A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2015 Update

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Chronic Hepatitis B Virus Infection in the United States: 2015 Update

Short title: Chronic Hepatitis B Treatment Algorithm

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**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CDC, Centers for Disease Control and Prevention; CHB, chronic hepatitis B; FDA, U.S. Food and Drug Administration; HAART, highly active antiretroviral therapy; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; HR, hazard ratio; IFN, interferon alfa; IL28B, interleukin 28B; IU, international units; MRI, magnetic resonance imaging; MU, million units; ORF, open reading frame; PCR, polymerase chain reaction; USPSTF, U.S. Preventive Services Task Force; ULN, upper limit of normal

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Abstract

Chronic hepatitis B (CHB) continues to be an important public health problem worldwide, including in the United States. An algorithm for managing CHB was developed by a panel of United States hepatologists in 2004 and subsequently updated in 2006 and 2008. Since 2008, additional data on long-term safety and efficacy of licensed therapies have become available and have better defined therapeutic options for CHB. The evidence indicates that potent antiviral therapy can lead to regression of extensive fibrosis or even cirrhosis, thus potentially altering the natural history of CHB. In addition, appropriate choice of antiviral agent can minimize the risk of resistance.

This updated algorithm for managing CHB is based primarily on evidence from the scientific literature. Where data were lacking, the panel relied on clinical experience and consensus expert opinion. The primary aim of antiviral therapy for CHB is durable suppression of serum hepatitis B virus (HBV) DNA to low or undetectable levels. CHB patients who have HBV DNA >2,000 IU/mL, elevated alanine aminotransferase (ALT), and any degree of fibrosis should receive antiviral therapy regardless of their hepatitis B e antigen (HBeAg) status. CHB patients with HBV DNA >2,000 IU/mL and elevated ALT but no evidence of fibrosis may also be considered for antiviral therapy. Approved antiviral therapies for CHB are interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir, although the preferred first-line treatment choices are peginterferon alfa-2a, entecavir, and tenofovir. In determining choice of therapy, considerations include efficacy, safety, rate of resistance, method of administration, duration, and cost.
**Introduction**

Chronic hepatitis B (CHB) is a substantial public health problem and the leading cause of hepatocellular carcinoma (HCC) worldwide. In the United States, the extent and burden of CHB is substantial but difficult to quantify. National Health and Nutrition Examination Survey Data suggest an estimated 704,000 individuals, or 0.27% of the population, have chronic infection with hepatitis B virus (HBV). This estimate, inclusive of years 1999 to 2008, is lower than estimates from 1988 to 1994 and suggests that the number of chronically infected individuals has diminished since the early 1990s, when a strategy to eliminate HBV transmission, including universal vaccination of infants, was implemented. Although these numbers are encouraging, they likely underestimate the number of persons with CHB living in the United States because they do not capture data from population groups with a high prevalence of HBV infection, such as immigrants from regions where HBV is endemic. It has been estimated that from 2004 through 2008 an average of 53,800 CHB cases were imported annually to the United States, and that immigrant cases account for approximately 95% of newly diagnosed cases. In addition, the incidence of HBV-related HCC has remained undiminished as older generations with long-standing CHB develop long-term sequelae, which, in addition to HCC, include cirrhosis and hepatic decompensation. Highlighting the impact of immigration on HBV demographics in North America, a recent report from the Hepatitis B Research Network found 82% of persons with chronic HBV had been borne outside North America.

To help guide clinicians managing patients with CHB, a panel of United States hepatologists developed a treatment algorithm in 2004, which was subsequently revised in 2006 and 2008 based on new developments in the field, such as availability of more sensitive diagnostic tests and novel therapies. Since the 2008 version of the algorithm was published, the
oral agent tenofovir was licensed, bringing to 7 the total number of U.S. Food and Drug Administration (FDA) approved antiviral agents for treating CHB. In addition, data on long-term safety and efficacy of licensed therapies have become available and made therapeutic options better defined. Potent antiviral therapy can lead to regression of histologic cirrhosis and minimize the risk of resistance. Additional advances include non-invasive measurement of fibrosis and more sensitive molecular diagnostic tests for evaluating virological response.

In light of these advances, a panel of 7 hepatologists (6 from the United States and 1 from Canada) met to reassess and revise the recommendations. The aim was to build on the existing algorithm, preserving its practical approach and comprehensiveness, and update the guidelines for the diagnosis, treatment, and monitoring of patients with chronic HBV infection in the United States. The panel reviewed the literature and current international guidelines. Where possible, the panel based their recommendations on the medical literature, but where data were lacking, panel members relied on their clinical experience and expert opinion.

The goal of the revised algorithm is to provide healthcare providers with the most current information on the screening, diagnosis, and treatment of CHB. The algorithm addresses a number of issues: (1) which patients are candidates for antiviral therapy; (2) what are the advantages and disadvantages of available treatment options; (3) when should therapy be initiated; (4) when can therapy be discontinued; (5) what is the role of on-treatment monitoring; and (6) which strategies should be used to decrease the risk of antiviral resistance?

Sections entitled Molecular Biology of HBV, the Natural History of Chronic HBV Infection, Risk Factors for Disease Progression, Screening and Patient Evaluation, and Managing Special Populations can be found in online supplementary material. The clinical terms and
definitions used to characterize the stages of CHB are presented in Figure 1 and Table 1. Other clinical terms relating to HBV infection are summarized in Table 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), controversy remains regarding identification of candidates for therapy and how to follow patients who are not initially recommended to receive therapy (Table 4), such as HBeAg-positive patients with high HBV DNA levels and normal ALT levels, or those in the indeterminate phases of hepatitis B.

Normal Versus Elevated Alanine Aminotransferase Levels

The level of serum ALT has been commonly used in assessing liver disease and as an important criterion for defining which patients are candidates for therapy. Historically, ALT levels were a factor in deciding whether to treat because ALT levels predicted HBeAg seroconversion.\(^\text{11–13}\) However, relying solely on increased ALT levels as a prerequisite to treatment candidacy has limitations. There is a lack of strict correlation between the extent of liver cell necrosis and the degree of increase in ALT, which means that ALT alone does not identify patients with necroinflammatory activity or fibrosis with optimal reliability.\(^\text{14}\) ALT activity may also be affected by additional factors such as body mass index, gender, abnormal lipid and carbohydrate metabolism, fatty liver, and uremia.\(^\text{14,15}\) Elevations in ALT may also occur under various circumstances, such as during spontaneous HBeAg loss, in association with some antiviral therapies, or during infection with other viruses.\(^\text{16}\)

Moreover, data from clinical studies have shown that the values of ALT that should be considered the upper limit of normal (ULN) are significantly lower than the previously established limits, and also significantly lower than values used by commercial laboratories. Data
from cohort studies involving first-time blood donors and healthy volunteers indicate that the ULNs for ALT and AST should be 30 IU/mL for men and 19 IU/mL for women.\textsuperscript{14,15} Clinical studies have shown that HBV-infected individuals with ALT values <40 to 45 IU/mL are at risk for significant liver disease,\textsuperscript{17,18} and even ALT levels between 20 and 30 IU/mL increase the risk of mortality from liver complications.\textsuperscript{19} The relationship between ALT level and disease progression has been confirmed in a long-term follow-up analysis of 3,233 CHB patients from Hong Kong.\textsuperscript{20} Thus, the panel recommends that serum ALT values of 30 IU/L for men and 19 IU/L for women be used as the ULN when making decisions regarding initiation of therapy.

HBeAg positive patients with high HBV DNA (>20,000 IU/mL) and normal ALT levels generally have less fibrosis on liver biopsy and lower rates of HBeAg seroconversion in response to antiviral therapy.\textsuperscript{11,21,22} Traditionally, this patient population has generally not been considered for treatment. However, data from several clinical studies suggest that up to one third of patients with persistently normal ALT levels have histologic evidence of significant fibrosis or inflammation upon biopsy, the risk of significant fibrosis is greater among patients 35 to 40 years of age or older.\textsuperscript{23–29} Therefore, in HBeAg-positive patients with HBV DNA levels ≥2,000 IU/mL and normal ALT levels, a liver biopsy or transient elastography should be considered, particularly in patients older than 35 to 40 years of age, who are less likely to be in the immune tolerance phase of infection. If significant disease is found (i.e., moderate fibrosis [stage 2] or greater, significant necroinflammation, or both), treatment should be initiated (Table 5).

Treatment can be considered for those >35 years of age with high HBV DNA levels even if no significant fibrosis is detected because these patients have an increased risk of HCC. When considering whether to treat HBeAg-positive patients with high HBV DNA and normal ALT
levels, it must be recognized that long-term therapy is likely to be needed as a result of the low incidence of HBeAg serconversion after 1 year in such patients.

Both HBeAg-positive and HBeAg-negative patients with HBV DNA levels ≥2,000 IU/mL and elevated ALT levels (1-2 × ULN) but no evidence of fibrosis can be considered for treatment (Tables 5 and 6). If patients with HBV DNA >2,000 IU/mL and elevated ALT without fibrosis do not undergo treatment, their HBV DNA and ALT levels should be monitored every 3-6 months. Those with HBV DNA ≥2,000 IU/mL, elevated ALT (> ULN), and any degree of fibrosis should be treated.

**Viral Threshold for Treatment**

Although moderately low HBV DNA levels (<10,000 IU/mL) have been associated with an increased risk for disease progression,\(^{30,31}\) in the United States, per the American Association for the Study of Liver Diseases (AASLD) Guidelines,\(^{32}\) the diagnostic threshold for defining the presence of CHB and indication for therapy remains at 20,000 IU/mL for patients with either HBeAg-positive or -negative disease. However, some HBeAg-positive patients and many HBeAg-negative patients have fluctuating HBV DNA levels that decrease to <20,000 IU/mL and even <2,000 IU/mL.\(^{33,34}\) In addition, low levels of HBV DNA might not indicate absence of progressive liver disease: 15% of patients with HCC have HBV DNA levels <10\(^3\) copies/mL.\(^{33}\)

For these reasons, it is often difficult to mandate a single HBV DNA level as a cut-off between HBeAg-negative hepatitis and the low viral replication state. Serial testing of serum HBV DNA using a sensitive real-time PCR-based assay is recommended to assist in making this distinction.

In the panel’s experience, patients can have advanced liver disease even if they have serum HBV DNA levels persistently <20,000 IU/mL; therefore, the consensus opinion of the panel is that all patients (HBeAg-positive or -negative) who have HBV DNA ≥2,000 IU/mL and
elevated ALT (> ULN) should be treated if they have any degree of fibrosis and can be considered for treatment even if they do not have fibrosis. If patients with HBV DNA ≥2,000 IU/mL and elevated ALT without fibrosis do not undergo treatment, their HBV DNA and ALT levels should be monitored every 3-6 months.

Goals of Therapy
The goal of therapy for CHB is to eliminate or significantly suppress HBV replication and thus prevent progression of liver disease to cirrhosis, liver failure, or HCC. Hence, the primary aim of treatment should be to reduce and maintain serum HBV DNA at the lowest possible levels (i.e., achieve durable HBV DNA suppression). This, in turn, will promote the other aims of therapy, including histologic improvement and ALT normalization. In patients who are HBeAg-positive before therapy, an additional goal of treatment is loss of HBeAg with seroconversion to anti-HBe, although the usefulness of this endpoint for determining long-term outcomes with oral antiviral therapies is unclear. Loss of HBsAg, although highly desirable, occurs in only a minority of patients who receive antiviral therapy.

Currently, there are 2 key treatment strategies for either HBeAg-positive or HBeAg-negative CHB: 1 year of therapy with peginterferon-alfa or long-term therapy with nucleoside/nucleotide analogues. Finite treatment with peginterferon-alfa has the advantage of higher rates of HBeAg seroconversion and loss of HBsAg relative to nucleoside or nucleotide analogues administered for an equivalent duration. However, peginterferon-alfa is administered via subcutaneous injection, can be difficult to tolerate, and is contraindicated in patients with decompensated cirrhosis. With the highly potent nucleoside/nucleotide analogues entecavir and tenofovir, longer-term therapy has rates of virologic remission (undetectable HBV DNA by a sensitive PCR assay) of >90% in treatment-adherent patients after ≥3 years.35–39
Nucleoside/nucleotide analogues are administered orally and have a favorable safety profile over the course of several years, although their safety over decades is unknown. Entecavir and tenofovir have high barriers to viral resistance. In addition, long-term therapy with entecavir or tenofovir can lead to regression of fibrosis and, frequently, even reversal of cirrhosis\textsuperscript{39–41} and thus change the course of CHB-related liver disease.

**Hepatitis B Therapies**

Currently, 7 drugs are available for managing chronic HBV infection in the United States: interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. The preferred first-line treatment choices among the oral nucleosides/nucleotides are entecavir and tenofovir because of their superior efficacy and favorable resistance profiles in HBeAg-positive and HBeAg-negative CHB over comparable drugs. Lamivudine is not a first-line choice because of its high rate of resistance and inferiority to entecavir and telbivudine.\textsuperscript{42–45} Adefovir is no longer a first-line drug because its efficacy and resistance profiles are inferior to those of tenofovir.\textsuperscript{46} Although telbivudine has superior efficacy to lamivudine and adefovir, it is associated with an intermediate rate of resistance compared with these agents.\textsuperscript{42,47} Therefore, telbivudine cannot be considered a first-line agent, although as a pregnancy category B drug it has a role in preventing vertical transmission of HBV in HBeAg-positive pregnant women.\textsuperscript{48,49} In routine practice, standard interferon alfa-2b has largely been replaced by peginterferon alfa-2a.

A brief summary of current data for the preferred first-line agents and treatment recommendations follows. Treatment-naïve patients who are beginning therapy for the first time should be treated with peginterferon-alfa, entecavir, or tenofovir on the basis of their superior potency and low rate or absence of antiviral drug resistance. Patients with any history of lamivudine use should not receive entecavir: they may have amino acid substitutions for
lamivudine resistance archived in the HBV cccDNA that could serve as a foundation for entecavir resistance.

