Dear Colleague:

Currently approved treatments for chronic infection with hepatitis B virus (HBV) are limited by low rates of sustained response, side effects, and, in some cases, the emergence of drug resistance. Thus, new treatments, characterized by more potent antiviral effects, less toxicity, and minimal or no risk of resistance, are needed. During the last few years, several agents have been developed that have increased potency and reduced potential for resistance, including two recently FDA-approved agents for the treatment of HBV: entecavir and peginterferon alfa-2a. In addition to these, several novel anti-HBV agents recently evaluated in phase II clinical trials, such as tenofovir, clevudine, telbivudine, pradefovir, and valtorcitabine, appear to be promising agents for the treatment of chronic hepatitis B.

While this progress holds promise, the availability of numerous treatment options has given rise to the challenge to keep up-to-date on complex diagnostic and treatment strategies. This Tx Reporter will focus upon current and emerging treatments for chronic hepatitis B in order to help clinicians improve patient outcomes and minimize adverse events and the risk of developing resistance. In addition, treatment strategies appropriate for complex patient populations will also be discussed.

We hope you find this publication informative and that the content will be helpful to your clinical practice.

Sincerely,

Chair

Adrian M. Di Bisceglie, MD, FACP
Professor of Internal Medicine
Chief of Hepatology
Saint Louis University School of Medicine
St. Louis, Missouri

Faculty

Gary L. Davis, MD
Director, Division of Hepatology
Baylor University Medical Center
Medical Director, Liver Transplantation
Baylor Regional Transplant Institute
Dallas, Texas

Robert P. Perrillo, MD
Director, Academic Affairs
Ochsner Clinic Foundation
New Orleans, Louisiana

Marion Peters, MD
Professor of Medicine
Chief of Hepatology Research
University of California, San Francisco
San Francisco, California

Mario Rizzetto, MD
Professor of Gastroenterology
Department of Gastroenterology
University of Torino Medical Center
Torino, Italy
Target Audience
Gastroenterologists and hepatologists who care for patients with hepatitis B infection and patients who are at increased risk for acquiring the infection.

Activity Goal
The goal of this CME/CE activity is to provide gastroenterologists and hepatologists who see patients with hepatitis B infection and patients who are at increased risk for acquiring the infection with state-of-the-art information on current and emerging therapies for the treatment of chronic HBV.

Learning Objectives
• Given the epidemiology and natural history of chronic HBV infection, evaluate the differences between the three clinical phases of chronic HBV to determine potential patient morbidity and mortality.
• Utilizing an understanding of the differences in HBV genotype, select treatment strategies to improve patient morbidity and mortality.
• Using the AASLD treatment guidelines, evaluate current diagnostic and monitoring approaches in chronic HBV patients to determine the stage of disease and implications for treatment.
• Utilizing the best predictors of HBV treatment response, evaluate the efficacy and safety of current and emerging therapies, and formulate treatment strategies to improve patient outcomes and minimize adverse events.
• Synthesizing the research and clinical knowledge to date, develop individualized treatment approaches for the “difficult-to-treat” chronic HBV patient to maximize patient outcomes.

CME Information: Physicians
Statement of Accreditation
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
Projects In Knowledge designates this educational activity for a maximum of 2.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity is planned and implemented as an independent CME activity in accordance with the ACCME Essential Areas and Policies.

CME Information: Physician Assistants
This program has been reviewed and is approved for a maximum of 1 hour of AAPA Category 1 (Preacted) CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of March 1, 2006. Participants may submit the self-assessment at any time during that period.

Robert P. Perrillo, MD, has received grant/research support from Roche Pharmaceuticals, Schering-Plough Corporation, and Vertex Pharmaceuticals Incorporated; is a consultant for Gilead Sciences Inc, GlaxoSmithKline, and Roche Pharmaceuticals; is on the speakers bureau of GlaxoSmithKline; is a member of advisory boards for Gilead Sciences Inc, GlaxoSmithKline, and Roche Pharmaceuticals; and has received honoraria from Gilead Sciences Inc, Roche Pharmaceuticals, and Schering-Plough Corporation.

Marion Peters, MD, has received grant/research support from Gilead Sciences, Inc, and Roche Pharmaceuticals; is a consultant for Bristol-Myers Squibb Company and Roche Pharmaceuticals; is on the speakers bureau of Axcan Pharma, Bristol-Myers Squibb Company, Gilead Sciences, Inc, Roche Pharmaceuticals, and Schering Corporation; and is on the advisory board of Roche Pharmaceuticals.

