

TREATMENT OF HEPATITIS B VIRUS INFECTION*

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ABSTRACT

In treating chronic hepatitis B virus (HBV) infection, the primary goal of therapy is to achieve sustained suppression of HBV replication, which ultimately leads to improvement in inflammation, reduces progression to cirrhosis and/or liver failure, reverses fibrosis, and may reduce (but not eliminate) the risk of hepatocellular carcinoma. Currently available HBV drugs include interferon and nucleos(t)ide analogues, with entecavir, tenofovir, and pegylated interferon alfa-2a considered the preferred first-line agents in both hepatitis B envelope antigen (HBeAg) (+) and HBeAg (-) chronic HBV infection. This article offers a summation of the clinical efficacy for each of the agents used, the recommended treatment duration and desired therapeutic end points, as well as the current standard of care for pregnant and chemotherapy-treated patients with chronic HBV infection. (*Adv Stud Med.* 2009;9(3):89-95)

The availability of newer antiviral agents, as well as comprehensive treatment recommendations, has equipped clinicians with sufficient options to individualize therapeutic strategies for chronic infection with hepatitis B virus (HBV). These advances are particularly pertinent in treating immigrant populations from highly endemic regions, which comprise the majority of chronic HBV infections in the United States. Although these patient populations may be more challenging to treat, as a result of early childhood or perinatal infection, a high risk of hepatocellular carcinoma (HCC) at an earlier age, and a somewhat different response to certain drugs (as will be discussed), the major principles of treatment for hepatitis B envelope antigen (HBeAg) (+) and HBeAg (-) infection apply to the general population, and not to any specific ethnic group.

All patients with active HBV infection are considered to be hepatitis B surface antigen (HBsAg) (+). In deciding on treatment, the 3 major factors that should be determined are HBeAg status, HBV viral load, and alanine aminotransferase (ALT) level. A simplified flowchart detailing how these factors guide therapeutic decisions is provided in Figure 1.¹ For HBeAg (+) patients, an HBV DNA level of 20 000 IU/mL (ie, 100 000 copies/mL) or higher and elevated ALT levels is generally used as a threshold for starting therapy.² Because patients with normal ALT levels may still have significant liver disease, a liver biopsy should be considered and treatment initiation based solely on the presence of inflammation or advanced fibrosis.²

For HBeAg (-) patients, an HBV DNA cut-off of 2000 IU/mL and elevated ALT levels should be used to initiate treatment because approximately 50% of these patients have active liver disease despite lower viral titers.³ HBeAg (-) patients tend to have lower levels of serum HBV DNA, but may progress to cirrhosis

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more rapidly (compared to HBeAg (+) patients). As with HBeAg (+) patients, HBeAg (-) patients with long-standing HBV infection should be considered for liver biopsy and treatment initiation based on significant biopsy findings.²

GOALS OF THERAPY

In chronic HBV infection, the primary goal of therapy is to achieve sustained suppression of HBV replication. Viral suppression or elimination generally improves inflammation, reduces progression to cirrhosis and/or liver failure, reverses fibrosis, and may reduce (but not eliminate) the risk of HCC.

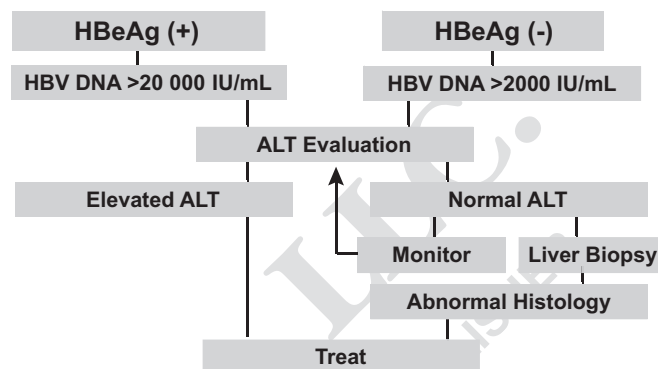
Hepatitis B virus resides in the hepatocyte in a mini-chromosome structure known as covalently closed circular (ccc) DNA. This form most likely persists for the life of the hepatocyte, thus the virus may persist in the liver long after it is cleared from the bloodstream. Antiviral agents may effectively block viral replication and reverse liver injury, without removing cccDNA. In this situation, HBsAg remains detectable in the absence of HBV DNA. Reactivation of HBV infection is possible as long as cccDNA remains in the liver. The ultimate goal of therapy should be complete elimination of virus from the liver, which is thought to occur when the patient loses HBsAg and converts to anti-hepatitis B surface antibody. Another important event is conversion from HBeAg (+) to hepatitis B envelope antibody (+); this occurrence may represent a first step in viral clearance, and it correlates with a decrease in the rate of viral replication.^{2,3}

