in persons who are HBsAg negative but positive for anti-HBc alone or anti-HBc plus anti-HBs, reactivation is infrequent and there is not enough information to recommend routine prophylaxis at this time. However, the panel was divided on this issue because some have seen flares of hepatitis B in patients with isolated anti-HBc with detection of HBsAg and severe biochemical and clinical sequelae; thus, consideration of prophylaxis is not unreasonable, and some experts prefer to use an oral agent in patients with negative HBsAg but detectable anti-HBc and/or anti-HBs.

Pregnancy

Lamivudine, entecavir, and adefovir are classified as category C; therefore, standard category C recommendations should be followed. All 3 drugs may be continued during pregnancy, although the safety experience with lamivudine in pregnant women is much greater than for adefovir or entecavir. Decisions about initiating and/or continuing antiviral therapy in pregnant women should depend on the stage of the mother's liver disease and her potential benefit vs 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 may be prudent. Treatment during the third trimester to prevent transmission to the newborn may be considered. Although some early success had been reported in preventing transmission of HBV to the newborn using lamivudine, reports suggest that HBV transmission to babies still may occur despite lamivudine and perinatal immune prophylaxis and vaccination.¹⁷⁰ A recent double-blind, placebo-controlled, multicenter trial of 114 HBsAg-positive pregnant women randomized them to receive either lamivudine 100 mg/day vs placebo at 32 weeks of gestation and then evaluated HBsAg seropositivity in the infants at 1 year of age; all infants received hepatitis B immune globulin and the HBV vaccine at birth.¹⁷¹ This study showed a lower HBV infection rate in the children born of mothers who received lamivudine vs placebo (18% vs 39%). If treatment is required during pregnancy, based on the experience of using lamivudine during pregnancy in the HIV field and the recent randomized trial, the panel recommends that lamivudine be considered as the first-line option. However, if long-term treatment is required beyond pregnancy, then consideration should be given to switching the patient in the postpartum period to treat-

ment with adefovir or entecavir. Any patients treated with lamivudine, entecavir, or adefovir should be reported to the respective pregnancy registry.

Resistance Monitoring

Resistance can be defined clinically (ie, genotyping is not used currently in routine practice) by a 1-log₁₀ increase in serum HBV DNA from the patient's lowest on-treatment level confirmed by measurement on 2 assays (Table 8).

Patients receiving lamivudine should be monitored every 3–6 months for resistance. Because of the significantly lower rates of resistance seen with adefovir and entecavir, patients treated with these agents should be monitored every 6 months for resistance after the first year of therapy. Patients with advanced liver disease should be monitored more frequently (ie, every 3 mo).

Conclusions

The goal of therapy for patients with chronic HBV infection is to prevent progression of liver disease to cirrhosis and HCC. Because HBV replication is implicated in the outcome of chronic HBV infection, the primary aim of therapy is durable suppression of serum HBV DNA to the lowest levels possible. The advent of molecular diagnostic assays such as PCR enables the accurate monitoring of HBV DNA at levels as low as 10 IU/mL and should be used to establish a patient's baseline HBV DNA level before treatment and to monitor response to antiviral therapy or viral rebound associated with resistance.

The threshold level of HBV DNA for determination of candidates for therapy is 20,000 IU/mL or higher for patients with HBeAg-positive CHB. Patients also should have increased ALT levels (using revised definitions) and/or evidence of hepatitis on liver biopsy examination. An individualized approach to liver biopsy examination and consideration of therapy in viremic patients with normal ALT levels is warranted, and future studies of this population of HBV-infected patients are needed because approximately 20%–25% have significant fibrosis. A lower serum HBV DNA threshold is needed for patients with HBeAg-negative CHB and those with decompensated cirrhosis, and the panel recommends thresholds of 2000 IU/mL and 200 IU/mL, respectively, for treatment of these patient groups. Patients with HBeAg-negative CHB and patients with cirrhosis require long-term antiviral therapy.

Adefovir, entecavir, IFN, lamivudine, and peginterferon alfa-2a all are approved as initial therapy for chronic hepatitis B. In choosing a therapy, however, consideration

should be given to the advantages and disadvantages of the 5 therapies. The issues to consider are efficacy, safety, resistance, method of administration, and cost.

Adefovir generally has comparable efficacy with lamivudine and is well tolerated. It has the advantage of a delayed and low rate of resistance development. Entecavir is the most potent oral agent and has shown superiority to lamivudine in randomized clinical trials. In addition, no resistance has been shown after 2 years of therapy in naive patients. However, long-term efficacy and resistance data are not available beyond 2 years. The cost of both entecavir and adefovir is higher than that of lamivudine. Although IFN and peginterferon alfa-2a have the advantage of a finite duration of treatment, durable response (in patients who respond), and lack of resistance, they are expensive to use, have to be given by injection, and have many side effects. In current practice, peginterferon alfa-2a is likely to supplant standard IFN. 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 patients receiving short-term antiviral prophylaxis during chemotherapy or in pregnancy, as part of an HIV regimen in patients with HBV/HIV co-infection, or in combination with adefovir in patients with hepatic decompensation. Patients requiring therapy for longer than 1 year probably are best treated with adefovir or entecavir, which have much lower incidence rates of resistance.

Several areas require further study. Combination therapy may prove to be more effective than monotherapy in suppressing viral replication and very likely will decrease or delay the incidence of drug resistance. Several large studies are underway exploring the use of 2 nucleoside/nucleotide antivirals or an antiviral plus peginterferon in compensated patients. Combination therapy with oral agents could be of particular value in decompensated cirrhosis, and a study comparing combination adefovir/lamivudine therapy with monotherapy in this patient group clearly is needed.

There are numerous candidate drugs including emtricitabine, telbivudine, and tenofovir currently under evaluation as potential therapies for chronic HBV infection, which should expand the number of treatment options further in the coming years.

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