**Peginterferon alfa-2a**

*HBeAg-positive patients.* The efficacy of peginterferon alfa-2a has been demonstrated in a large phase III randomized study that compared peginterferon alfa-2a 180 µg/wk, lamivudine 100 mg/day, and both drugs in combination for 48 weeks in patients with HBeAg-positive CHB. At the end of treatment, 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. At 24 weeks after treatment, the HBeAg seroconversion rate was 32% in the peginterferon alfa-2a arm, compared with 27% in the peginterferon alfa-2a plus lamivudine arm and 19% in the lamivudine monotherapy arm. Although the combination of peginterferon alfa-2a and lamivudine resulted in a greater degree of on-treatment viral load reduction, the rate of HBeAg seroconversion was not different from treatment with peginterferon alfa-2a monotherapy. Higher rates of HBeAg seroconversion were observed in patients who had HBV genotype A, low baseline HBV DNA concentrations, or increased baseline serum ALT levels. The licensed peginterferon alfa-2a treatment regimen (180 µg weekly for 48 weeks) appears to be more effective at inducing HBeAg seroconversion than regimens with shorter (24 weeks) or lower (90 µg/wk) dosing. Similar findings have been reported in clinical trials evaluating the efficacy of peginterferon alfa-2b in patients with CHB. The presence of HBV precore or basal core promoter mutants negatively affects response to treatment with peginterferon alfa-2b: in a retrospective analysis of a global randomized trial, patients with wild type virus were more
likely to achieve HBeAg loss with HBV DNA <10,000 copies/mL (34% versus 11%, P < 0.001) and HBsAg clearance (18% versus 2%, P < 0.001) than patients with detectable precore and/or basal core promoter viral mutations. For patients who do respond to peginterferon alfa-2b treatment, response appears to be durable. In a follow-up analysis of patients who lost HBeAg within 26 weeks after treatment with peginterferon alfa-2b alone or in combination with lamivudine, a high proportion (81%) maintained HBeAg loss long-term (mean 3 years) after treatment. Among these patients, 52% had HBV DNA <400 copies/mL and 30% were HBsAg negative. Rates of loss of HBsAg and maintenance of HBeAg negativity were highest in patients with HBV genotype A. Of note, peginterferon alfa-2b has not been approved for treatment of CHB in the United States.

The side effect profile of peginterferon alfa is similar to that of standard interferon; the most common side effects are influenza-like illness characterized by fever, chills, headache, malaise, and myalgia as well as cytopenias and psychological side effects. Therefore, patients undergoing peginterferon alfa therapy require careful monitoring.

Peginterferon alfa-2a is a reasonable choice as first-line therapy especially in genotype A or B patients who are young, lack significant comorbidities, and have no detectable precore or basal core promoter viral mutants, HBV DNA levels ≤10^9 copies/mL, and ALT levels at >2 × ULN. In HBeAg-positive patients, having no decline in levels of HBsAg during peginterferon-alfa therapy is a strong predictor of non-response. In an analysis of 803 HBeAg-positive patients treated with peginterferon-alfa, response rates were low in patients with genotypes A or D if there was no decline of HBsAg by week 12 (negative predictive value [NPV]: 97%-100%), and in patients with genotypes B or C if HBsAg at week 12 was >20,000 IU/mL (NPV: 92%-98%). At week 24 of treatment, nearly all patients with HBsAg >20,000 IU/mL failed to achieve a
response, irrespective of HBV genotype (NPV for response and HBsAg loss 99% and 100%). These data support response-guided therapy whereby HBeAg-positive patients with genotypes A or D who have no decline in HBsAg at week 12 are justified in stopping perinterferon-alfa therapy, as are genotype B or C patients with HBsAg >20,000 IU/mL at week 12 and all patients with HBsAg >20,000 IU/mL at 24 weeks.\textsuperscript{57,58}

**HBeAg-negative patients.** In a global study comparing 48 weeks of peginterferon alfa-2a versus lamivudine in HBeAg-negative patients, rates of sustained suppression of HBV DNA (<400 copies/mL) 24 weeks after therapy were 19% with peginterferon alfa-2a monotherapy, 20% with combination peginterferon alfa-2a and lamivudine, and 7% with lamivudine alone (P < 0.001 for both comparisons with lamivudine alone).\textsuperscript{59} HBsAg seroconversion was reported in 3% of patients treated with peginterferon alfa-2a, 2% of those treated with peginterferon alfa-2a plus lamivudine, and no patients treated with lamivudine alone. The safety profile of peginterferon alfa-2a was judged to compare favorably with previous experience with conventional interferon.

In a 3-year post-treatment follow-up study, patients who had been treated with peginterferon alfa-2a had significantly higher rates of ALT normalization, HBV DNA suppression, HBsAg loss, and HBsAg seroconversion than patients treated with lamivudine alone.\textsuperscript{60} Among patients who received peginterferon alfa-2a, 28% had HBV DNA levels ≤10,000 copies/mL, compared with 15% of patients who received lamivudine. The rate of HBsAg clearance increased during follow-up for peginterferon alfa-2a–treated patients, reaching 9% at 3 years\textsuperscript{60} and 12% at 5 years.\textsuperscript{61} In contrast, none of the lamivudine-treated patients (0/85) experienced HBsAg loss at 3 years and only 4% did at 5 years.\textsuperscript{60,61}

In a multivariate logistic regression analysis of 518 HBeAg-negative patients treated with peginterferon alfa-2a with or without lamivudine, pretreatment factors predicting response at 24
weeks after treatment included younger age, female gender, high baseline ALT, low baseline HBV DNA, and HBV genotype B or C.\textsuperscript{13}

HBeAg-negative patients who have no decline in HBsAg and <2-log decline in HBV DNA at week 12 of treatment with peginterferon alfa therapy have a very low chance of achieving a sustained virological response.\textsuperscript{62,63} Stopping therapy is warranted for such patients.

**Entecavir**

Entecavir is a cyclopentyl guanosine analog that inhibits both the priming and elongation steps of viral replication. It is a highly potent inhibitor of HBV polymerase. In vitro, entecavir demonstrates greater antiviral potency than lamivudine or adefovir and retains activity against lamivudine-resistant HBV mutants,\textsuperscript{22} although their presence reduces its clinical efficacy.

**HBeAg-positive patients.** The phase III registration study of entecavir (ETV-022) included 715 nucleoside-naïve, HBeAg-positive patients with compensated liver disease who were randomly assigned to entecavir 0.5 mg/day or lamivudine 100 mg/day for 48 weeks.\textsuperscript{43} At 48 weeks, the entecavir-treated patients had higher rates of histologic improvement (72% vs 62%), HBV DNA reduction (–6.9 vs –5.4 log_{10}), HBV DNA undetectability (<300 copies/mL) (67% vs 36%), and ALT normalization (≤1 × ULN) (68% vs 60%).\textsuperscript{43} Entecavir and lamivudine had similar rates of HBeAg loss (22% vs 20%) and seroconversion (21% vs 18%).

In a follow-up to the study described above, protocol-defined virologic responders (HBV DNA <0.7 mEq/mL, but positive for HBeAg) could continue blinded treatment for up to 96 weeks.\textsuperscript{64} At year 2, a greater proportion of entecavir-treated (n = 243) than lamivudine-treated patients (n = 164) achieved HBV DNA <300 copies/mL (74% vs 37%) and ALT normalization (79% vs 68%). Similar proportions of entecavir-treated and lamivudine-treated patients achieved HBeAg seroconversion (11% vs 12%). Significantly higher proportions of entecavir-treated than
lamivudine-treated patients achieved cumulative, confirmed HBV DNA <300 copies/mL (80% vs 39%) and ALT normalization (87% vs 79%) through 96 weeks. Cumulative, confirmed HBeAg seroconversion occurred in 31% of entecavir-treated and 25% of lamivudine-treated patients. HBsAg loss was confirmed in 5% of entecavir-treated patients and 3% of lamivudine-treated patients.

In a second follow-up study (ETV-901), a total of 146 entecavir-treated patients from the registration study (ETV-022) continued entecavir treatment at 1 mg/day for up to 5 years. At Year 5, 94% (88/94) had HBV DNA <300 copies/mL and 80% (78/98) had normal ALT levels. In addition to patients who achieved serologic responses during study ETV-022, 23% (33/141) achieved HBeAg seroconversion and 1.4% (2/145) lost HBsAg during ETV-901.

The safety profile for long-term therapy with entecavir is favorable. In study ETV-901, adverse events potentially associated with entecavir were infrequent, and only 1% of patients discontinued therapy because of an adverse event.

**HBeAg-negative patients.** A phase III clinical trial compared the safety and efficacy of entecavir and lamivudine in patients with HBeAg-negative compensated liver disease. A total of 648 patients were randomized to receive either entecavir 0.5 mg/day or lamivudine 100 mg/day for 48 weeks. Compared with lamivudine treatment, treatment with entecavir resulted in a significantly higher rate of histologic improvement (70% vs. 61%, P = 0.01), mean reduction in HBV DNA (-5.0 vs. -4.5 log\(_{10}\) copies/mL, P<0.001), and HBV DNA undetectability (<300 copies/mL) (90% vs. 72%, P<0.001). ALT normalization was also observed more frequently with entecavir than with lamivudine (78% vs. 71%), but there was no difference in improvement in fibrosis compared with lamivudine. The safety profile of entecavir during a period of 48 weeks was similar to that observed with lamivudine.
Antiviral resistance. Long-term resistance data from 6 phase 2 and 3 clinical studies of entecavir indicate it has a low rate of genotypic resistance (1.2%) in nucleoside-naïve patients (HBeAg-positive or -negative) treated for up to 5 years. Rates of genotypic resistance are higher (51% at 5 years) in entecavir-treated patients with preexisting lamivudine-resistant CHB.

Tenofovir

Tenofovir disoproxil fumarate is an acyclic nucleotide analog with a molecular structure related to adefovir. It is a potent inhibitor of HBV replication.

HBeAg-positive patients. In a multicenter, randomized, phase III trial, a total of 266 HBeAg-positive patients received tenofovir 300 mg (n=176) or adefovir 10 mg (n=90) for 48 weeks. Complete response at week 48 was defined as HBV DNA <400 copies/mL and a ≥2-point reduction in Knodell inflammatory score without worsening of fibrosis. At 48 weeks, 67% of patients receiving tenofovir and 12% receiving adefovir had a complete response. A higher proportion of patients in the tenofovir arm than in the adefovir arm achieved undetectable HBV DNA levels at week 48 (<400 copies/mL: 76% vs 13%). The respective rates for ALT normalization were 69% versus 54% and for HBeAg seroconversion were 21% versus 18%. A higher proportion of patients treated with tenofovir had HBsAg loss (3% vs 0%), and HBsAg seroconversion (1.3% vs 0%). The incidence of grade 2 to 4 adverse events was similar in the tenofovir and adefovir arms. No patients taking tenofovir experienced a 0.5-mg increase in serum creatinine or creatinine clearance of <50 mL/min (possible indicators of kidney toxicity, which has been associated with tenofovir in some studies of patients with HIV or HBV infection), compared with 1% of patients taking adefovir. As with adefovir therapy, new onset or worsening renal impairment might occur, and it is recommended that baseline calculated
creatinine clearance be obtained and creatinine clearance and serum phosphorus be monitored every 3 months in patients at risk during therapy.

After the initial 48 weeks of therapy, patients could enter a 7-year open-label study of tenofovir. Results for 5 years of treatment have been published.\textsuperscript{39} For 175 HBeAg-positive patients who remained on therapy at 5 years, 97% (n=170) had HBV DNA <400 copies/mL. HBeAg seroconversion occurred in 40% (66/164) of patients, and 18 patients experienced HBsAg seroconversion. More recently, 8-year data became available for 266 of the original 375 HBeAg-negative patients and 146 of the 266 HBeAg-positive evaluation.\textsuperscript{69} Observed viral suppression rates were 99.6% for HBeAg-negative and 98% for HBeAg-positive patients. For HBeAg-positive patients, cumulative HBeAg seroconversion at year 8 was 31% and HBsAg seroclearance was 13%. Serum creatinine increases to \( \geq 0.5 \text{ mg/dL} \) above baseline occurred in 2.2% of patients and creatinine clearance below 50 mL/minute occurred in 1%. No viral resistance was detected.

**HBeAg-negative patients.** In a phase III study, 375 HBeAg-negative patients were randomized to receive tenofovir 300 mg (n = 250) or adefovir 10 mg (n = 125) for 48 weeks.\textsuperscript{46} Complete response at week 48 was defined as HBV DNA <400 copies/mL and histologic improvement (defined as a \( \geq 2 \)-point reduction in Knodell inflammatory score without worsening of fibrosis). At week 48, a significantly higher proportion of patients treated with tenofovir achieved the primary endpoint compared with those treated with adefovir (71% vs 49%). At the end of treatment, 93% of the patients in the tenofovir group had HBV DNA <400 copies/mL, compared with 63% of patients in the adefovir group. The rates of ALT normalization were similar in both treatment groups. No patients treated with tenofovir had a confirmed 0.5 mg increase in serum creatinine or creatinine clearance < 50 mL/min. The incidence of ALT flare (>10 × ULN and 2 ×
baseline) was low and similar in the two treatment groups (1.2% vs. 0.8%). Eight-year data for entecavir in HBeAg-negative patients is described in the prior section with HBeAg-positive patients.\textsuperscript{69}

**HBeAg-positive and -negative patients.** Patients from parallel studies of tenofovir in HBeAg-positive and -negative CHB\textsuperscript{46} were pooled in an analysis of liver histology via biopsy after 5 years of treatment.\textsuperscript{69} Of 348 patients evaluated, 176 (51\%) had regression of fibrosis and 304 (87\%) had histological improvement. Of the 96 (28\%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74\%) no longer had cirrhosis ($\geq$1 unit decrease in score), whereas 3 of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5.

**Antiviral resistance.** Resistance analyses have been completed for patients receiving up to 8 years of tenofovir.\textsuperscript{69} Within 2 phase 3 studies, no evidence of genotypic resistance to tenofovir has been detected in 585 patients after 6 years and 412 patients after 8 years. Virologic breakthrough with tenofovir is rare and usually associated with nonadherence to the treatment regimen.