DURATION OF TREATMENT AND TREATMENT END POINTS

Currently available HBV drugs include interferon (IFN) and nucleos(t)ide analogues, with each agent having an individual risk-benefit profile (Table 1).⁴ IFNs are usually administered for predefined durations, whereas nucleos(t)ide analogs are continued until specific end points are met.³

Long-term viral suppression with current treatment may be sustained in 50% to 90% of HBeAg (+) patients, if treatment is extended 6 to 12 months beyond HBeAg seroconversion.³ HBV DNA clearance from the serum is an essential first step in this process. HBeAg (+) patients who fail to seroconvert (do not lose HBeAg) should be treated indefinitely, those who

Figure 1. Chronic HBV Treatment: Simplified Flowchart



ALT = alanine aminotransferase; HBeAg = hepatitis B envelope antigen; HBV = hepatitis B virus.
Data from Keeffe et al.¹

relapse after treatment should be retreated, and those with cirrhosis require long-term therapy. In patients whose treatment has ended, ALT, HBV DNA, HBeAg, and anti-HBe should be monitored every 3 months for 1 year and HBsAg should be assessed annually.²

In HBeAg (-) patients, the treatment end point is also sustained viral suppression, but the duration of therapy is less certain. Because relapse is common after stopping therapy, long-term treatment without a defined end date is currently recommended. Ongoing studies are expected to better define future guidelines for discontinuation of therapy.

Many of the treatment end points outlined in current guidelines (eg, HBeAg seroconversion, significant decrease in HBV DNA load, and normalization of ALT levels) are based on the assumption that chronic HBV is likely to progress to HCC and cirrhosis only in patients with ALT elevation and a detectable viral load, and that treatment can be stopped once a patient achieves an inactive HBV carrier state. But this may not be true because recent studies suggest that the majority of patients with chronic HBV infection may have disease progression despite HBeAg seroconversion, HBsAg clearance, HBV DNA levels lower than 20 000 IU/mL (or even <2000 IU/mL), and ALT levels between 2 and 5 times the upper limit of normal (ULN).^{5,6} Therefore, HBeAg seroconversion may not be an adequate end

point for these patients. Instead, the ideal treatment end points are permanent suppression of HBV DNA to undetectable levels and normalization of ALT levels to less than 0.5 times the ULN.⁵⁻⁷

US FOOD AND DRUG ADMINISTRATION-APPROVED TREATMENT OPTIONS

As a result of superior efficacy, tolerability, and low rate of resistance, the preferred first-line agents in both HBeAg (+) and HBeAg (-) chronic HBV infection include entecavir, tenofovir, and pegylated interferon (PEG-IFN) alfa-2a.²

Pegylated IFN alfa-2a has replaced conventional IFN because of convenience (weekly vs daily or thrice-weekly dosing) and a more favorable safety profile.³ In regard to efficacy, a study comparing PEG-IFN alfa-2a (with or without lamivudine) to lamivudine monotherapy in HBeAg (+) patients found IFN to produce significantly higher rates of HBeAg seroconversion, reduction in HBV DNA to undetectable levels, and normalization of ALT after 48 weeks of treatment. Six months after treatment, the HBeAg seroconversion rate was actually higher (32%) among patients treated with PEG-IFN alfa-2a monotherapy than in those given both drugs (27%) or lamivudine