Mario Rizzetto, MD, is a member of advisory boards for Gilead Sciences Inc, Roche Pharmaceuticals, and Schering-Plough Corporation.

Peer Reviewer has disclosed no significant relationships.

Projects In Knowledge’s staff members have no significant relationships to disclose.

This CME/CE activity will contain a discussion of the unlabeled/unapproved uses of alamivudine, clevudine, emtricitabine, IFN, telbivudine, and tenofovir.

Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge.

This CME/CE activity is provided by Projects In Knowledge solely as an educational service. Specific patient care decisions are the responsibility of the clinician caring for the patient.

Contract for Mutual Responsibility in CME/CE
Projects In Knowledge has developed the contract to demonstrate our commitment to providing the highest quality professional education to clinicians, and to help clinicians set educational goals to challenge and enhance their learning experience.

For more information on the contract, please go to www.projectsinknowledge.com/Contract.html

This independent CME/CE activity is supported by an educational grant from Bristol-Myers Squibb Company.

Copyright © 2006, Projects In Knowledge, Inc. Little Falls, NJ 07424. All rights reserved.
Introduction

The American Association for the Study of Liver Diseases recently issued a press release which called upon Americans to renew their efforts to fight liver disease in the United States. This call to action was based, in part, upon a recent study which revealed an alarmingly high prevalence of hepatitis B infection among Asian Americans in New York City as a result of a mass screening that occurred through April, 2005. Twenty-one percent of the Asians screened in New York were positive for hepatitis B, a prevalence markedly higher than in previous screenings in this country\(^1\) and a rate 50 times higher than the general public.\(^2\) Raising the level of awareness about liver disease among both health professionals and patients, especially among those who are at risk, is critical, yet a new American Liver Foundation Survey\(^3\) assessing public awareness of liver disease found that 80% of US adults erroneously believe that alcohol abuse, not viral hepatitis, is the leading cause of liver disease. More than half of those surveyed did not know that hepatitis B can be transmitted through sexual contact, a lack of awareness which has significant implications for prevention.

**“80% of US adults erroneously believe that alcohol abuse, not viral hepatitis, is the leading cause of liver disease.”**

Fortunately, there has been a dramatic change in the landscape of treatment choices over the past few years. Specifically, two new drugs have been approved by the FDA in 2005 for treatment of HBV infection in addition to the existing therapeutic armamentarium: entecavir and pegylated interferon alfa-2a.

While the introduction of new and effective treatments is cause for optimism, there remain significant challenges to address with respect to the complexities that surround the choice of treatment. Variations in efficacy, adverse reactions, and the risk of resistance all interact to provide a context which can be challenging for physicians as they seek to tailor treatments to provide the best possible outcomes for their patients.

This *Tx Reporter* will help physicians choose treatments that will optimize outcomes and minimize risks for their patients, including those patients who present with comorbid conditions. We will begin with an overview of the epidemiology and natural history of chronic hepatitis B viral infection, and then focus upon current and emerging treatments with an emphasis upon strategies for improving outcomes.

**Epidemiology and Natural History of Chronic HBV**

Chronic hepatitis B virus (HBV) is a major health problem with approximately 350 million persons affected worldwide. The chronicity and progression of disease in those with HBV are related to the age and immune status of the infected patient. For example, those who are infected during infancy or early childhood have a high rate of progression to chronic infection, whereas those who are infected in adulthood have a chronic infection rate of less than 5%.\(^4\) If left untreated, approximately 15% to 25% of chronic hepatitis patients will go on to develop cirrhosis and its complications, including liver failure or hepatocellular carcinoma (HCC).\(^4\)

**“Chronic hepatitis B virus (HBV) is a major health problem with approximately 350 million persons affected worldwide.”**

The worldwide prevalence of hepatitis B varies markedly. Areas such as Asia Minor and sub-Saharan Africa, where maternal to infant transmission is common, have a high prevalence, with a carrier rate of up to 19%. Chronicity is lower in the United States, the Southern Canadian provinces, and many parts of Europe, with a carrier rate of less than 2%.\(^5\)