**Combination Therapy**

**De Novo Combination**

For nearly all HBV patients, monotherapy with entecavir or tenofovir is the appropriate first-line treatment because both have potent antiviral activity and high barriers to resistance. Combination therapy with entecavir and tenofovir has been evaluated in a superiority study of 379 patients with HBeAg-positive or –negative CHB. After 96 weeks of treatment, the group receiving entecavir monotherapy had a similar percentage of patients with HBV DNA <50 IU/mL as the group receiving combination therapy with entecavir plus tenofovir (83\% vs 76\%).\textsuperscript{70} The combination of entecavir plus tenofovir did have incremental benefit in HBeAg-positive patients.
with baseline levels of HBV DNA $\geq 10^8$ IU/mL: 79% of those receiving combination therapy had HBV DNA < 50 IU/mL versus 62% receiving entecavir alone, although the clinical relevance of this difference is unclear.\textsuperscript{70}

Monotherapy with tenofovir appears to be sufficient for maintaining virologic suppression even in patients with high viral load at the start of treatment. In an analysis comparing response to long-term tenofovir monotherapy in patients with or without high viral load ($\geq 9 \log_{10}$ copies/mL), rates of virological suppression (HBV DNA <400 copies/mL) at 5 years were similar in both groups (96% vs 99%).\textsuperscript{71}

In immune tolerant patients, there is evidence that combination therapy with tenofovir and emtricitabine provides better viral suppression than tenofovir alone. In a study of 126 HBeAg-positive patients with high levels of HBV DNA ($>1.7 \times 10^7$ IU/mL) and normal levels of ALT, 55% of patients who received tenofovir monotherapy and 76% of patients who received tenofovir plus emtricitabine had HBV DNA <69 IU/mL ($p=0.016$) after 192 weeks of therapy.\textsuperscript{72} However, HBeAg seroconversion occurred in only 3 patients (5%), all of whom had received tenofovir monotherapy.

Combining lamivudine with peginterferon alfa can lead to increased rates of on-treatment virological response relative to peginterferon alfa alone, but the combination does not appear to impact sustained virological or serological response off treatment.\textsuperscript{50,52} Adding telbivudine to peginterferon alfa has a potent antiviral effect but should be avoided because of the increased risk of severe polyneuropathy.\textsuperscript{73} A recently reported study of 740 patients compared tenofovir plus PEG-IFN alfa-2a for 48 weeks, tenofovir plus peginterferon alfa for 16 weeks followed by tenofovir for 32 additional weeks, tenofovir monotherapy for 96 weeks, and peginterferon alfa monotherapy for 48 weeks. The degree of HBsAg decline at 48 weeks was -1.2 log, -0.5 log, -...
0.3 log, and -0.8 log, respectively. At 72 weeks, rates of HBsAg loss were 9.0%, 2.8%, 0%, and 2.8%. Sixty percent of patients in the study were HBeAg-positive. The highest rate of HBeAg seroconversion (30%) occurred in the 48 week combination therapy group, and HBsAg loss was somewhat more common in, but not exclusive to, the HBeAg-positive group. Therefore, there may still be the potential to combine peginterferon with a potent nucleoside/nucleotide.

**Adding or Switching Therapies**

The concept of add-on therapy stemmed from experience using adefovir in the setting of lamivudine resistance. In patients with lamivudine resistance, switching to adefovir monotherapy results in a greater likelihood of developing resistance to adefovir than adding adefovir in combination with lamivudine.

Unlike substituting adefovir, switching to tenofovir monotherapy in the setting of lamivudine resistance confers effective virologic suppression and does not appear to increase the risk of resistance to tenofovir. A retrospective study involving 121 patients with CHB evaluated the efficacy of switching to tenofovir monotherapy in nucleoside- and nucleotide-experienced patients with CHB. Eligible patients included those with HBV DNA >10^5 copies/mL and prior treatment with lamivudine or lamivudine with consecutive adefovir therapy as a result of lamivudine resistance. Patients with genotypic resistance to adefovir (n = 14) were excluded. At week 48, 91% of patients had undetectable HBV DNA and 78% had normal ALT levels. HBeAg seroconversion occurred in 23% of patients after an average of 9 months. HBsAg loss was observed in 4% of patients after an average of 13 months. A randomized study of tenofovir versus tenofovir combined with emtricitabine convincingly demonstrated that tenofovir monotherapy is sufficient in lamivudine-resistant patients, attaining HBV DNA <400 copies/mL in 89% of patients at 96 weeks of monotherapy compared with 86% in those receiving dual
therapy, with no emergent resistance in either group.\textsuperscript{77}

In the setting of adefovir resistance, tenofovir monotherapy is less effective. A study involving a small cohort of 10 patients with lamivudine-resistant CHB who were switched to adefovir monotherapy showed limited efficacy with subsequent tenofovir monotherapy.\textsuperscript{78} These patients had all developed genotypic resistance to adefovir after receiving an average of 24 months of adefovir monotherapy. After 48 weeks of tenofovir monotherapy, 8 patients had detectable HBV DNA, and 8 had elevated ALT levels. In a retrospective analysis of antiviral response to tenofovir therapy in 127 patients with prior nucleoside/nucleotide analog experience with lamivudine, adefovir, or both, patients with genotypic adefovir resistance had a significantly slower decrease of HBV DNA levels at month 12 than did patients without adefovir resistance,\textsuperscript{79} an effect that persisted through a median treatment duration of 23 months.\textsuperscript{80}

Similar findings were reported in a study investigating virologic response to tenofovir alone or in combination with emtricitabine in patients with adefovir-resistant CHB. Combination therapy resulted in a greater reduction in HBV DNA levels than did tenofovir monotherapy in patients with virologic breakthrough or a suboptimal response to adefovir.\textsuperscript{81} Of 3 patients who received combination therapy, all had undetectable HBV DNA levels within 3-12 months, including 2 patients who had adefovir resistance at baseline. Despite findings indicating that tenofovir has antiviral efficacy in patients with genotypic adefovir resistance, the suppression of HBV DNA replication with tenofovir occurs at a slower rate, and complete suppression of HBV DNA replication occurs in only a minority of patients. Moreover, the selection of adefovir resistance mutations is not prevented.

The efficacy of switching to entecavir therapy in CHB patients with adefovir experience has been evaluated.\textsuperscript{82} Among a cohort of 80 patients with partial response to adefovir, 66\%
achieved complete virologic suppression (HBV DNA <60 IU/mL) 12 months after switching to entecavir, and 84% achieved complete virologic suppression 24 months after switching. Fifteen of the partial responders had prior exposure to lamivudine, and they had lower rates of complete virologic response than lamivudine-naïve patients (71% versus 87%) 24 months after switching to entecavir. No genotypic or phenotypic resistance to entecavir was observed in lamivudine-experienced patients.

**Treatment Recommendations**

**Hepatitis B e Antigen–Positive Patients**

The recommendations for the treatment of HBeAg-positive patients are summarized in Table 5. The panel recommends an HBV DNA level of 2,000 IU/mL or higher as a reasonable threshold for determining candidacy for treatment, in combination with elevated ALT levels.

Because patients with normal ALT levels can have significant liver disease, they should be considered for biopsy examination or transient elastography as well as ongoing ALT monitoring, particularly in individuals older than 35 to 40 years. Such patients should be treated if evidence of liver disease is found. Further studies are required to investigate the efficacy of antiviral therapy in patients with high viral load and normal ALT levels, especially in the younger individuals, who are typically in the immune tolerance phase of infection.

For patients with serum HBV DNA levels ≥2,000 IU/mL and elevated ALT levels, peginterferon alfa-2a, entecavir, or tenofovir are considered first-line options. Entecavir or tenofovir would be preferred for patients with high levels of serum HBV DNA and/or normal ALT levels, given that response to interferon-based therapy is low in this population. Entecavir should not be administered to CHB patients with lamivudine experience. Peginterferon alfa-2a is a reasonable choice particularly in genotype A or B patients who are young, lack significant
comorbidities, have no detectable precore or basal core promoter viral mutants, and have HBV DNA levels $\leq 10^9$ copies/mL and ALT $>2 \times$ ULN. Prior to initiating treatment for CHB, all patients should have a baseline assessment of liver fibrosis for evaluating histologic response to therapy.

Lamivudine is not recommended as a first-line therapy in HBeAg-positive patients because its efficacy and, especially, resistance profile, are inferior to the first line agents. Although telbivudine is potent and less prone to resistance than lamivudine, it is associated with a higher rate of resistance compared with entecavir and tenofovir. However, as a category B drug telbivudine may have a role in preventing vertical transmission of HBV in HBeAg-positive pregnant women. Adefovir is not recommended as a first-line therapy because of inferior potency at the approved dose of 10 mg daily and an intermediate resistance profile.

**Duration of therapy.** The optimal duration of therapy with peginterferon alfa remains unclear, although the standard duration of 48 weeks appears to induce higher rates of HBeAg seroconversion than 24 weeks. Evidence from a small study has indicated that the extension of peginterferon therapy to 96 weeks improves rates of sustainable HBeAg and HBsAg seroconversion. However, the benefits of extending interferon-based therapy need to be weighed against tolerability in individual patients. During peginterferon-alfa therapy, levels of HBsAg at week 12 can guide decisions about continuing therapy. HBeAg-positive patients with no decline in HBsAg or an HBsAg level $>20,000$ IU/mL at week 12 are justified in stopping peginterferon-alfa therapy.

For nucleoside/nucleotide analogues, the panel recommends lifelong treatment for all patients with decompensated cirrhosis at the start of therapy and for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy. Patients with
compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6-12 months or longer or HBsAg seroconversion. For HBeAg-positive patients with histology less than F3, the duration of therapy is less clear. HBeAg-positive patients who fail to lose HBeAg should be treated long term because the chance of HBeAg seroconversion increases with time, and there is a high risk of recurring viremia if therapy is stopped in the absence of HBeAg seroconversion. Historically, HBeAg seroconversion was considered to portend a durable response, and discontinuation of antiviral therapy was recommended after a period of consolidation therapy of 6 to 12 months from the time of HBeAg seroconversion. However, a substantial number or even the majority of patients who discontinue therapy after completing such consolidation therapy can experience recurrent viremia. In one study 38% of patients who discontinued therapy experienced ALT flares. Thus, long-term therapy can be justified even after HBeAg seroconversion and virologic suppression. For patients without HBsAg loss or seroconversion, the panel does not recommend stopping treatment. However, if patients prefer to stop treatment, they should undergo liver biopsy or transient elastography prior to stopping therapy to ensure they have only mild histologic fibrosis (F0-F1). Patients who stop therapy should be monitored for HBV DNA and ALT levels. Those who relapse can be re-treated.

**Hepatitis B e Antigen–Negative Patients**

For HBeAg-negative patients with chronic HBV infection, HBV DNA suppression and ALT normalization are the only practical measures of response to therapy. Long-term therapy is most often required to maintain these responses.

Recommendations for the treatment of HBeAg-negative patients are shown in Table 6. The recommendations are similar to those for HBeAg-positive patients. Peginterferon alfa-2a,
entecavir, and tenofovir can be considered first-line options. Prior to initiating treatment for CHB, all patients should have a baseline assessment of liver fibrosis for evaluating histologic response to therapy. Lamivudine, adefovir, and telbivudine are not preferred for the same reasons related to efficacy and resistance profiles outlined in the discussion of HBeAg-positive patients.

**Duration of therapy.** HBeAg-negative patients receiving therapy should be monitored every 3-6 months. The duration of therapy with peginterferon alfa is 12 months. During therapy with peginterferon alfa, the absence of HBsAg decline and a <2-log IU/mL decline in HBV DNA at week 12 is a good predictor of non-response and is justification to stop therapy. In a study of HBeAg-negative patients with genotype D HBV infection, extending peginterferon therapy to 96 weeks improved rates of virologic suppression and ALT normalization. The potential benefits of extending therapy with peginterferon alfa must be weighed against its tolerability.

For nucleoside/nucleotide analogues, the panel recommends lifelong treatment for all patients with decompensated cirrhosis at the start of therapy and for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy. Patients with compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6-12 months or HBsAg seroconversion. However, they must undergo lifelong screening for HCC even if they no longer have cirrhosis. For patients without HBsAg seroconversion, the panel does not recommend stopping treatment. However, if patients prefer to stop treatment, physicians can have a dialogue with patients who have only mild histologic fibrosis (F0-F1) and inflammation about the pros and cons of stopping after 5 years. This is based upon observations indicating that even though most patients have virologic relapse, many have persistently normal ALT and some may clear not only viremia but HBsAg without reinstitution of treatment over the next 5 years.
Patients who stop therapy should be monitored for HBV DNA and ALT levels. Those who relapse can be re-treated.

**Monitoring for Renal Toxicity**

For all nucleos(t)ide analogs except telbivudine, a decline in renal function has been reported. Before starting therapy with a nucleoside/nucleotide analogue, patients should have serum creatinine levels and estimated creatinine clearance obtained. Risk factors for renal events include decompensated cirrhosis, pre-treatment creatinine clearance <60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, and solid organ transplantation. For patients at risk of renal events or for those taking tenofovir or adefovir, creatinine clearance (eGFR) and serum phosphorus should be monitored every 3 months during the first year of therapy. If renal function is unchanged, monitoring can be extended to every 6 months thereafter. Dose adjustments can be made either prior to treatment for high-risk patients or during therapy based on assessments of renal functioning.

**Bone Density Measurements**

Patients with chronic liver disease have increased risk for osteopenia. During the first year of treatment with tenofovir, a minority of HIV and HBV patients experience bone density decreases of 4%-7%. Therefore, some members of the panel perform a bone mineral density scan in patients prior to starting oral antiviral therapy. Additionally, some members monitor levels of 25-hydroxy vitamin D during therapy and provide oral supplementation for deficiency.