Table 1. Advantages and Disadvantages of Current FDA-Approved Therapies for Chronic HBV

Agent	Advantages	Disadvantages
Interferon	Higher rate of HBsAg loss Short treatment duration No drug resistance	Parenteral administration Frequent side effects
Lamivudine	Oral administration Excellent tolerance Use in ESLD	Drug resistance: common (~20%/yr, and up to 70% with 4-5 yrs of therapy)
Adefovir	Oral administration Excellent tolerance Use in ESLD Use in lamivudine failures	Less potent, with suboptimal responses not uncommon Drug resistance: delayed (0% at yr 1 and 3% at yr 2) but reaches 29% at yr 5 Monitoring for renal toxicity required
Entecavir	Oral administration Excellent tolerance High potency in lowering HBV DNA levels Low rate of drug resistance	Drug resistance: rare in nucleoside-naïve patients (0.2% at yr 1, 0.5% at yr 2, and 1.2% at yr 5), but common in patients with lamivudine resistance (6% at yr 1, 14% at yr 2, and 51% at yr 5) Administration on empty stomach
PEG-IFN	Higher rate of HBsAg loss Fixed duration of treatment No drug resistance	Parenteral administration Frequent side effects, but less than interferon
Telbivudine	Oral administration Excellent tolerance High potency in lowering HBV DNA levels Use in pregnancy (class B)	Drug resistance: intermediate rates (5% at yr 1, and 21.6% at yr 2 in HBeAg (+) patients, and 11% in HBeAg (-) patients)
Tenofovir	Oral administration Excellent tolerance High potency in lowering HBV DNA levels Absent resistance at yr 2 Use in pregnancy (class B)	Monitoring for renal toxicity required

ESLD = end-stage liver disease; FDA = US Food and Drug Administration; HBeAb = hepatitis B envelope antibody; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

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alone (19%). Similar findings were seen among HBeAg (-) patients, in whom PEG-IFN alfa-2a (vs lamivudine) was associated with higher rates of ALT normalization, HBV DNA suppression, HBsAg loss, and HBsAg seroconversion.³

Factors that predict HBeAg seroconversion following treatment with PEG-IFN alfa-2a include infection with genotype A virus, a low baseline HBV DNA, and elevated ALT levels. Asian patients tend to exhibit lower responses to IFN therapy, rarely experiencing permanent clearance of HBV DNA. In one study, 91% of Chinese patients had detectable HBV DNA following IFN treatment, even after HBeAg seroconversion.⁴ Based on these findings, IFN therapy is considered to be a more reasonable choice in patients with ALT levels 2 to 3 times the ULN and HBV DNA levels of less than 109 copies/mL. Despite its numerous adverse effects (eg, flu-like symptoms, fatigue, anorexia, depression, and leukopenia) and the need for subcutaneous injections, PEG-IFN alfa-2a generally remains in favor because it is not associated with antiviral resistance and is given for a fixed treatment course.

Entecavir, an orally administered nucleoside analog, has been shown (in vitro) to have greater antiviral potency than lamivudine or adefovir, and appears to have a low rate of drug resistance. In one long-term analysis of HBeAg (+) patients, entecavir was shown to be superior to lamivudine after 96 weeks of therapy, with 74% of entecavir-treated patients achieving HBV DNA less than 300 copies/mL and 79% achieving ALT normalization, compared with 37% and 68%, respectively, of those given lamivudine.³ Among a cohort of HBeAg (+), entecavir-treated patients followed for 5 years, 96% achieved undetectable serum HBV DNA and 80% attained normal ALT levels. In studies of HBeAg (-) patients with compensated liver disease, entecavir was also found to be superior to lamivudine, producing significantly higher rates of histologic improvement, ALT normalization, and suppression of HBV DNA.³

High entecavir resistance rates (51% at 5 years) were reported in lamivudine-resistant patients with chronic HBV, however, nucleoside-naïve patients tend to have considerably lower resistance rates (1.2% at 5 years). Entecavir-resistant strains of HBV appear to be sensitive to adefovir and tenofovir.⁸

Entecavir appears to have similar efficacy in Asian and Caucasian patients, across HBV genotypes, and in a wide range of pretreatment HBV DNA levels.