**“If left untreated, approximately 15% to 25% of chronic hepatitis patients will go on to develop cirrhosis and its complications, including liver failure or hepatocellular carcinoma.”**

Hepatitis B is a highly infectious virus, approximately 100 times more infectious than HIV, and there are more than 2 billion persons worldwide who have been infected or are infected with this virus.\(^6\) Approximately 4 million new cases of hepatitis B are diagnosed per year and about 350 million persons are chronic carriers of this virus. Nearly 75% of chronic carriers are Asian.\(^6\) Twenty-five percent or more of these carriers die from disease-related liver disease, including cirrhosis or HCC and, in all, approximately 1 million deaths per year can be attributed to hepatitis B infection.\(^6\)
While the mortality in the United States due to this disease is declining as a result of mass vaccination efforts, there are still over 70,000 acute cases of hepatitis B each year and approximately 5000 deaths yearly.7 Data from the Centers for Disease Control indicate that the major route of transmission of hepatitis B infection in the United States is sexual, accounting for almost 40% of cases of acute hepatitis B.8

“Approximately 1 million deaths per year can be attributed to hepatitis B infection.”

Three clinical patterns or profiles of chronic HBV infection have been identified (Table 1).9,10 Some patients exhibit each of these profiles in a sequential manner, while others do not. The phase of immune tolerant infection is common in those who are infected at birth. In this phase, subclinical or mild disease exists along with normal ALT levels, despite high levels of virus. A second clinical profile is chronic hepatitis B associated with high replication of HBV, either wild type (HBeAg +) or core, pre-core mutant (HBeAg -), with the latter HBV replication usually fluctuating over the years.

Table 1. Clinical Profiles of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Immune Tolerant “Carrier”</th>
<th>Chronic Hep B (High Replication) (HBeAg + or -)</th>
<th>Chronic Hep B (Low Replication) “Inactive”</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>↑/↑</td>
</tr>
<tr>
<td>HBV DNA (copies/mL)</td>
<td>&gt;10^5</td>
<td>&gt;10^5/10^6</td>
</tr>
<tr>
<td>Histology</td>
<td>Normal/Mild</td>
<td>Active/Active</td>
</tr>
</tbody>
</table>

*Expert opinions vary as to this value.

Active liver disease is also evident histologically. While the hepatitis B antigen (HBeAg) may be present initially, patients may lose HBeAg positivity. A third profile is the low replication or inactive form of chronic hepatitis B. These patients have lost HBeAg as a result of seroconversion to anti-HBe. HBV DNA levels typically fall to <10^5 copies/mL. Hepatitis B surface antigen (HBsAg) persists, but ALT levels and liver histology return to normal.

“Genotype is important to consider since it might influence disease progression and response to therapy.”

There are 8 genotypes of hepatitis B, A through H, which differ in their worldwide geographic distribution (Table 2). Genotype A is most common in the United States and Western Europe, B and C are most common in Asia, and D is more frequently found in the Mediterranean. In the past few years, there has been a significant expansion of knowledge on HBV genotypes and their association with disease progression and response to therapy. Although genotyping is not routinely performed in clinical practice, it is becoming increasingly important because of growing evidence of its correlation with clinical outcomes in chronic HBV infection. Genotype A is most likely to seroconvert from HBeAg positive to HBeAg negative, either spontaneously or in response to treatment, and also appears to be associated with a slower progression of disease. In contrast, genotype C, more common in Asia, appears to be associated with higher levels of replication, and a greater likelihood of developing cirrhosis and HCC.

Interferon is more effective in patients with genotype A than in those with genotype B. Genotype B, in turn,
appears to be more responsive to this therapy than genotype C or D). Lamivudine may be more effective in patients with genotype B than in those with genotype C. Although data are still limited, physicians may want to consider genotyping Asian patients to determine if they are genotype B or C. Since interferon has been reported to be more effective in Asian patients who are genotype B than those who are genotype C, interferon may be a reasonable first choice in these patients, while a nucleos(t)ide analog may be a better choice in Asian patients with genotype C.

Finally, identifying the genotype of patients is important because of its relationship to hepatitis B viral mutations, the most common of which is the pre-core or HBeAg negative mutation of the virus. This is a nucleotide mutation that prevents the expression of HBeAg while viral replication remains unaffected. Thus, while these patients are HBeAg negative, they have active liver disease and viral replication. This clinical situation is restricted to genotypes B, C, D, E, and some F.