**Monitoring Virologic Response and Managing Resistance to Oral Antiviral Therapy**

Prolonged therapy with an oral nucleoside or nucleotide can lead to the development of antiviral resistance. The rate of resistance depends on a number of factors, including pretreatment HBV
DNA level, potency of the antiviral agent, prior exposure to oral nucleoside or nucleotide antiviral therapy, duration of treatment, and the degree of genetic barrier to resistance to the individual drug. The long-term rates of resistance are highest for lamivudine (65% to 70% at 4 to 5 years), intermediate for telbivudine (25% in HBeAg-positive patients and 11% in HBeAg-negative patients at 2 years), lower for adefovir (29% at 5 years), and lowest for entecavir in the absence of prior lamivudine resistance (1.2% after 5 years) and for tenofovir in treatment-naïve patients (0% at 6 years). Among patients with lamivudine resistance, 51% develop genotypic resistance mutations to entecavir within 5 years after being switched to entecavir.

The development of resistance is associated with loss of initial response and HBV DNA rebound, which may be followed by biochemical breakthrough and eventual reversion of histologic improvement; in some cases, resistance leads to severe exacerbations, which may be particularly problematic for patients with cirrhosis. Thus, either entecavir or tenofovir, which possess the lowest genotypic resistance, should be used as the initial therapy in patients who have not received oral antiviral therapy for HBV.

**Antiviral Resistance Testing**

Standardized nomenclature and definitions of terms used to define resistance are shown in Table 7. Clinically, antiviral resistance manifests as virologic breakthrough, defined as a \(\geq 1 \log_{10}\) IU/mL increase in serum HBV DNA levels from nadir in 2 consecutive samples taken 1 month apart in patients who have responded and have been adherent to therapy with antiviral medications. When virologic breakthrough occurs in a patient who has adhered to antiviral therapy, the presence of mutations directly associated with drug resistance should be confirmed using an in vitro assay. There are 2 types of HBV resistance analyses: genotypic and phenotypic. Genotypic
resistance testing can be used to monitor treatment responses and diagnose primary and secondary treatment failures. Genotypic resistance assays use the direct sequencing of PCR products to identify the mutations in HBV polymerase that confer resistance. Information from genotypic resistance testing can aid in the selection of appropriate add-on or alternative antiviral therapy. In clinical practice, genotypic resistance testing is recommended when virologic breakthrough occurs to confirm the presence of mutations directly associated with drug resistance to a particular nucleoside or nucleotide analog. In contrast, in vitro phenotypic resistance analyses can be used to confirm, by cell culture–based or enzymatic assays, that a mutation confers resistance and the level of susceptibility or resistance conferred by a specific mutation. Phenotypic assays are typically reserved for research studies. Baseline genotypic testing is not recommended for routine use in treatment-naïve patients at this time because of the low incidence of drug-resistance mutations at baseline as reported in clinical studies and the absence of data indicating that, when present, they affect the outcome of therapy.

Methods for resistance testing are shown in Table 8. Direct sequencing–based assays such as population-based sequencing and ultradeep pyrosequencing are the gold standard for genotypic HBV resistance testing because they detect the full variety of mutations that confer resistance, including those not previously identified. Other methods available that identify resistance mutations include real-time PCR analysis with specific probes, hybridization methods (line probe assay), restriction fragment length polymorphism analysis, allele-specific PCR analysis, and DNA chip technology. The most commonly used methods in clinical practice include standard population-based direct sequencing and line probe assays. Standard population-based sequencing allows the identification of mutations that comprise >20% of the total viral population. More sensitive assays involving hybridization and real-time PCR methods can detect
emerging viral resistance when the HBV DNA encoding the resistance mutations comprises 5% of the total HBV population. Although more sensitive tests enable the early identification of patients who harbor HBV encoding resistance mutations at baseline, before the definition of clinical resistance is met, their use is currently restricted to clinical research and high-risk populations because of the expense involved and the complicated nature of performing the tests.

**On-Treatment Monitoring**

Serum HBV DNA levels should be monitored at 12 weeks to identify primary treatment failure (HBV DNA decline of \(<1 \log_{10} \text{IU/mL}\)) and at 24 weeks to confirm continued virologic suppression by antiviral therapy. Monitoring of HBV DNA levels should occur every 3 to 6 months during the first year to confirm adequate viral suppression and detect viral breakthrough.

**Primary treatment failure.** Primary nonresponse to entecavir, tenofovir, telbivudine, or lamivudine is rare; therefore, any patients who are not responsive to a nucleoside or nucleotide analogue after 12-24 weeks should be evaluated for compliance. In patients who have been compliant, resistance analyses should be performed after 24 weeks to determine an optimal rescue strategy in case drug-resistant variants are present. Nucleoside/nucleotide-naïve patients who have a primary or complete non-response to adefovir should be immediately switched to tenofovir or entecavir.  

**Partial or inadequate virological response.** Patients with a partial or inadequate virological response (HBV DNA \(\geq 2,000 \text{ IU/mL}\) at 24 weeks or HBV DNA positive at 48 weeks of therapy) to a nucleoside or nucleotide analogue should also be evaluated for compliance. If patients receiving lamivudine or telbivudine have a partial or inadequate virological response at 24 weeks, they should be switched to entecavir or tenofovir. Published reports indicate patients who have an inadequate virological response after 24 weeks of adefovir therapy can be switched to either
entecavir or tenofovir. \(^{82,97}\)

The optimal management of patients who have detectable HBV DNA after 48 weeks of entecavir or tenofovir therapy is unclear. Patients with declining serum HBV DNA levels may continue with entecavir or tenofovir given the rise in rates of virological response over time and the very low risk of resistance to either drug. \(^{71,98}\) Patients with partial response to entecavir but HBV DNA < 1,000 IU/mL after 1 year of therapy often achieve viral suppression by continuing entecavir through at least 2 years total. \(^{99}\) Patients with partial response to entecavir and higher residual HBV DNA level after 1 year of therapy can either be switched to tenofovir monotherapy or tenofovir plus entecavir combination therapy. \(^{100}\) For patients with partial response to entecavir 0.5 mg daily, increasing the dose to 1.0 mg daily does not appear to benefit the likelihood of achieving complete viral suppression. \(^{101}\)

**Virological resistance.** Recommendations for managing resistance vary \(^{32,96,102}\) but generally involve either adding a drug in a separate class or switching to a more potent drug within the same class. In clinical practice, most members of the panel generally avoid monotherapy in patients with resistance and either use add-on therapy with tenofovir or entecavir or switch to tenofovir/emtricitabine (a combination drug containing tenofovir 300 mg and emtricitabine 200 mg that has not been approved for anti-HBV therapy) (Table 9). However, in the case of lamivudine resistance, as discussed previously there are data providing compelling reassurance that tenofovir monotherapy is sufficient. \(^{77}\) Limited data suggest that tenofovir may also be sufficient for patients with adefovir resistance. \(^{97}\) However, with newer anti-HBV agents such as entecavir and tenofovir, viral resistance in previously treatment-naïve patients is very rare and the vast majority of cases of virologic breakthrough in clinical practice are due to nonadherence. \(^{103,104}\)
Conclusions

The primary goal of CHB treatment is to eliminate or significantly suppress replication of HBV, thereby preventing progression of liver disease to cirrhosis, liver failure, or HCC. Suppression of HBV replication not only prevents progression of disease, it promotes ALT normalization and histologic improvement. For HBeAg-positive patients, an additional goal of treatment is loss of HBeAg with seroconversion to anti-HBe, although the importance of this endpoint for patients receiving oral antiviral therapy is unclear. Loss of HBsAg is a highly desirable outcome but happens only in a minority of patients who receive antiviral therapy.

For patients with HBeAg-positive or -negative CHB and elevated ALT levels, an HBV DNA level of 2,000 IU/mL or higher is a reasonable threshold for determining candidates for treatment. CHB patients with HBV DNA ≥ 2,000 IU/mL and normal ALT should undergo biopsy or transient elastography to assess liver histology. If histologic disease is detected, patients should initiate treatment. In the absence of histologic data, patients should be observed for rises in HBV DNA and ALT levels. All CHB patients with either compensated or decompensated cirrhosis who have detectable HBV DNA should initiate treatment, regardless of ALT level.

The preferred first-line treatments for CHB are entecavir, tenofovir, or peginterferon alfa-2a. Issues to consider in choosing a therapy are efficacy, safety, resistance, and method of administration. Currently the 2 main treatment strategies for both HBeAg-positive and HBeAg-negative CHB are either 1 year of treatment with peginterferon-alfa or long-term therapy with a nucleoside or nucleotide analogue. Finite treatment with peginterferon-alfa has the advantage of higher rates of HBeAg seroconversion and loss of HBsAg relative to nucleoside or nucleotide analogues. However, peginterferon-alfa is administered via subcutaneous injection, can be
difficult to tolerate, and is contraindicated in patients with decompensated cirrhosis. The
nucleoside analogue entecavir and nucleotide analogue tenofovir are both highly potent antiviral
agents, with rates of virologic remission of >90% in treatment-adherent patients after ≥3 years.
Entecavir and tenofovir are administered orally and have a favorable safety profile over the
course of several years, although their safety over decades is unknown. Both entecavir and
tenofovir have high barriers to viral resistance, and long-term therapy with either can lead to
regression of fibrosis and even reversal of cirrhosis, changing the course of CHB-related liver
disease.

Prior to initiating treatment for CHB, all patients should have a baseline assessment of
liver fibrosis. A baseline assessment is necessary for evaluating histologic response to therapy
and informs decisions regarding duration of therapy. The panel recommends lifelong therapy for
all HBeAg-positive or -negative patients with decompensated cirrhosis at the start of therapy and
for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the
start of therapy. Patients with compensated liver disease at the start of therapy may be
discontinued from therapy if they experience HBsAg loss for 6-12 months or longer or HBsAg
seroconversion. However, they must undergo lifelong screening for HCC even if they no longer
have cirrhosis. For HBeAg-positive patients with histology <F3, the optimal duration of therapy
is less clear. Historically, HBeAg seroconversion was considered a durable response, and
discontinuation of antiviral therapy was recommended after a period of consolidation therapy of
6 to 12 months from the time of HBeAg seroconversion. However, patients who discontinue
therapy after completing consolidation therapy can experience recurrent viremia and ALT flares.
Thus, long-term therapy is justified even after HBeAg seroconversion and virologic suppression.
HBeAg-positive patients who fail to lose HBeAg should be treated long term because the chance
of HBeAg seroconversion increases with time, and there is a high risk of recurring viremia if therapy is stopped in the absence of HBeAg seroconversion.

For managing resistance to oral antiviral therapies, the members of the panel generally either use add-on therapy with tenofovir or entecavir or switch to combination tenofovir and emtricitabine. The exception is rescuing lamivudine resistance with tenofovir monotherapy.

Although there have been many advances in the treatment of CHB in recent years, several unmet needs exist. For example, more definitive data on the optimal duration of therapy for nucleoside and nucleotide analogues is needed. Long-term (>5 years) safety, efficacy, and resistance data for entecavir and tenofovir are also needed. Optimal management of immunotolerant patients remains unclear. Although HBsAg quantification has become commonly used in clinical trial research, its role in evaluating response to therapy in the clinical setting is largely undefined. In addition, the majority of HBV-infected individuals in the U.S. remain undiagnosed, and the linkage to care in patients with known HBV infection remains suboptimal. On a positive note, research is rapidly expanding in the area of curing HBV, with a variety of promising agents in clinical trials now. The next time this algorithm is revised, there may be many ways to treat and even cure HBV.

Acknowledgments

The authors dedicate this paper to the memory of Emmett B. Keeffe, colleague, mentor, and friend, who conceived the HBV Algorithm and led its development in 2004, 2006, and 2008.

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Table 1. Phases of Chronic Hepatitis B Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>Liver histology</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune tolerance phase</strong></td>
<td>Normal or minimally elevated</td>
<td>Minimal activity; absent or scant fibrosis</td>
<td>High levels: serum HBV DNA &gt;20,000 IU/mL</td>
<td>Positive; anti-HBe negative</td>
<td>Positive &gt;6 months</td>
</tr>
<tr>
<td><strong>Immune clearance phase</strong></td>
<td>Elevated, usually persistently or with intermittent elevations</td>
<td>Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)*</td>
<td>High levels: serum HBV DNA &gt;20,000 IU/mL</td>
<td>Positive; anti-HBe negative</td>
<td>Positive &gt;6 months</td>
</tr>
<tr>
<td><strong>Low viral replication</strong></td>
<td>Persistently normal</td>
<td>Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score &lt;4)*</td>
<td>Low or undetectable levels: serum HBV DNA negative or &lt;2,000 IU/mL</td>
<td>Negative; anti-HBe positive</td>
<td>Positive &gt;6 months</td>
</tr>
<tr>
<td><strong>Reactivation phase</strong></td>
<td>Elevated, often fluctuating levels</td>
<td>Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥4)*</td>
<td>Moderate, often fluctuating levels: serum HBV DNA &gt;2,000 IU/mL</td>
<td>Negative; anti-HBe positive</td>
<td>Positive &gt;6 months</td>
</tr>
</tbody>
</table>

*For HBeAg-positive CHB (immune clearance phase) and HBeAg-negative CHB (reactivation phase).
<table>
<thead>
<tr>
<th>Resolution</th>
<th>Normal</th>
<th>Inactive; scant fibrosis</th>
<th>No detectable serum HBV DNA (low levels may be detectable in the liver)</th>
<th>Negative; anti-HBe positive</th>
<th>Negative</th>
</tr>
</thead>
</table>

*Liver biopsy optional.*

*bMost of these patients have precore or core promoter variants.*

Data from Yim and Lok\textsuperscript{105} and Hoofnagle et al.\textsuperscript{106}

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.
### Table 2. Definitions of Clinical Terms Used in the Course of HBV Infection