HBeAg seroconversion rates tend to be higher in patients with increased pretreatment ALT levels.⁹ Entecavir's adverse-effect profile is similar to that of lamivudine and commonly includes headache, fatigue, dizziness, and nausea.

Tenofovir, an oral nucleotide analog approved for both HBV and HIV infection, is similar to adefovir but is less nephrotoxic and more effective against lamivudine-resistant HBV strains.^{3,8,10} Studies in both HBeAg (+) and HBeAg (-) patients have shown tenofovir to be considerably more effective than adefovir in achieving and maintaining (through 96 weeks) undetectable serum HBV DNA levels, with no development of resistance. Tenofovir is generally well tolerated, but because Fanconi syndrome and renal insufficiency have been reported, renal monitoring is required.³

Lamivudine, the first nucleoside analog to become available for chronic HBV, has been primarily used as a continuous, long-term therapy and has historically been effective in achieving HBV DNA suppression, ALT normalization, and improvement in liver histology in both HBeAg (+) and HBeAg (-) patients.^{10,11} HBeAg seroconversion after 1 year of lamivudine therapy is reported to be approximately 17%, a rate that is similar to that associated with a 16-week course of standard IFN, but lower than that of a 1-year course of PEG-IFN.^{3,11} In HBeAg (+) patients, higher pretreatment ALT levels are associated with better responses to lamivudine. In general, lamivudine is well tolerated, with mild increases in ALT levels being the main adverse event.³ The durability of response appears to be low in patients with genotype C HBV infection, in older patients, Asian patients, and if treatment is continued for less than 4 to 8 months after HBeAg seroconversion.¹¹

Lamivudine is no longer considered a first-line agent, primarily because it is associated with a high rate of antiviral resistance, affecting 70% to 80% of patients after 4 to 5 years of treatment.^{12,13} Those patients who are already being treated with lamivudine and who have successfully achieved persistently undetectable viral levels do not require changes in therapy. Emtricitabine is structurally similar to lamivudine and is, therefore, comparable to lamivudine in efficacy and pattern of resistance. A combination product containing tenofovir and emtricitabine is approved for treating HIV, but is not yet approved for HBV, despite known efficacy.

Telbivudine, an oral L-nucleoside analog of thymidine and a potent inhibitor of HBV DNA, has been shown to be more effective than lamivudine in suppressing HBV replication, with 75% of HBeAg (+) patients achieving a reduction in HBV DNA to undetectable levels and loss of HBeAg or normalization of ALT (vs 67% of those on lamivudine). Telbivudine may have lower rates of resistance compared to lamivudine, but the agent is still associated with higher rates of resistance compared to other therapies and exhibits cross-resistance with lamivudine.^{10,14} Moreover, the rate of resistance increases exponentially after the first year of treatment, from 4.4% at 1 year to 21.6% (in HBeAg (+) patients) and 8.6% (in HBeAg (-) patients) at 2 years.

Adefovir is associated with a modest decrease in HBV DNA levels and an improvement in ALT levels in approximately 33% of HBeAg (+) patients, but its slow onset of action and no apparent advantage over tenofovir limit its utility.

COMBINATION THERAPY

Combination therapy may ultimately prove to be more effective than monotherapy in suppressing viral replication and decreasing the development of resistance, but limited evidence prevents routine use in all patients with chronic HBV infection. Thus far, preliminary studies suggest enhanced or synergistic anti-HBV activity with the use of nucleosides (lamivudine, emtricitabine, telbivudine, and entecavir) in combination with nucleotides (tenofovir and adefovir).² In one study, the combination of lamivudine and adefovir (vs monotherapy with either agent) produced a better virologic outcome (greater reductions in HBV DNA and lower rate of viral breakthrough), but only after 104 weeks of therapy.³ In one large randomized study, the combination of lamivudine and PEG-IFN was compared to monotherapy with either agent and was found to produce a more profound decrease in viral load, but did not result in a significant difference in viral suppression, HBeAg seroconversion, and HBsAg clearance.² Preliminary results from another randomized study found the combination of PEG-IFN and adefovir to be more effective than either agent alone in achieving undetectable HBV DNA levels in HBeAg (-) patients.