**HBV Treatment Challenges**

**Who to Treat**

Chronic HBV patients with active infection and liver disease should be the targets for treatment, whether HBeAg positive or HBeAg negative (Table 3). There is no indication to treat HBsAg positive patients when they are in the immune tolerant or inactive phases of infection since treatment is ineffective. However, it is important to recognize that the phases of the infection are not static and can change: immunotolerant patients can exhibit a break in tolerance characterized by increased ALT levels, or re activate inactive infection to active disease with increased ALT levels and HBV DNA rising above a threshold of 10^4 or 10^5 copies/mL. In particular, HBeAg negative patients can have periodic flares of their disease with prolonged intervals of viral and disease quiescence. Therefore, it is critical to monitor patients to recognize activation of chronic hepatitis B so that treatment can be initiated quickly.

For untreated HBeAg positive patients with HBV DNA ≥10^5 copies/mL and normal ALT levels, ALT levels should be monitored every 3 to 6 months; for untreated inactive HBeAg carriers, ALT levels should be monitored every 6 to 12 months.

Professional guidelines exist to aid clinicians in making treatment decisions, although this process is not always straightforward. The American Association for the Study of Liver Diseases (AASLD) identifies a threshold for treatment of >10^5 HBV DNA copies/mL in both HBeAg positive and HBeAg negative patients (Table 4). In contrast, the US algorithm draws a distinction in treatment thresholds between HBeAg positive (≥10^5 HBV DNA copies/mL) and HBeAg negative (≥10^4 HBV DNA copies/mL) patients. HBeAg negative patients usually have a lower level of HBV DNA, and HBV DNA as well as ALT levels often fluctuate over time in many of these patients.

A biopsy to diagnose cirrhosis is recommended in the US algorithm only. In decompensated cirrhosis, the HBV DNA threshold for initiating treatment is less critical (<10^3 or ≥10^5) and therapy is recommended at lower viral levels. Differences between guidelines also exist with respect to treatment recommendations related to ALT levels. AASLD recommends the initiation of treatment when ALT levels are more than twice the upper limit of normal (normal range, 1–21
units/L), whereas the US algorithm recommends treatment whenever ALT levels rise above the upper limit of normal.

**Treatment Response**

Viral suppression below $10^4$ to $10^7$ copies/mL is considered indicative of remission and is also the threshold below which seroconversion to anti-HBe occurs. While a primary goal of treatment is durable suppression of the virus below the level that causes disease, it is important to recognize that individual variability exists with respect to this level. Generally, HBV DNA ≥ $10^5$ copies/mL is indicative of active disease.

Baseline ALT level is the best predictor of response to all classes of drugs used in the treatment of chronic HBV (Figure 1). In an analysis of four lamivudine-controlled Phase III trials of 805 adults with chronic hepatitis B treated with either lamivudine, a placebo, interferon, or lamivudine plus interferon, the rate of HBeAg loss was highest among patients with pretreatment ALT levels greater than five times the upper limit of normal.17 As ALT levels reflect the extent of the host immune attack to HBV-containing hepatocytes, these findings indicate that the immune response is an important determinant of the response to antiviral therapy.

Concomitantly, several studies have indicated that the magnitude of HBV DNA decline, at least for the first year, does not predict outcome as defined by HBeAg seroconversion or HBeAg loss.18,21

When a patient is receiving treatment for chronic HBV, HBV DNA and ALT levels should be assessed every three months in order to quickly identify the development of resistance. HBV DNA levels will rise anywhere from one to three months before ALT levels increase. When a patient is off treatment, ALT levels can be assessed every 3 to 6 months and more frequently than HBV DNA if cost is a consideration. If ALT levels increase, HBV DNA should then be evaluated.