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute exacerbation or flare of hepatitis B</strong></td>
<td>Intermittent increase of aminotransferase activity to &gt;10 × ULN and &gt; 2 × baseline value</td>
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<td><strong>Reactivation of hepatitis B</strong></td>
<td>Reappearance of active necroinflammatory disease of the liver in a person known to be in the low viral replication state or to have resolved hepatitis B</td>
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<tr>
<td><strong>HBeAg clearance</strong></td>
<td>Loss of HBeAg in a person who was previously HBeAg-positive</td>
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<tr>
<td><strong>HBeAg seroconversion</strong></td>
<td>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 &lt;20,000 IU/mL</td>
</tr>
<tr>
<td><strong>HBeAg reversion</strong></td>
<td>Reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe-positive</td>
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<td><strong>Occult hepatitis B</strong></td>
<td>Having detectable HBV DNA while being negative for HBsAg</td>
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<tr>
<td><strong>Resolution</strong></td>
<td>Loss of HBsAg and no further virologic, biochemical, or histologic evidence of active virus infection or disease</td>
</tr>
<tr>
<td><strong>Seroreversion</strong></td>
<td>Reappearance of HBsAg in a person with previously resolved HBV and loss of HBsAg</td>
</tr>
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</table>

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus
Table 3. Pretreatment Evaluation for Chronic Hepatitis B

**History and Physical Examination**

- Risk factors for viral hepatitis
- Duration of infection
- Route of transmission
- Risk factors for HIV coinfection
- Alcohol history
- Presence of comorbid diseases
- Family history of liver cancer
- HBV testing of family members
- General counseling regarding transmission
- Vaccination of at-risk household and sexual contacts
- Family planning

**Pretreatment Tests**

- Serial testing of ALT and HBV DNA level for 6-months
- Liver function tests
  - Complete blood count with platelets
  - Hepatic function panel
  - Prothrombin time
- HBeAg and anti-HBe
- HBV genotype
- Tests to rule out other causes of liver disease
  - Anti-HCV
  - Anti-HDV
- Hepatitis A immunity: anti-HAV IgG or total
- HIV: anti-HIV
- Screen for HCC in high-risk patients: MRI (preferred), CT, AFP, or ultrasound
- Transient elastography to grade histologic fibrosis or liver biopsy examination to grade and stage liver disease
- Urinalysis; if abnormal, do 24-hour urine for creatinine and protein

Liver biopsy is optional for patients meeting treatment criteria, but may be especially helpful in those with normal ALT levels and age greater than 35 to 40 years of age.

AFP, alpha-fetoprotein; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.
Table 4. Suggested Follow-up for Patients Not Initiating Treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
</table>
| HBeAg-positive or -negative CHB with HBV DNA ≥ 2,000 IU/mL and normal ALT | - Assess ALT levels every 3–6 months  
- Consider liver biopsy or transient elastography to assess fibrosis  
- Consider initiating treatment when ALT levels increase or fibrosis is present |
| HBV DNA <2,000 IU/mL and normal ALT            | - Assess ALT levels every 6–12 months  
- If ALT levels become increased, check serum HBV DNA and exclude other causes of disease |
### Table 5. Recommendations for Treatment: HBeAg-Positive Chronic Hepatitis B

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>ALT $^a$</th>
<th>Treatment Strategy</th>
</tr>
</thead>
</table>
| < 2,000 IU/mL | Normal | • No treatment  
• Monitor every 6–12 months  
• Consider therapy in patients with known significant histologic disease, even if low-level viral replication |
| $\geq$ 2,000 IU/mL | Normal | • Low rate of HBeAg seroconversion for all current treatments  
• Younger patients often immune tolerant  
• Consider liver biopsy or transient elastography, particularly if older than 35–40 years; treat if disease. In the absence of histologic data, observe for increase in ALT levels  
• If treated, entecavir, tenofovir, or peginterferon alfa-2a are preferred |
| $\geq$ 2,000 IU/mL | Elevated | • Entecavir, tenofovir, or peginterferon alfa-2a are preferred  
• Long-term treatment may be needed for oral agents |

$^a$The upper limits of normal for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women.  
$^b$Upon initial diagnosis, monitor every 3 months for 1 year to ensure stability.
Table 6. Recommendations for Treatment: HBeAg-Negative Chronic Hepatitis B

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>ALT&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment Strategy</th>
</tr>
</thead>
</table>
| <2,000 IU/mL | Normal | • No treatment; majority are in low viral replication state  
                  • Monitor every 6–12 months<sup>b</sup>  
                  • Consider therapy in patients with known significant histologic disease, even if low-level viral replication |
| ≥2,000 IU/mL | Normal | • Consider biopsy or transient elastography; treat if disease present. In the absence of histologic data, observe for rise in serum ALT levels.  
                  • If treated, entecavir, tenofovir, or peginterferon alfa-2a are preferred |
| ≥2,000 IU/mL | Elevated | • Entecavir, tenofovir, or peginterferon alfa-2 are preferred  
                  • Long-term treatment required for oral agents |

<sup>a</sup>The upper limits of normal for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women.<br><sup>b</sup>Upon initial diagnosis, monitor every 3 months for 1 year to ensure stability.
Table 7. Definitions of Terms Relating to Antiviral Resistance to Nucleoside and Nucleotide Analog Treatment for Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic resistance</td>
<td>Detection of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV genome that have been shown to confer resistance to an antiviral in phenotypic assays during antiviral therapy. These mutations are usually detected in patients with virologic breakthrough but can also be present in patients with persistent viremia and no virologic breakthrough.</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in serum HBV DNA level by ( &gt;1 \log_{10} \text{IU/mL} ) above nadir after achieving a virologic response during continued therapy</td>
</tr>
<tr>
<td>Viral rebound</td>
<td>Increase in serum HBV DNA to ( &gt;20,000 \text{IU/mL} ) or above pretreatment level after achieving virologic response during continued therapy</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT level above the ULN after achieving normalization during continued therapy</td>
</tr>
<tr>
<td>Cross resistance</td>
<td>Decreased susceptibility to more than one antiviral drug conferred by the same amino acid substitution or combination of amino acid substitutions</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal
### Table 8. Methods to Detect Antiviral Resistance

<table>
<thead>
<tr>
<th>Method</th>
<th>Commercially Available</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard population-based</td>
<td>• Detects variants present at &gt;20% of viral population</td>
<td></td>
</tr>
<tr>
<td>sequencing</td>
<td>• Needed to detect substitutions not previously described</td>
<td></td>
</tr>
<tr>
<td>INNO-LiPA</td>
<td>• Detects variants present at 5% of viral population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Only detects known mutations</td>
<td></td>
</tr>
<tr>
<td>Restriction fragment length</td>
<td>• Detects variants present at 1% of viral population</td>
<td></td>
</tr>
<tr>
<td>polymorphism analysis</td>
<td>• Like INNO-LiPA, only detects known mutations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Technically difficult and expensive</td>
<td></td>
</tr>
<tr>
<td>Allele-specific PCR</td>
<td>• Detects variants present at 1% of viral population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Like INNO-LiPA, only detects known mutations</td>
<td></td>
</tr>
<tr>
<td>DNA chip</td>
<td>• Detects variants present at 10% of viral population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Capable of detecting multiple mutations and polymorphisms simultaneously</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Like INNO-LiPA, only detects known mutations</td>
<td></td>
</tr>
<tr>
<td>Ultradeep pyrosequencing</td>
<td>• Detects variants present at 0.1% of viral population</td>
<td></td>
</tr>
</tbody>
</table>
Table 9. Antiviral Resistance and Salvage Therapy

<table>
<thead>
<tr>
<th>Antiviral Resistance</th>
<th>Salvage Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine-R</td>
<td>Switch to tenofovir or Truvada&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adefovir-R</td>
<td>Switch to Truvada or combination of entecavir plus tenofovir</td>
</tr>
<tr>
<td>Entecavir-R</td>
<td>Add tenofovir or switch to Truvada</td>
</tr>
<tr>
<td>Telbivudine-R</td>
<td>Add tenofovir or switch to Truvada</td>
</tr>
</tbody>
</table>

<sup>a</sup>Truvada is a combination drug containing tenofovir 300 mg and emtricitabine 200 mg and has not been approved for anti-HBV therapy.
Figure 1. The Natural Course of Chronic Hepatitis B Infection.
The immune tolerance phase is characterized by the presence of HBeAg, high HBV DNA levels, and persistently normal ALT levels, but no evidence of active liver disease. The immune clearance (or immune active) phase is characterized by the presence of HBeAg and high or fluctuating HBV DNA and ALT levels. An outcome of the immune clearance phase is HBeAg seroconversion. Most patients then enter the low viral replication phase, which is characterized by the absence of HBeAg and the presence of anti-HBe, low or undetectable HBV DNA levels (<2000 IU/mL), normal ALT levels, and no/minimal inflammation on liver biopsy. The reactivation phase is characterized by the absence of HBeAg, intermittent or persistently increased ALT and HBV DNA levels, and inflammation on liver biopsy. Modified and reprinted with permission from Yapali and Lok, 2014.107
A Treatment Algorithm for the Management of
Chronic Hepatitis B Virus Infection in the United States: 2015 Update

Molecular Biology of Hepatitis B Virus

HBV is a small, enveloped, 3.2-kilobase DNA virus composed of a 27-nm nucleocapsid core (hepatitis B c antigen) surrounded by an outer lipoprotein envelope containing the surface antigen (HBsAg). HBV genomic DNA has a very compact organization with 4 partially overlapping open reading frames (ORFs): ORF C encodes the nucleocapsid protein and the secreted protein hepatitis B e antigen (HBeAg), which is encoded by both the precore and core regions of ORF C and has shared sequences with core protein; ORF P encodes the polymerase and the terminal protein; ORF S/pre-S encodes 3 envelope glycoproteins; and ORF X encodes the regulatory X-protein.\textsuperscript{1,2} After binding to the hepatocyte surface and entering the cytoplasm, the virus disassembles and the nucleocapsid delivers the viral genome to the nucleus. In the nucleus, second-strand DNA synthesis is completed, the gaps in both strands are repaired, and the relaxed circular HBV genome is super-coiled and chromatinized to form a covalently closed circular DNA genome (cccDNA). Transcription of the cccDNA by host RNA polymerases yields 4 messenger RNAs, which are exported to the cytoplasm for translation.

The longest transcripts, which span the entire genome, are referred to as pregenomic viral RNA. Viral core protein polymerization around pregenomic RNA and the viral polymerase forms immature nucleocapsids. Inside the nucleocapsid, viral reverse transcription occurs and converts the pregenomic mRNA into a partially double-stranded DNA genome. Because the reverse transcriptase lacks proofreading function, the viral genome mutates frequently, creating genetically distinct viral quasispecies within individuals.\textsuperscript{3} The mature nucleocapsids can either
be reimported into the nucleus to form additional cccDNA or acquire an HBsAg-containing envelope and then be secreted from the cell. The infectious virions, 42 nanometers in diameter, are known as Dane particles. Also secreted from the cells are HBeAg proteins and noninfectious particles containing HBsAg particles that take the form of either small spheres or tubular filaments. HBV DNA can integrate into host DNA at a variety of insertion sites. This is distinct from the minichromosomal cccDNA, which coexists in nonintegrated form with host chromosomes in the nucleus.

On the basis of genome sequencing, to date 10 genotypes of HBV (A–J) have been identified as having at least 8% divergence. Distribution of the genotypes varies globally: genotype A is highly prevalent in North America, Northwestern areas of Europe, sub-Saharan Africa, and West Africa; genotypes B and C are common in Southeast Asia; genotype D is prevalent in Africa, Europe, the Mediterranean region, and India; and genotype E is restricted to West Africa. HBV genotype appears to affect the course of disease as well as response to interferon-alfa therapy.

References


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Natural History of Chronic Hepatitis B Virus Infection

The natural course of HBV infection reflects complex interactions involving the virus, the hepatocyte, and the host immune response, which, together with the influence of various external factors, determines disease severity and progression. The natural history of HBV infection is traditionally divided into four phases: immune tolerance, immune clearance (also referred to as immune active), low viral replication (historically referred to as inactive carrier of HBsAg), and reactivation (Figure 1).

Each phase is characterized by distinct patterns of serologic markers, HBV DNA levels, and changes in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflecting the immunologic and hepatic necroinflammatory status of the patient. More than 10% of patients cannot be categorized into any of the 4 phases and are considered to be in an indeterminate phase. The clinical terms and definitions used to characterize the stages of CHB are summarized in Table 1. Other clinical terms relating to HBV infection are summarized in Table 2.

The clinical course of CHB is variable, and not all patients will experience each phase of infection. Acquisition of HBV at birth or in early childhood is typically associated with a longer period of immune tolerance, which may last for 1 to 4 decades, prior to immune clearance with HBeAg seroconversion, whereas initial infection later in life is associated with a very short immune tolerant phase or none at all. The transition from acute to chronic HBV infection is marked by the continued presence of HBsAg, high levels of serum HBV DNA, and the presence of HBeAg in serum. HBsAg-positive individuals in the immune tolerance phase exhibit minimal
histologic changes, and those remaining in the immune tolerant phase experience no or minimal
disease progression; however, persistently high levels of HBV DNA (≥10,000 copies/mL) over
many years can increase the risk of HCC. Transition to the immune clearance phase is
characterized by fluctuating HBV DNA levels with frequent hepatitis flares and hepatic
necroinflammatory damage that may lead to cirrhosis. The culmination of the immune clearance
phase is HBeAg seroconversion, with loss of HBeAg and acquisition of antibody to HBeAg
(anti-HBe). Loss of HBeAg and seroconversion to anti-HBe usually are preceded by a marked
decrease in serum HBV DNA levels to <20,000 IU/mL and are typically followed by
normalization of ALT levels. HBV genotype B is associated with earlier HBeAg serconversion
than genotype C. HBeAg seroconversion usually represents a transition from the immune
clearance phase to the low viral replication state.