As of now, oral combination therapy may be useful in select patients, including those with cirrhosis,

HIV/HBV coinfection, suboptimal response to initial monotherapy, or established resistance to an anti-HBV drug.²

TREATMENT MONITORING

During treatment, serum HBV DNA levels should be monitored at 12 weeks to determine whether there is treatment failure ($<1 \log^{10}$ IU/mL) and at 24 weeks to categorize virologic suppression, which may be defined as either complete (HBV DNA level <60 IU/mL), partial (HBV DNA 60 to <2000 IU/mL), or inadequate (HBV DNA ≥ 2000 IU/mL).² HBV DNA should be monitored every 3 to 6 months to detect potential resistance to antiviral therapy, which is manifested by persistence of viral DNA (failure to clear HBV DNA) or increasing HBV DNA levels after an initial decline. Increasing HBV DNA levels (viral breakthrough) usually precede biochemical breakthrough (increasing ALT). In cases of HBV resistance, a drug from another class should be added to the original regimen or therapy should be changed altogether to a more potent drug (see Table 2 for management of drug resistance).² The major risk factor for developing antiviral resistance is prior treatment with lower potency drugs (eg, lamivudine or adefovir). As such, resistance may be less of an issue with entecavir and tenofovir, both of which are known to have high potency and high barriers to resistance.

When treating patients, it is also critical to monitor for risk factors that may lead to disease progression and cirrhosis (eg, coinfection with hepatitis C or HIV, presence of core promoter mutations, and severity and frequency of ALT elevations), to screen for HCC (see article by Tarek Hassanein, MD, for more information), and to recognize that patients with certain comorbid complications (Table 3) should be referred to a hepatologist for optimal management.²

HBV MANAGEMENT IN SPECIAL POPULATIONS

PREGNANCY

Despite implementation of immunization programs throughout much of the world, perinatal transmission remains the most common cause of chronic HBV infection in highly endemic areas. Eighty percent to 90% of infants born to HBeAg (+) mothers becoming chronically infected with HBV, so timely immunoprophylaxis is needed to prevent these perina-

tal infections. Because high maternal serum HBV DNA concentrations have been associated with failure of immunoprophylaxis, antiviral therapy should be considered in pregnant women with HBV DNA greater than 108 copies/mL, or in those who already have an HBsAg (+) child. For these patients, treatment during the third trimester with lamivudine, telbivudine, or tenofovir is recommended. Although lamivudine is the only drug from these options with US Food and Drug Administration safety classification of pregnancy category C (the others are classified as pregnancy category B), it has an extensive safety history as a treatment of HIV during pregnancy. When used in the last month of pregnancy, antiviral drugs can prevent mother-to-infant HBV transmission in women with high viral levels. However, use of lamivudine in long-term therapy is limited by the increased risk of resistance, and it may not prevent perinatal transmission of precore mutant HBV.²

In young women with mild disease, treatment of HBV can usually be postponed until after delivery. For women who are immune tolerant (high HBV DNA and normal ALT levels) and plan to become pregnant, a biopsy is recommended. If significant fibrosis is found, a limited course of PEG-IFN therapy may be considered. Women with chronic HBV infection who become pregnant while receiving therapy have several options, including continuing treatment, stopping and restarting therapy after delivery, or switching to an agent that is considered relatively safe in pregnancy (eg, lamivudine). With a recent publication confirming the safety of tenofovir, 2 options seem reasonable. Discontinuing antiviral therapy should be done with extreme caution because it carries the risk of reactivating active liver disease with potentially fatal consequences.²

PATIENTS RECEIVING CHEMOTHERAPY

Reactivation of HBV has been reported in 20% to 50% of HBsAg carriers undergoing immunosuppressive or cytotoxic chemotherapy.³