**HBV Treatment Choices**

**Interferons**

Interferons have immunomodulatory and antiviral actions and suppress HBV replication (Table 5). A limitation to their use is that the immunomodulatory effect varies from patient to patient. Although the effects of interferons on viral replication tend to be more modest, they are more reliable. One of the important advantages of interferon therapy is that it is a finite therapy that can sometimes achieve surface antigen clearance, an important criterion of treatment response. In addition, immunologic benefits in the form of incremental HBeAg loss continue after interferon is withdrawn.22

Several factors contribute to the decision to use interferon therapy, including patient profile and predictors of response.11,23,24 In view of the potentially serious side effects of interferon, ideally patients should be without significant comorbidity. Thus, younger patients are often better suited to receiving this therapy. Patients with genotype A have responded best to interferon treatment; those

**Table 5. Interferon**

- Both immunomodulatory and antiviral actions on HBV replication
- Immunomodulatory actions are variable
- Modest but reliable effect on HBV replication
- HBeAg loss continues after termination of treatment
- Potentially serious side effects

ALT levels should be assessed every three months in order to quickly identify the development of resistance. HBV DNA levels will rise anywhere from one to three months before ALT levels increase. When a patient is off treatment, ALT levels can be
with genotype B and C have also responded, but the rate of the response has been inferior to that observed with genotype A. By contrast, HBeAg negative chronic HBV patients with genotype D have the poorest response to interferon. HBV DNA levels indicate whether a patient is a good candidate for interferon therapy. Analysis of a large phase III study of pegylated interferon has shown that patients have a significantly higher rate of response if they have <10^9 HBV DNA copies/mL. ALT levels are another factor to consider when deciding whether to use interferons. High ALT levels, particularly over five times the upper limit of normal, are indicators of a good response to therapy, irrespective of the type of treatment.

Personal factors such as patient preference may also play a role in choosing interferon therapy. For example, patients receiving interferons must often be evaluated frequently, making adherence to the demands of therapy more difficult. Termination of therapy with interferon differs from the approach used with nucleoside analogs. Nucleos(t)ides are typically given for a period of several months after HBeAg seroconversion occurs.

**Lamivudine**

Lamivudine is a first-generation nucleoside analog (Table 6). While it is a potent treatment modality for chronic HBV, a significant problem with its use is increasing rates of resistance over time. In a long-term study of the safety of lamivudine treatment in patients with chronic HBV, Lok and colleagues reviewed data on 998 patients who were HBeAg positive who received lamivudine for up to 6 years. The proportion of patients with lamivudine-resistant mutations steadily increased from 23% in year 1 to 65% in year 5. Further, during each year of the study, patients with lamivudine-resistant mutations had significantly more hepatitis flares than those without these mutations, leading the authors to conclude that patients with long-standing lamivudine-resistant mutations may experience worsening liver disease. A later study by Colombo and colleagues found that exposure to lamivudine is a prerequisite for the development of entecavir resistance. Given these significant difficulties with the development of resistance, the future role of this medication as a first-line treatment for chronic HBV remains unclear. However, when the course of treatment is finite, for example during pregnancy, in patients on chemotherapy, and when treating acute hepatitis B, lamivudine may still represent a reasonable first-line treatment choice. It should be noted that there is no FDA indication for the treatment of acute HBV.

**Adefovir**

Adefovir is an acyclic nucleotide with a better resistance profile than lamivudine (Table 7). Locarnini and colleagues examined data from five studies to determine the incidence of adeovir resistance mutations after 192 weeks of therapy. At baseline, patients had either wild-type or lamivudine-resistant HBV. The cumulative probability for developing adefovir resistance by four years was 15% for all patients and 18% for patients in adefovir monotherapy trials. Logistic regression analyses of baseline factors identified only higher serum HBV DNA at week 48 as a predictor of adefovir resistance.

"Adefovir is an acyclic nucleotide with a better resistance profile than lamivudine.”

The efficacy of adefovir was evaluated in a placebo controlled, randomized trial of 185 HBeAg negative patients with chronic HBV. Treatment with adefovir resulted in a median decrease in serum HBV DNA of 3.63 log copies/mL at 144 weeks, and HBV DNA levels were less than 1000 copies/mL in 79% of patients at week 144. Similar reductions were observed in ALT levels. In patients who continued to receive adefovir at week 144, ALT normalization was observed in 69%.

While problems with resistance are comparatively low and adefovir has made a difference in the treatment of patients with lamivudine
resistance, there is some potential for nephrotoxicity with adefovir at doses higher than 10 mg and in renally compromised patients. In addition, adefovir is not as potent as other nucleos(t)ides. In a study of 53 patients with high HBV DNA levels and genotypic evidence of lamivudine resistance, patients received either tenofovir for 72 to 130 weeks or adefovir for 60 to 80 weeks.29 Changes in HBV DNA levels were followed for 48 weeks and compared on matched subgroups of five patients each. At week 48, only 44% of patients receiving adefovir had HBV DNA levels below 105 copies/mL in contrast to 100% of patients receiving tenofovir ($P = .001$).