During the low viral replicative state, there is little evidence of hepatitis by clinical and
laboratory evaluation, and serum HBV DNA levels are reduced or undetectable. A minority of
patients (annual incidence, 0.1% to 0.8% for Asians and 0.4% to 2% for Caucasians) will
spontaneously lose HBsAg, which is referred to as “resolution” of HBV infection, although
cccDNA is believed to persist in hepatocytes after serum HBsAg clearance. Rates of spontaneous
HBsAg seroclearance appear to be higher in persons with HBV genotype A or B versus C or
D. A small percentage (3-7%) of patients in the low viral replication state experience reversion
back to HBeAg positivity or reactivation of disease, either spontaneously or through immune
suppression after years of inactivity. Even after HBsAg seroconversion patients who were
seropositive for many years may still develop HCC. This may reflect a number of factors,
including genomically integrated HBV DNA and prior necroinflammatory activity with residual
fibrosis or cirrhosis.
A third or more of patients in the low viral replication state experience a return of high levels of HBV DNA and persistent or intermittent increases of ALT despite absence of HBeAg.\textsuperscript{11,12} This form of chronic HBV infection, referred to as the reactivation phase or HBeAg-negative CHB, is associated with the selection of viral variants with diminished or absent production of HBeAg.\textsuperscript{13} The most common mutation is a guanine to adenine substitution at nucleotide 1896 in the precore region. This classical precore variant results in a TAG stop codon at codon 28 of the precore protein, thereby preventing HBeAg production. A second dual mutation, the double basic core promoter mutant involving 2 nucleotide substitutions (A1762T and G1764A), can result in loss of HBeAg synthesis or reduced HBeAg expression.\textsuperscript{13} Alone or in combination, these mutations account for the majority of HBeAg-negative CHB. The HBeAg-negative form of CHB has been reported to occur more frequently in patients with HBV genotypes B, C, or D as compared with genotype A.\textsuperscript{14} There is emerging data that these naturally occurring mutations co-exist with the wild type virus even in earlier phases of HBV infection, suggesting an evolution of genomic mutations over time.\textsuperscript{15}

Sustained spontaneous remission is uncommon in patients with HBeAg-negative CHB (6\%–15\%), and the long-term prognosis is reportedly poorer compared with HBeAg-positive patients, although this may in part reflect longer duration of HBV infection and older age of this population.\textsuperscript{12} In a long-term follow-up study involving 1965 asymptomatic “inactive HBsAg carriers” who were followed for 20,298 person-years, HBeAg-negative chronic hepatitis occurred at an annual rate of 1.5\%, with a cumulative probability of 10\% at 5 years, 17\% at 10 years, and approximately 20\% after 15 years.\textsuperscript{16} In this study, spontaneous HBsAg seroclearance occurred at an annual incidence up to 1.15\%, with a cumulative probability of 8\% at 10 years,
25% at 20 years, and 45% at 25 years of follow-up. Patients who lose HBsAg have a much better prognosis than patients with HBsAg persistence.\cite{17}

References


5. Chu C-J, Hussain M, Lok ASF. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. *Gastroenterology*. 2002;122(7):1756-1762.


### Table 1. Phases of Chronic Hepatitis B Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>Liver histology</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>HBsAg</th>
</tr>
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<tr>
<td>Immune tolerance phase</td>
<td>Normal or minimally elevated</td>
<td>Minimal activity; absent or scant fibrosis</td>
<td>High levels: serum HBV DNA &gt;20,000 IU/mL</td>
<td>Positive; anti-HBe negative</td>
<td>Positive &gt; 6 months</td>
</tr>
<tr>
<td>Immune clearance phase</td>
<td>Elevated, usually persistently or with intermittent elevations</td>
<td>Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High levels: serum HBV DNA &gt;20,000 IU/mL</td>
<td>Positive; anti-HBe negative</td>
<td>Positive &gt; 6 months</td>
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<tr>
<td>Low viral replication</td>
<td>Persistently normal</td>
<td>Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score &lt;4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low or undetectable levels: serum HBV DNA negative or &lt;2,000 IU/mL</td>
<td>Negative; anti-HBe positive</td>
<td>Positive &gt; 6 months</td>
</tr>
<tr>
<td>Reactivation phase (HBeAg-negative CHB&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>Elevated, often fluctuating levels</td>
<td>Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderate, often fluctuating levels: serum HBV DNA &gt;2,000 IU/mL</td>
<td>Negative; anti-HBe positive</td>
<td>Positive &gt; 6 months</td>
</tr>
<tr>
<td>Resolution</td>
<td>Normal</td>
<td>Inactive; scant fibrosis</td>
<td>No detectable serum HBV DNA (low levels may be detectable in the liver)</td>
<td>Negative; anti-HBe positive</td>
<td>Negative</td>
</tr>
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<td>--------------------------------------------------------------------------------</td>
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</tbody>
</table>

*a* Liver biopsy optional.

*b* Most of these patients have precore or core promoter variants.

Data from Yim and Lok\(^1\) and Hoofnagle et al.\(^{18}\)

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.
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HBeAg, hepatitis B e antigen; HBV, hepatitis B virus
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Risk Factors for Disease Progression

Several viral and host factors influence the risk of CHB-associated complications, namely cirrhosis or HCC.\(^1\)

HBV genotype C infection has a greater association with severe liver disease, cirrhosis, and HCC than genotype B. Genotype D has been associated with a greater incidence of severe liver disease or HCC than genotype A.\(^2\) Specific mutations within the basal core promoter and precore sequences and deletions within the preS gene have been implicated in disease progression. Basal core promoter mutations including A1762T and G1764A have been associated with an increased incidence of HCC.\(^3-5\) There is conflicting evidence about whether mutations in the precore region (G1896A) increase the risk of HCC.\(^4,6\) Patients with the preS1 deletion have more severe liver disease (cirrhosis and HCC) than those without the deletion.\(^6,7\) Because specific mutations within the core promoter, precore, and preS are more closely linked to certain genotypes than others, this may have a confounding effect on the apparent association of specific genotype with disease progression.

Serum HBV DNA level is an important and independent risk factor for development of cirrhosis or HCC in CHB.\(^8\) The relationship between HBV DNA level and risk of disease progression provides a rationale for antiviral use. The most extensive data regarding HBV DNA levels and disease progression has come from the REVEAL (Risk Evaluation Viral Load Elevation and Associated Liver Disease) study, a large, prospective cohort study that assessed the natural history of chronic hepatitis B in 3,653 untreated HBsAg-positive Asian adults (>30
years old). In the REVEAL cohort, the cumulative incidence of cirrhosis increased with HBV DNA levels and ranged from 4.5% for patients with HBV DNA < 300 copies/mL to 36.2% for patients with HBV DNA ≥ 10^6 copies/mL (P < 0.001). (For HBV DNA, 5 copies/mL is approximately equal to 1 IU/mL.) Risk of cirrhosis was independent of HBeAg status and serum ALT level. The cumulative incidence of HCC increased progressively in a direct relationship with HBV DNA levels at study entry. The multivariable-adjusted relative risk (RR) of HCC increased from 1.1 at HBV DNA levels of 300 to < 10^4 copies/mL to 6.1 at HBV DNA levels of > 10^6 copies/mL. However, patients with levels of ≥ 10^4 to 10^5 copies/mL also were at a significant risk of HCC (RR, 2.3), and patients with increasing levels of HBV DNA over time or with persistently increased levels during follow-up were at highest risk for HCC. In contrast, a lowering of HBV DNA levels from the highest levels was linked with a reduction in risk of HCC, but only when the HBV DNA level decreased to < 10^4 copies/mL. Reanalysis of the REVEAL study data with more sensitive real-time polymerase chain reaction (PCR) methods for quantifying serum HBV levels showed an increasing risk of HCC up to > 10^6 copies/mL. Moreover, individuals with low levels of HBV DNA (< 10^4 copies/mL), who are often classified as having “inactive” disease, were found to be at increased risk of HCC development compared with uninfected (HBsAg negative) individuals.

In the REVEAL dataset, other factors predictive of HCC included the presence of HBeAg (hazard ratio [HR] = 4.2), male gender (HR = 3.0), advanced age (HR = 3.6-8.3), alcohol consumption (HR = 2.6), and cigarette smoking (HR = 1.7). Additional factors that have been reported to adversely influence the course of HBV-related liver disease include elevated ALT and coinfection with hepatitis C virus (HCV), hepatitis delta virus (HDV), or human immunodeficiency virus (HIV).
References


A Treatment Algorithm for the Management of

Chronic Hepatitis B Virus Infection in the United States: 2015 Update

Screening, Linkage to Care, and Initial Patient Evaluation

Candidates for Hepatitis B Virus Screening

Since 2008, recommendations for screening for HBV infection have been revised by both the Centers for Disease Control and Prevention (CDC) and the United States Preventive Services Task Force (USPSTF) to include foreign-born individuals from areas with HBV prevalence of 2% or higher.\textsuperscript{1,2} Individuals in high-risk groups for hepatitis B (see Table 1) should be screened for serum HBsAg. A confirmed HBsAg-positive result indicates active HBV infection, either acute or chronic. Chronic infection is confirmed by the absence of IgM anti-HBc and by the persistence of HBsAg or HBV DNA for at least 6 months. All HBsAg-positive persons should be considered infectious and capable of transmitting HBV via blood/serum or sexual contact.

Linkage to Care

A substantial proportion of persons who test positive for HBsAg fail to seek further evaluation for treatment eligibility. Barriers to seeking follow-up evaluation and treatment vary but have been reported to be related to low income, lack of health insurance, and, especially in immigrant populations, linguistic isolation or cultural or spiritual beliefs.\textsuperscript{3–6} Persons with CHB who visit specialists for management are more likely to undergo a complete laboratory evaluation and receive treatment with a preferred antiviral agent than those who see primary care providers only.\textsuperscript{7} Therefore, it is the opinion of the panel that all HBsAg-positive persons should be referred to a specialist or primary care provider who is experienced in treating hepatitis B.

Initial Patient Evaluation
Key elements in initial evaluation of chronic HBV infection include a thorough history and physical examination, with particular attention to family history of HBV infection and liver cancer, risk factors for coinfections, and alcohol use (Table 2). Laboratory tests should include assessment of liver disease, markers of HBV replication, HBV genotype in selected patients, and tests for coinfection with other viruses for individuals at risk. Evaluation of histologic inflammation and fibrosis is recommended—but not mandatory—in patients who have intermittent or persistent increases in ALT levels. For assessing extent of fibrosis, non-invasive transient elastography may be used instead of liver biopsy (see Screening for Fibrosis section below). It is the opinion of the panel that screening for HCC should be conducted in all HBsAg-positive persons 20 years and older, including a baseline ultrasound when the patient is first encountered. Although the risk for HCC increases significantly after 40 years of age, younger patients can develop HCC. Delayed diagnosis of HCC results in limited therapeutic options and poor prognosis. Patients also should be counseled on precautions to prevent transmission of HBV infection, and sexual and household contacts should be vaccinated. Patients should be counseled about alcohol, and abstinence should be recommended. Individuals with chronic HBV infection lacking immunity to hepatitis A should be vaccinated according to CDC recommendations (i.e., 2 doses of hepatitis A vaccine, with an initial injection at baseline and a booster injection at 6 to 12 or 6 to 18 months depending on the vaccine used). A detailed discussion of diagnostic testing for hepatitis B follows.

Serologic Tests. Serologic tests for virologic markers of HBV infection, including HBsAg and antibodies to the surface antigen (anti-HBs) and core antigen (anti-HBc), can distinguish acute, chronic, or prior infection, as well as confirm immunity in individuals who have been vaccinated. Acute HBV infection can be diagnosed by detection of HBsAg and IgM anti-HBc but not of total
(IgG plus IgM) anti-HBc. A pattern also indicative of acute infection is presence of isolated IgM anti-HBc in the period between the disappearance of HBsAg and the development of anti-HBs. This is observed more commonly in patients with severe or fulminant hepatitis B. Patients with this serologic pattern should be followed with repeat testing of HBsAg, anti-HBc, and anti-HBs in 3 to 6 months to confirm recovery from acute hepatitis B. Isolated total anti-HBc, predominantly IgG anti-HBc, usually indicates prior infection with spontaneous recovery. However, it may also indicate the presence of occult hepatitis B, especially among immunocompromised patients with unexplained elevation of serum aminotransferases. In this latter case, measurement of HBV DNA is important to diagnose occult hepatitis B.

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

Resolved HBV infection is characterized by the absence of HBsAg and the detection of anti-HBs and total anti-HBc, or only anti-HBc over time. Vaccine recipients are differentiated from patients with resolved infection by the detection of anti-HBs without total anti-HBc. Although anti-HBs titers after vaccination decline over time, the majority of successfully vaccinated individuals have anamnestic responses to single doses of vaccine. Approximately 5% of the population do not develop anti-HBs after a standard course of vaccination, with nonresponse occurring more frequently with advanced age, immune suppression, or renal failure. Confirmation of immunity can be done by testing for anti-HBs 6 months after the last dose of vaccine.
Quantification of serial HBsAg levels has been used in clinical trials but has not yet had widespread application in the United States. Quantifying HBsAg levels can potentially be useful for staging the natural history of infection and in evaluating response to therapy.\textsuperscript{12,13} Low levels of both HBV DNA (<2,000 IU/mL) and HBsAg (<1,000 IU/mL) has been associated with a decreased risk of HCC in all CHB patients and an increased likelihood of HBsAg loss among HBeAg-negative CHB patients.\textsuperscript{12,14–17} During peginterferon-alfa therapy for HBeAg-positive and -negative patients, an absence of decline in HBsAg and HBV DNA by week 12 is a robust predictor of non-response and provides justification to stop therapy.\textsuperscript{18–20} Declines in HBsAg and HBV DNA at week 24 indicate therapy with peginterferon-alfa should continue to 48 weeks.\textsuperscript{21,22} With nucleoside/nucleotide analogue therapy, HBsAg tends to decline more slowly than with peginterferon-alfa therapy, and the value of HBsAg quantification in monitoring long-term nucleoside/nucleotide treatment of CHB and in predicting sustained response is unclear.

The assays for HBsAg quantification—Architect QT (Abbott Laboratories, Abbott Park, Illinois) and Elecsys HBsAg II Quant (Roche Diagnostics, Indianapolis, Indiana)—have excellent correlation between logarithmically transformed HBsAg measurements ($r = 0.96$).\textsuperscript{23} However, these assays need to be validated prior to routine standard of care application.