It is well known that immunosuppressive drugs or chemotherapy may stimulate replication of HBV and precipitate severe flares of HBV infection, leading to hepatic decompensation and even death. Although the risk of HBV reactivation is highest in hematopoietic stem cell or solid organ transplant recipients and in those undergoing chemotherapy for hematologic malignancies, it has been described following almost any

form of immunosuppressive treatment. More specific risk factors for chemotherapy-induced HBV reactivation include high HBV DNA levels prior to chemotherapy induction, use of highly myelosuppressive or glucocorticoid-containing regimens, use of rituximab or antitumor necrosis factor therapies (eg, infliximab), treatment with bone marrow transplant, having a hematologic malignancy, male gender, young age, and infection with precore/core promoter mutations.¹⁵

Table 2. Potential Management of Hepatitis B Antiviral Drug Resistance

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

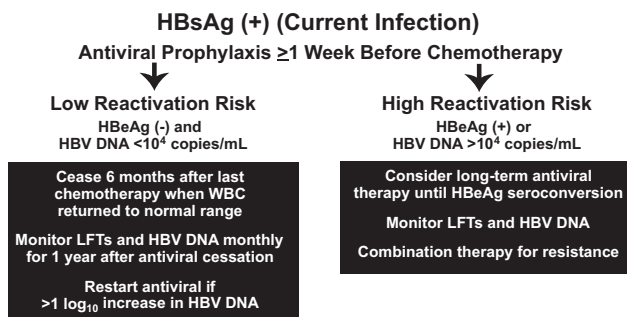
*Tenofovir might be preferred over adefovir as the add-on agent. Reprinted with permission from Keeffe et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.²

Table 3. When to Refer to Tertiary Care/Hepatology

- Cirrhosis and decompensated cirrhosis
- Organ transplantation
- Acute hepatitis B with or without acute liver failure
- Acute reactivation due to immunocompromised state (ie, malignancy or chemotherapy)
- Pregnancy
- Coinfection with HCV, HDV, or HIV
- Chronic renal failure
- High HBV DNA levels (?)
- Presence of HCC
- Family history of liver cancer
- Development of resistance

HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus.

Figure 2. Algorithm for Antiviral Prophylaxis in Chemotherapy and Stem Cell Transplantation



HBsAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; LFT = liver function test; WBC = white blood cell. Reprinted with permission of Blackwell Publishing Ltd from Lubel et al. *Intern Med J.* 2007;37:705-712.¹⁶

All patients undergoing chemotherapy for solid organ or hematologic malignancies (including bone marrow transplantation) should undergo screening for HBV (with serum HBsAg and hepatitis B core antibody) and known HBV carriers who will be undergoing chemotherapy or immunosuppressive therapy should be given prophylactic antiviral treatment. According to guidelines on prevention and management of HBV infection during immunosuppressive therapy, patients who are HBsAg (+) should be given prophylaxis with lamivudine, starting at least 1 week prior to chemotherapy. Lamivudine has been shown in several clinical studies of patients on immunosuppressive therapy to reduce the rate of HBV reactivation, severity of hepatitis flares, and mortality.³ As illustrated in Figure 2, patients considered at low reactivation risk (HBeAg (-) and low HBV DNA) may discontinue lamivudine 6 months after their white blood cell count returns to normal, with monthly liver function tests and HBV DNA monitoring for 1 year.¹⁶ Patients at high risk for reactivation should receive long-term lamivudine therapy, with HBeAg seroconversion as a treatment goal.

CONCLUSIONS

The ultimate goal in treating patients with chronic HBV infection is to prevent the need for transplantation and premature death due to progression of liver disease or HCC. In accomplishing this goal, it is

important to treat patients for the recommended duration, to choose therapy based on the individual's expected tolerance of adverse effects and resistance history, and to consider the ideal treatment end point to be permanent suppression of HBV DNA to undetectable levels and normalization of ALT levels to less than 0.5 times the ULN.

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