Finally, a recent problem was noted when reactivation of the hepatitis B virus occurred after a treatment switch to adefovir. Van Bommel and Berg reported that of three patients with lamivudine-resistant HBV who were placed on tenofovir and then switched to adefovir, all three virologically relapsed within 4 weeks of the medication switch. The authors suggested that the failure of adefovir to sustain an antiviral response may have occurred due to insufficient dosing of adefovir, variable antiviral effects on HBV DNA decline, or differences in the intracellular metabolism of the 2 drugs.30 Because of the risk of relapse, many clinicians utilize overlapping regimens of 2 nucleos(t)ides when changing from one nucleos(t)ide analog to another.

**Entecavir**

Entecavir is a guanosine nucleoside analog that was licensed in March 2005 (Table 8). In a review of this drug in the treatment of chronic HBV, Rivkin31 found that entecavir is a potent inhibitor of HBV DNA, is not associated with any major adverse effects, and has a good resistance profile, although long-term efficacy and safety studies are still warranted. In the phase II and III clinical trials reviewed, entecavir was more efficacious than lamivudine in both nucleoside-naive and lamivudine-resistant patients. It represents a first-line treatment for patients with chronic HBV when the goal is to achieve a rapid decrease in HBV DNA.

Entecavir had significant histological improvement (72% versus 62%, respectively; $P < .01$), as well as normalization of ALT levels (78% versus 70%, respectively; $P = .0136$) when compared to their lamivudine counterparts. There were no significant differences in HBeAg seroconversion between groups (21%, entecavir versus 18%, lamivudine). Virologic-only responders (HBV DNA < 0.7 MEq/mL but positive for HBeAg) continued into the second year of the study and received blinded treatment up to week 96.32 By 96 weeks of treatment, 80% of patients receiving entecavir versus 39% of patients receiving lamivudine had levels of HBV DNA < 300 copies/mL by polymerase chain reaction (PCR) ($P < .0001$). No evidence of resistance to entecavir emerged through 96 weeks of treatment.

Colono and colleagues33 found that while there was no evidence of emerging resistance in nucleoside-naive HBeAg positive and HBeAg negative patients after two years of entecavir therapy, resistance occurred among lamivudine refractory patients. Virologic rebounds due to resistance were observed in 9% of these patients during the second year of treatment with entecavir. Since there is less chance for resistance, entecavir represents a first-line treatment in patients who will be treated long term to obtain a rapid decrease in HBV DNA.

**Combination Therapy**

While the goal of combination therapy is to increase efficacy and reduce the development of viral resistance, data are limited in support of this strategy to treat chronic hepatitis B. For

---

**Table 8. Entecavir**

- Guanosine nucleoside analog
- Selective inhibitor of HBV replication
- More potent than lamivudine
- Rates of HBeAg seroconversion comparable to other nucleoside analogs
- No resistance at 2 years of treatment in naive patients
- Resistance only in lamivudine-resistant patients
  - 9% at year 2

---

**“Entecavir represents a first-line treatment for patients with chronic HBV when the goal is to achieve a rapid decrease in HBV DNA.”**

A randomized, double-blind trial compared the efficacy and safety of entecavir versus lamivudine in 715 HBeAg positive nucleoside-naive patients receiving treatment for 48 weeks.31 At the end of the interval, a greater proportion of patients receiving entecavir had viral loads of HBV DNA < 400 copies/mL when compared with those receiving lamivudine (69% versus 38%, respectively; $P < .0001$). A greater proportion of patients receiving entecavir had significant histological improvement (72% versus 62%, respectively; $P < .01$), as well as normalization of ALT levels (78% versus 70%, respectively; $P = .0136$) when compared to their lamivudine counterparts. There were no significant differences in HBeAg seroconversion between groups (21%, entecavir versus 18%, lamivudine). Virologic-only responders (HBV DNA < 0.7 MEq/mL but positive for HBeAg) continued into the second year of the study and received blinded treatment up to week 96.32 By 96 weeks of treatment, 80% of patients receiving entecavir versus 39% of patients receiving lamivudine had levels of HBV DNA < 300 copies/mL by polymerase chain reaction (PCR) ($P < .0001$). No evidence of resistance to entecavir emerged through 96 weeks of treatment.