Individual patients should be monitored with the same assay over time because the Elecsys assay generally produces higher values (on average $0.01 \log_{10} \text{IU/mL}$), and the disparity could affect clinical decision making.\textsuperscript{24}

**Interleukin 28B Testing.** Specific polymorphisms in the *interleukin 28B* (*IL28B*) gene have been associated with natural clearance of HCV\textsuperscript{25,26} and are highly predictive of response to interferon-based therapy in patients with genotype 1 HCV.\textsuperscript{27–29} Some evidence suggests *IL28B* polymorphisms are associated with response to peginterferon-alfa in HBeAg-positive and -
negative patients;\textsuperscript{30,31} however, this result has not been consistently replicated.\textsuperscript{32,33(p3),34} Until further studies in large cohorts confirm the utility of $IL28B$ testing in patients with CHB, it is not recommended in routine practice.

Hepatitis B Virus DNA Testing. Serum HBV DNA quantification is a direct measure of viral replication and is important for characterizing viral activity and predicting the risk of cirrhosis and HCC. Therefore, serum HBV DNA quantification should be obtained in all persons diagnosed with CHB. The introduction of an international unit (IU), which is equivalent to approximately 5 to 6 copies, as the standard reporting unit for HBV DNA has allowed for standardized reporting and comparison of serum HBV DNA levels in clinical trials and daily practice.\textsuperscript{35}

The ideal HBV DNA assay should have a linear, broad dynamic range of quantification to allow evaluation of viremia at both the lowest and highest concentrations. Hybridization assays reliably quantify HBV DNA but are limited by a narrow range of detection (10$^3$–10$^7$ IU/mL). Earlier generation PCR-based assays had increased sensitivity, with detection of HBV DNA levels as low as 10$^2$ IU/mL; however, quantification was not reliable at viral levels > 10$^6$ IU/mL. In contrast, real-time PCR-based assays demonstrate sensitivity as low as 10 IU/mL and have a broad linear range of quantification (10$^1$–10$^9$ IU/mL).\textsuperscript{36}

The panel recommends real-time PCR assays, such as Abbott RealTime HBV assay (Abbott Molecular, Des Plaines, IL) and COBAS AmpliPrep (Roche Diagnostics), as the preferred tests for initial evaluation of patients and, even more importantly, for monitoring both treated and untreated patients. Because clinicians may not be able to specify the assay used, they should be aware of the sensitivity and dynamic range of the test used in individual cases. When
monitoring HBV DNA levels for a given patient over time, the same assay should be used consistently.

**Hepatitis B Virus Genotype Testing.** Specific HBV genotypes have been reported to influence progression of disease, risk of HCC, and response to interferon therapy.\textsuperscript{37} Some studies in Asia suggest that genotype C is more frequently associated with HBV reactivation, severe liver disease, and HCC than genotype B is.\textsuperscript{38–41} Genotype B appears to be associated with seroconversion from HBeAg to anti-HBe at a younger age than genotype C.\textsuperscript{40,42} It is possible that genotype C is responsible for more cases of perinatal transmission, given that HBeAg seroconversion generally occurs decades later in patients with HBV genotype C versus other genotypes.\textsuperscript{38–41} Genotype F HBV is significantly associated with development of HCC in Alaskan Native patients.\textsuperscript{43} There are no robust data comparing the possible impacts of HBV genotype in different patient populations; therefore, it is unclear whether a genotype’s impact in one geographic population would be the same elsewhere.

Specific genotype has not been shown to consistently influence the outcome of therapy with oral nucleoside and nucleotide analogs, although genotypes A and D have been reported to have more pronounced drops in HBsAg with entecavir and tenofovir therapy than other genotypes.\textsuperscript{44,45} Genotype does affect response to interferon therapy, whereby genotypes A is associated with the highest rate of antiviral response to interferon alfa-2b therapy, followed by genotype B, and then genotypes D and C, respectively.\textsuperscript{46} In a study evaluating patients treated with peginterferon alfa-2a with or without lamivudine, HBV genotype, in addition to baseline ALT and HBV DNA levels, patient age, and gender, significantly influenced the likelihood of ALT normalization and HBV DNA suppression <20,000 copies/mL at 24 weeks post-treatment.\textsuperscript{47} At 1 year after treatment, HBV genotype was significantly predictive of efficacy for
patients treated with peginterferon alfa-2a with or without lamivudine.\textsuperscript{47} In addition, higher rates of HBeAg seroconversion after treatment with peginterferon alfa-2a have been reported in patients with genotype A than in patients with other genotypes,\textsuperscript{48,49} and higher rates of HBeAg loss after treatment with peginterferon alfa-2b have been reported in patients with either genotypes A or B.\textsuperscript{50}

In light of these data, the panel recommends that genotyping be performed selectively to help identify patients potentially at greater risk for disease progression and routinely when there is consideration of peginterferon-alfa therapy. Knowing the likelihood of response to peginterferon-alfa therapy can inform the decision whether to treat with it versus an oral agent.

Commercial tests for HBV genotyping are available through referral laboratories as part of the standard panel of tests for HBV infection. These tests differ from in vitro HBV phenotype tests conducted during therapy for analysis of viral resistance (see section on HBV resistance testing). The diagnostic tests currently available to determine genotype include sequencing-based assays, which are the gold standard for HBV genotyping, and a line probe assay (INNO-LiPA HBV$^\text{\textregistered}$ genotype, Innogenetics NV; Ghent, Belgium).\textsuperscript{51} Real-time PCR or multiplex PCR assays can also be used for genotype analysis if validated against the gold standard.

**Screening for Fibrosis.** After initial serologic testing and HBV DNA quantification, it is helpful to establish the baseline liver histology and to exclude other causes of liver disease. Liver biopsy remains the gold standard to assess hepatic inflammation and rule out other disease processes. However, the use of liver biopsy is limited because it is invasive, only samples a small portion of the liver, and has limited interobserver and intraobserver concordance. Noninvasive methods for assessing fibrosis include measurement of serum biomarkers (for example, FibroTest) and measurement of liver stiffness through transient elastography (Fibroscan). Fibroscan was
approved by the FDA in 2013. Both FibroTest and Fibroscan have a prognostic value similar to liver biopsy for predicting complications and outcome of liver disease.\textsuperscript{52,53} In a meta-analysis evaluating performance of transient elastography in patients with CHB, the diagnostic accuracy for quantifying liver fibrosis was good: the mean AUROC for diagnosing fibrosis (F2) was 0.859 (95% CI, 0.857-0.860), for severe fibrosis (F3) was 0.887 (0.886-0.887), and for cirrhosis (F4) was 0.929 (0.928-0.929).\textsuperscript{54} Fibroscan cannot accurately be used in patients who have ascites, morbid obesity, or large amounts of chest wall fat.\textsuperscript{55} Moreover, with Fibroscan histologic inflammation\textsuperscript{56} and recent food intake\textsuperscript{57} can increase the score and overestimate the amount of fibrosis. The panel believes transient elastography has a useful role assessing histologic fibrosis but is limited by its inability to assess inflammation or rule out other causes of chronic liver disease.

**Screening and Surveillance for Hepatocellular Carcinoma.** Screening CHB patients for HCC can help detect tumors at a resectable stage and improves survival rates.\textsuperscript{58,59} Most, but not all, members of the panel recommend that all HBsAg-positive persons 20 years of age and older be surveyed twice annually for HCC. HBsAg-positive persons who have a family history of primary hepatocellular carcinoma should be screened twice annually for HCC regardless of age. Standard tools for HCC screening and surveillance include alpha-fetoprotein (AFP) testing and ultrasound. The utility of AFP quantification is limited because the sensitivity of the test is only approximately 60% and because AFP can be elevated in patients with active hepatitis or cirrhosis but without HCC.\textsuperscript{60} Magnetic resonance imaging (MRI) and computed tomography are considered to be more sensitive than ultrasound in identifying smaller tumors <1 cm. Although the expense of MRI limits its feasibility for routine surveillance, because of its sensitivity and lack of radiation exposure, the panel recommends MRI testing especially for patients with rising
AFP levels but normal ultrasound, cirrhosis, obesity with limited ultrasound exam, heterogenous echotexture, or indeterminate lesions.

References


32. Galmozzi E, Viganò M, Lampertico P. Systematic review with meta-analysis: do interferon lambda 3 polymorphisms predict the outcome of interferon-therapy in


Table 1. Groups at High Risk for HBV Infection Who Should Be Screened for HBV\textsuperscript{1,2,61}

**Individuals born in areas of high and intermediate endemicity HBV (HBsAg prevalence ≥ 2%), including immigrants and adopted children**

- Africa
- Asia: Southeast Asia, East Asia, and Northern Asia
- South Pacific: all countries except New Zealand
- Middle East: all countries except Cyprus and Israel
- Eastern Europe: all countries except Hungary
- Western Europe: Malta, Spain, Portugal, Greece, and indigenous populations in Greenland
- North America: Alaska Natives and indigenous populations in Northern Canada
- Mexico and Central America: Guatemala and Honduras
- South America: Ecuador, Guyana, Suriname, Venezuela, and Amazonian areas of Bolivia, Brazil, Colombia, and Peru
- Caribbean: Antigua-Barbados, Dominica, Grenada, Haiti, Jamaica, St. Kitts-Nevis, St. Lucia, and Turks and Caicos Islands

**Other high-risk groups recommended for screening**

- US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥ 8%)
- Injection-drug users
- Men who have sex with men
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic, dermatologic, or gastroenterologic disorders (e.g. biologic response modifiers)
- Persons with elevated ALT/AST of unknown etiology
- Donors of blood, plasma, organs, tissues, or semen
• Household and sexual contacts of HBsAg-positive persons
• Hemodialysis patients
• All pregnant women
• Infants born to HBsAg-positive mothers
• Household contacts of persons with HBV infection
• Inmates of correctional facilities
• Individuals infected with HIV

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus
Table 2. Pretreatment Evaluation for Chronic Hepatitis B

<table>
<thead>
<tr>
<th>History and Physical Examination</th>
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<tbody>
<tr>
<td>• Risk factors for viral hepatitis</td>
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<tr>
<td>• Duration of infection</td>
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<tr>
<td>• Route of transmission</td>
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<tr>
<td>• Risk factors for HIV coinfection</td>
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<tr>
<td>• Alcohol history</td>
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<tr>
<td>• Presence of comorbid diseases</td>
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<tr>
<td>• Family history of liver cancer</td>
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<tr>
<td>• HBV testing of family members</td>
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<tr>
<td>• General counseling regarding transmission</td>
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<tr>
<td>• Vaccination of at-risk household and sexual contacts</td>
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<tr>
<td>• Family planning</td>
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<table>
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<tr>
<th>Pretreatment Tests</th>
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<tbody>
<tr>
<td>• Serial testing of ALT and HBV DNA level for 6-months</td>
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<tr>
<td>• Liver function tests</td>
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<tr>
<td>o Complete blood count with platelets</td>
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<tr>
<td>o Hepatic function panel</td>
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<tr>
<td>o Prothrombin time</td>
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<tr>
<td>• HBeAg and anti-HBe</td>
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<tr>
<td>• HBV genotype</td>
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<tr>
<td>• Tests to rule out other causes of liver disease</td>
</tr>
<tr>
<td>o Anti-HCV</td>
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<tr>
<td>o Anti-HDV</td>
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<tr>
<td>• Hepatitis A immunity: anti-HAV IgG or total</td>
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<tr>
<td>• HIV: anti-HIV</td>
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<tr>
<td>• Screen for HCC in high-risk patients: MRI (preferred), CT, AFP, or ultrasound</td>
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<tr>
<td>• Transient elastography to grade histologic fibrosis or liver biopsy examination to grade and stage liver disease(^a)</td>
</tr>
<tr>
<td>• Urinalysis; if abnormal, do 24-hour urine for creatinine and protein</td>
</tr>
</tbody>
</table>

\(^a\)Liver biopsy is optional for patients meeting treatment criteria, but may be especially helpful in those with normal ALT levels and age greater than 35 to 40 years of age.

AFP, alpha-fetoprotein; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.
A Treatment Algorithm for the Management of
Chronic Hepatitis B Virus Infection in the United States: 2015 Update

Special Patient Populations

Patients With Cirrhosis

Prolonged and adequate suppression of HBV DNA can prevent disease progression in patients with cirrhosis. Reversal of cirrhosis has been reported with long-term therapy with entecavir or tenofovir. In addition, long-term virologic suppression with entecavir or tenofovir reduces the incidence of HCC in CHB patients with cirrhosis.

All HBeAg-positive or HBeAg-negative patients with cirrhosis (compensated or decompensated) and any level of detectable HBV DNA should receive treatment for CHB (Table 1). For patients with compensated cirrhosis, monotherapy with tenofovir or entecavir is recommended because of their potency and minimal risk of resistance. Peginterferon alfa can be used for treating CHB patients with well-compensated cirrhosis. Lamivudine should not be used in patients with cirrhosis because of the high risk for resistance, which could result in clinical decompensation.

The aim of treatment in decompensated patients is to improve their status such that they eventually might be removed from the transplantation wait list. For patients with decompensated cirrhosis, entecavir or tenofovir monotherapy are the preferred first-line options. The licensed entecavir dose for patients with decompensated cirrhosis is 1 mg (instead of 0.5 mg for patients with compensated liver disease) once daily. Peginterferon alfa is contraindicated in patients with decompensated cirrhosis.
**Duration of therapy and on-treatment monitoring.** The panel believes that patients with cirrhosis should receive long-term therapy. Given the data on long-term benefits of nucleoside and nucleotide analogs and their excellent safety profiles, therapy can be continued indefinitely. On-treatment monitoring should be performed every 3 months. Monitoring of renal function before and during therapy is particularly important in patients who have multiple risk factors for renal impairment. Adjustments to the dosing frequency of entecavir and tenofovir should be made as recommended by the manufacturers.