Colono and colleagues33 found that while there was no evidence of emerging resistance in nucleoside-naive HBeAg positive and HBeAg negative patients after two years of entecavir therapy, resistance occurred among lamivudine refractory patients. Virologic rebounds due to resistance were observed in 9% of these patients during the second year of treatment with entecavir. Since there is less chance for resistance, entecavir represents a first-line treatment in patients who will be treated long term to obtain a rapid decrease in HBV DNA.

---

**Combination Therapy**

While the goal of combination therapy is to increase efficacy and reduce the development of viral resistance, data are limited in support of this strategy to treat chronic hepatitis B. For
example, a 1-year randomized, double-blind, multicenter trial was undertaken to evaluate the efficacy and safety of telbivudine alone, lamivudine alone, and the two in combination in hepatitis B e antigen-positive adults with compensated chronic hepatitis B. Results at week 52 showed that telbivudine monotherapy caused a significantly greater mean reduction in HBV DNA levels, clearance of PCR reaction-detectable HBV DNA, and normalization of ALT levels compared with lamivudine monotherapy. Combination treatment was not better than telbivudine alone. Since empirical support is lacking, it is not surprising that disagreement exists about what combinations of drugs are most effective in reducing the virus and limiting the frequency of resistance, as well as which patients may be the best candidates for therapy. The optimal drugs to combine would have different sites of action on HBV DNA replication, a potent antiviral effect, a good safety profile, and would induce a sustained response with a finite duration of therapy.

### Special Patient Populations

#### Cirrhosis

The main goal of treatment in patients with cirrhosis is to decrease HBV DNA levels to improve survival and decrease the risk of cancer and decompensation, regardless of ALT levels. Disagreement exists over whether to treat patients with compensated cirrhosis who have HBV DNA levels less than $10^4$ copies/mL. A conservative approach may indicate treatment with a combination of nucleos(t)ide analogs in order to reduce the chance of resistance as these patients will not tolerate a flare associated with the development of resistance to a single drug. When patients are decompensated, a further goal is not only to reduce the viral load, but to achieve this reduction as quickly as possible to halt ongoing liver disease.

Interferon is contraindicated in patients with chronic HBV infection with decompensated cirrhosis because of the risk of further decompensation associated with interferon-related flares of hepatitis. It is also contraindicated in cirrhotic patients who are decompensated. Adefovir, lamivudine or entecavir are drugs of first choice for these patients.

In addition to a risk of hepatic decompensation, patients with cirrhosis due to HBV also deserve special attention because of their substantially increased risk of hepatocellular carcinoma (HCC). This is illustrated by data from the Beasley study in Taiwan in which more than 22,000 Chinese carriers of HBsAg were observed longitudinally. Compared with uninfected controls, they had a substantially greater rate of HCC. However, the risk of HCC among HBsAg positive subjects with clinical evidence of cirrhosis was almost five times as high as that of HBsAg carriers without clinical cirrhosis.

Finally, while the risk of complications diminishes for cirrhotic patients when they enter the inactive phase of chronic HBV, complications and the risk of developing HCC can still arise. Therefore, monitoring must be ongoing, even when patients are in the inactive phase of the disease.

#### Coinfected Patients

There is a delicate balance between the chronic HBV patient’s immune response and liver damage. If the immune system is severely compromised, there is no liver damage. For example, HIV positive patients with no CD4 counts often have minimal or no liver damage. However, when the immune system is reactivated, virally infected hepatocytes increase and liver damage is induced. Thus, when a chronic HBV patient coinfected with HIV is being treated for HIV, an anti-hepatitis B drug must always be included in the antiretroviral therapy.

### Table 9. Which Drugs Are Effective for HBV and/or HIV?

<table>
<thead>
<tr>
<th>Drug</th>
<th>HBV Wild Type</th>
<th>HBV YMDD</th>
<th>HIV Effective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>S</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>Adefovir</td>
<td>S</td>
<td>S</td>
<td>No</td>
</tr>
<tr>
<td>Entecavir</td>
<td>S</td>
<td>↓S</td>
<td>No</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>S</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>S</td>
<td>R</td>
<td>No</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>S</td>
<td>S</td>
<td>Yes</td>
</tr>
</tbody>
</table>

S = sensitive; R = resistant.