**Human Immunodeficiency Virus–Hepatitis B Virus Coinfection**

Coinfection with HBV and HIV is common because of their shared routes of transmission. In the United States, approximately 10% of all patients who are HIV-positive are coinfected with HBV.\(^1\) HBV-HIV coinfected individuals are more likely to develop chronic HBV infection than are individuals with HBV monoinfection (23% vs 4%).\(^2\) Compared with HBV monoinfection, HIV-HBV coinfection is associated with higher HBeAg positivity rates and HBV DNA levels, longer duration of viremia, lower aminotransferase values, milder necroinflammation, and more rapid progression to cirrhosis. Data from large cohort studies have indicated that liver-related mortality in HIV-HBV coinfected patients is as much as 14-fold higher than in patients with either virus alone.\(^3,4\) HIV-positive patients with CHB have a significantly higher risk of progressing to AIDS or having a fatal event than those without CHB.\(^5,6\)

The general principles of diagnosis are similar for HBV-infected persons with or without HIV infection. However, HIV-HBV coinfection is often associated with atypical patterns of serologic markers of HBV infection, which hinder an appropriate diagnosis. The presence of occult hepatitis B, defined as the presence of HBV DNA without circulating HBsAg, might also complicate the diagnosis and management of HIV-HBV coinfected individuals.\(^7,8\) Patients
should be monitored for liver disease, particularly if HIV infection is not be treated immediately, because of the increased risk for cirrhosis and liver-related mortality.\textsuperscript{13,20} HIV is associated with an increased risk of HCC,\textsuperscript{21} and thus most members of the panel recommend that all HIV- and HBsAg-positive persons 20 years of age and older be screened twice annually for HCC. Those with a family history of primary hepatocellular carcinoma should be screened twice annually for HCC regardless of age.

The panel recommends initiating therapy for CHB in any patient who is coinfected with HBV and HIV. Both the U.S. Department of Health and Human Services\textsuperscript{22} and International AIDS Society—USA panel\textsuperscript{23} guidelines suggest initiating HIV treatment with tenofovir plus either emtricitabine or lamivudine in HIV-HBV coinfected patients regardless of their CD4 count or HIV RNA value.

Management of HBV infection in HIV coinfection is complicated by several factors. Many of the nucleoside or nucleotide analogs, including lamivudine, tenofovir, emtricitabine, and entecavir, possess dual activity against HBV and HIV.\textsuperscript{24,25} Of greatest concern is the potential for the development of resistance, which could compromise the future management of either virus. The rate of hepatitis B–related lamivudine resistance is much higher in HIV-HBV coinfected patients, reaching 90\% at 4 years.\textsuperscript{26} Prolonged treatment with lamivudine has been shown to be associated with the development of vaccine-escape mutations to HBV, which could have important public health implications for transmission of the virus.\textsuperscript{27}

For patients with HIV-HBV coinfection who have not received treatment for HBV, the panel recommends initiation of a fully suppressive antiretroviral regimen that includes tenofovir and either lamivudine or emtricitabine (Table 2). Entecavir plus highly active antiretroviral therapy (HAART) may also be administered but is used less commonly. Monotherapy with any
HBV agent should be avoided because of the increased risk of resistance to HBV or HIV. For patients with HIV-HBV coinfection who have lamivudine-resistant HBV, the panel recommends initiation of a fully suppressive antiretroviral regimen that includes tenofovir and emtricitabine. Monotherapy with entecavir should be avoided because it is associated with viral breakthrough with lamivudine-resistant HBV\textsuperscript{28} and because it increases the risk of lamivudine resistance mutations in HIV\textsuperscript{24(p-)}.

In HIV-HBV coinfected patients, treatment for CHB and HIV should be continued long-term. Patients who discontinue therapy for HIV should be monitored for aminotransferase flares.

**Chemotherapy and Immunosuppressed Patients**

Reactivation of HBV replication, as indicated by increased serum HBV DNA and ALT levels, is a well-recognized complication in HBsAg-positive individuals undergoing chemotherapy for hemato-oncological malignancies or immunosuppression for autoimmune diseases with biologic response modifiers.\textsuperscript{29} For patients receiving rituximab alone or in combination with steroids, the risk of reactivation can occur well after cessation of therapy, with reports of reverse seroconversion occurring as late as 110 days after completion of treatment.\textsuperscript{30} Although less common, seroreversion with development of HBsAg may occur in patients with resolved infection (HBsAg negative, but anti-HBc positive, with or without anti-HBs) many months after the last dose of rituximab or after stem cell transplant. In some cases, hepatitis flares associated with reactivation of HBV are asymptomatic; however, HBV reactivation might lead to severe, even life-threatening, hepatitis flares that must be recognized and treated promptly.

Screening for HBsAg, HBsAb, and HBcAb should be done in all patients who are candidates for chemotherapy or immunosuppressive therapy, including patients receiving anti-
tumor necrosis factor (TNF)-alpha agents such as etanercept, adalimumab, and infliximab for rheumatic diseases.\textsuperscript{31–33} If patients are positive for anti-HBc then HBV DNA should be tested.

HBsAg-positive patients should be tested for HBV DNA levels and receive prophylactic administration of a nucleotide or nucleoside analogue several weeks before, during, and for 12 months after chemotherapy or immunosuppressive therapy. The panel recommends tenofovir or entecavir, although data are limited on their use during chemotherapy or immunosuppressive therapy. Lamivudine may suffice for patients with HBV DNA levels <2,000 IU/mL for short, finite durations of immunosuppression.\textsuperscript{34} HBV DNA should be monitored every 3 months as it typically rises some weeks before ALT.

Patients who are HBsAg-negative and anti-HBc positive with detectable serum HBV DNA should be treated with prophylactic therapy as in HBsAg positive patients. HBsAg-negative and anti-HBc positive patients who are HBV DNA negative can be monitored every 1-3 months for ALT and HBV DNA levels during chemotherapy or immunosuppression\textsuperscript{35} with the following exceptions. If patients are to receive rituximab-containing therapy or bone marrow transplants, a growing body of opinion supports the prophylactic administration of antiviral therapy as for HBsAg-positive patients because of the significant potential for seroreversion and hepatitis flares.\textsuperscript{36,37} A 2014 report by Huang et al indicates that entecavir is more effective in preventing HBV reactivation with chemotherapy than lamivudine.\textsuperscript{38}

\textit{Liver Transplant Patients}

Risk factors for recurrence of HBV infection post liver transplant include active HBV replication, absence of hepatitis delta coinfection, a non-fulminant presentation, as well as the presence of HCC at the time of liver transplantation.\textsuperscript{39} All HBsAg-positive patients undergoing liver transplantation for HBV-related end-stage liver disease or HCC should undergo pre-transplant
therapy with entecavir or tenofovir with the goal of controlling HBV replication prior to transplant. Post-transplant, treatment with hepatitis B immune globulin (HBIG) and oral antivirals should be administered to reduce the risk of reinfection. Long-term prophylaxis with HBIG is expensive and inconvenient and has been associated with the development of HBsAg mutations. Post-transplant entecavir prophylaxis without HBIG has been shown to be safe and effective in preventing HBV recurrence in a study of 362 patients, in which virological relapse rates were 5%, 10%, 13%, and 16% at 1, 3, 5, and 8 years, respectively. Relapse of HBV post transplant is higher in patients who either have lamivudine resistance, are HBV DNA positive at time of transplant, are coinfected with hepatitis C or D or HIV, or have HCC. For patients who are who are HBV DNA negative at time of transplant, the panel recommends a short-term course of HBIG (6-12 months) with long-term entecavir, tenofovir, or combination therapy. For patients at high risk of recurrence, both HBIG and antiviral therapy with entecavir or tenofovir should be administered long term. These include recipients with HBV replication at the time of transplant, and patients with limited options should HBV recur such as those with HDV or HIV coinfection or HBV with a high risk of recurrence.

**Pregnancy**

Screening all pregnant women for HBsAg is recommended. The standard approach for preventing HBV perinatal transmission from HBsAg-positive mothers is based on a combination of passive and active immunization of the infant, whereby infants receive HBIG within 12 hours of birth and HBV vaccination starting at birth and then at 1 and 3 or 6 months of age. However, this strategy is not always effective: newborns whose mothers are HBsAg positive have a 4-10% risk of vertical HBV transmission despite HBIG and vaccination. Recent evidence suggests that in mothers with high concentrations of HBV DNA, treatment with nucleoside or nucleotide
therapy in the third trimester of pregnancy might eliminate the risk of perinatal transmission in the setting of HBIG and vaccination.\textsuperscript{50} In a study of 700 pregnant mothers with HBV DNA $>6 \log_{10}$ copies/mL, none of the infants whose mothers completed treatment with telbivudine or lamivudine from week 28 of gestation through postpartum week 4 became HBsAg-positive, whereas 2.8\% of infants whose mothers did not receive telbivudine or lamivudine became HBsAg-positive ($P = 0.002$).\textsuperscript{30}

Of the currently available oral nucleoside and nucleotide analogs, only telbivudine and tenofovir are classified as pregnancy category B (i.e., not teratogenic). Although classified as category C, lamivudine has demonstrated safety in HIV patients during pregnancy and remains in use for treating pregnant women with CHB.

Mothers who are HBsAg positive require closer monitoring during pregnancy and in the immediate post partum period for their need for therapy. Hepatitis B may flare because of immunologic changes that occur in pregnancy, so more frequent monitoring is recommended (every 12 weeks during pregnancy and at 4-6 weeks postpartum). Therapy should be considered per standard guidelines (see above). Although many mothers prefer to avoid therapy during pregnancy, they should be counseled about risks and benefits. Decisions about initiating or continuing antiviral therapy in pregnant women should depend on the stage of the mother’s liver disease and the potential benefit to her versus the small risk to the fetus. Because treatment mostly concerns young women who are likely to have only mild liver disease, postponement of therapy until after pregnancy, or until the third trimester if viral levels are high, may be prudent. Similarly, discontinuation of therapy prior to planned conception in women with mild disease may be considered. The panel recommends that all HBsAg-positive mothers have HBV DNA and ALT levels evaluated at 26 to 28 weeks of gestation. Women who have HBV DNA levels
>10^6 IU/mL should receive antiviral therapy for the remainder of the pregnancy and through 4 weeks postpartum. Antiviral therapy with tenofovir, telbivudine, or lamivudine is recommended. Caution is advised when using lamivudine for those who require long-term therapy because of the increased risk for resistance. Patients who had been taking entecavir prior to becoming pregnant should be switched to tenofovir. The clinical course of HBV infection during pregnancy can be variable, and some members of the panel monitor HBV DNA and ALT levels every 4 to 6 weeks in the third trimester of pregnancy to minimize the risk of severe flares. An elective Caesarean section does not have proven benefit of preventing vertical transmission. Patients who stop antiviral therapy postpartum should also be monitored for flares and reactivation of HBV. Mothers undergoing antiviral therapy with a nucleoside or nucleotide analogue should not breastfeed.

**Vaccination**

The CDC recommends that all children receive a first dose of hepatitis B vaccine at birth and complete the vaccine series by age 6-18 months. Children and adolescents through 18 years of age who did not receive the vaccine when they were younger should also be vaccinated. Administration of hepatitis B vaccine is recommended for individuals in high-risk populations (listed in Table 3) who are HBsAg seronegative. HBV seronegative patients who are planned to initiate chemotherapy or immunosuppressive therapy should also be vaccinated.

**References**


Table 1. Recommendations for Treatment: Patients With Cirrhosis (HBeAg-Positive or -Negative) and Detectable HBV DNA

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Treatment Strategy</th>
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<tr>
<td>Compensated</td>
<td>• Entecavir (0.5 mg) or tenofovir (300 mg)</td>
</tr>
<tr>
<td></td>
<td>• Peginterferon alfa can be used in patients with well-compensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• For oral antivirals, long-term treatment is required</td>
</tr>
<tr>
<td>Decompensated</td>
<td>• Entecavir (1 mg) or tenofovir (300 mg)</td>
</tr>
<tr>
<td></td>
<td>• Peginterferon alfa is contraindicated</td>
</tr>
<tr>
<td></td>
<td>• Long-term treatment is required</td>
</tr>
<tr>
<td></td>
<td>• Wait list for liver transplantation</td>
</tr>
</tbody>
</table>

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus
### Table 2. Recommendations for Treatment: Patients with Human Immunodeficiency Virus and Hepatitis B Virus Coinfection.

<table>
<thead>
<tr>
<th>Criteria for Treatment</th>
<th>Pretreatment Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA</td>
<td>CD4 Count</td>
</tr>
<tr>
<td>Any value</td>
<td>Any value</td>
</tr>
</tbody>
</table>

#### Pretreatment Assessments
- Assess extent of fibrosis via biopsy or transient elastography
- Screen for hepatocellular carcinoma
- Patients with platelets <120,000/µL or severe fibrosis should undergo endoscopy to detect varices

<table>
<thead>
<tr>
<th>Treatment (Both HBV and HIV Should Be Treated)</th>
<th>Preferred</th>
<th>Other Options</th>
<th>Comments</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV treatment-naïve patients</td>
<td>Truvada or tenofovir plus lamivudine</td>
<td>Entecavir plus HAART</td>
<td>Avoid single-agent HBV therapy</td>
<td>Long term</td>
</tr>
<tr>
<td>Patients with lamivudine-resistant HBV</td>
<td>Truvada or tenofovir plus entecavir</td>
<td></td>
<td>Avoid single-agent HBV therapy</td>
<td>Long term</td>
</tr>
</tbody>
</table>

HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus

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*Martin et al*
Table 3. Adults Who Should Be Vaccinated for Hepatitis B Virus\textsuperscript{52}

- Household contacts of persons with HBV infection
- Sexual partners of persons with HBV infection
- Persons who have multiple sex partners
- Patients who seek care in a clinic for sexually transmitted diseases, HIV testing or treatment, or drug treatment
- Men who have sex with other men
- Injection drug users
- Healthcare personnel with the potential for contacting human blood
- Personnel or clients of institutions for the developmentally disabled
- Patients on dialysis or with end-stage renal disease
- Persons with HIV infection
- Persons with chronic liver disease
- Persons <60 years of age who have diabetes
- Travelers to areas of high and intermediate endemicity HBV
- Prisoners in a correctional facility