---

“When a chronic HBV patient coinfected with HIV is being treated for HIV, an anti-hepatitis B drug must always be included in the antiretroviral therapy.”

---
will treat only HBV (Table 9, see page 9). However, the presence of drug resistant virus (HIV or HBV) will impact the selection of drugs for both infections.

HBV patients who are coinfected with HIV must have their ALT and HBV DNA levels monitored every 3 months. Ongoing surveillance for HCC should also be performed in this patient population.

**Chemotherapy**

All patients undergoing chemotherapy must be tested for hepatitis B, including surface antigen and total core antibody, in order to determine if they have active disease. HBV may reactivate under the pressure of aggressive chemotherapy, especially when patients are receiving prednisone. Patients with active disease—ie, those who are HBeAg positive, with high HBV DNA levels and a high ALT—should be treated for hepatitis B.

Patients with inactive disease, characterized by a normal ALT and low levels of HBV DNA, have less chance of reactivating under the pressure of immunosuppression related to chemotherapy. Nevertheless, treatment should be initiated. AASLD practice guidelines recommend prophylactic antiviral therapy with lamivudine at the onset of chemotherapy, with continued treatment for six months after the cessation of chemotherapy. Since the publication of these guidelines, other therapies, such as entecavir, have become available that may also be effective in these patients.

When patients are surface antigen negative and core antibody positive, they have a low likelihood of reactivating and developing active hepatitis B. In these cases, patients can be monitored closely to determine if and when treatment should be initiated. Similarly, when patients have HBeAg seroconverted, close monitoring is indicated.

**Dialysis**

Dialysis patients with chronic HBV infection are difficult to manage. These patients have very poor immune responses and are unlikely to HBeAg seroconvert. Often, the hepatitis B infection itself can complicate the evaluation for renal transplantation. Interferon is usually ineffective in patients on dialysis and not well tolerated. Therefore, nucleos(t)ides are used in patients on dialysis or with end stage renal disease. However, since these drugs are excreted primarily through the kidney, they must be dose adjusted in this patient population. Long-term maintenance therapy is common because immune clearance is not a realistic objective.

**Pregnancy**

All pregnant women in the United States should be tested for hepatitis B so that the neonate can receive vaccine and hepatitis B immune globulin (HBIG) at birth if the mother is HBsAg positive. Women can reactivate HBV during pregnancy and, if active disease is present, treatment can be initiated with lamivudine, which is safe in pregnancy. However, if a pregnant woman is immunotolerant with a high viral load of >10^6 copies/mL and a normal ALT level, treatment in the third trimester should be considered in order to decrease the risk of vertical transmission to the fetus.

The efficacy and safety of a finite period of treatment with lamivudine therapy in pregnant women infected with HBV were supported in a study by van Zonneveld et al. Eight mothers were treated with 150 mg of lamivudine daily during the last month of pregnancy and their children were evaluated at birth and followed for 12 months after delivery. When compared to 24 children born to untreated HBsAg positive mothers, the eight children in the lamivudine group were less likely to be HBsAg and HBV DNA positive at 12 months (28% versus 12.5%, respectively). However, large controlled trials are still needed to support these findings.

**Summary**

The focus of this *Tx Reporter* has been the presentation of current and emerging treatments for chronic hepatitis B in order to help clinicians improve patient outcomes and minimize adverse events and the risk of developing resistance. The complexities of monitoring and treating HBV are many, not the least of which is the continually changing face of the disease itself. However, progress in the development of therapies for HBV offers clinicians new strategies for the effective treatment of this virus and the prevention of its devastating consequences.

Several patient populations with chronic hepatitis B present unique challenges to the clinician. Complex patients require highly individualized care, including careful evaluation in order to select the appropriate course of treatment. Ongoing interaction must occur between involved specialties such as gastroenterology, hepatology, infectious diseases, immunology, oncology, renal, and obstetrics. Further, these patients often require very careful and frequent monitoring over an extended period of time. With vigilant monitoring and the timely initiation of therapy, these patients can achieve improved outcomes.
References


32. Gish R, Chang TT, De Man RA, et al. Entecavir results in substantial virologic and biochemical improvement and HbeAg seroconversion through 96 weeks of treatment in HbeAg(+) chronic hepatitis B patients (Study ETV-022). Hepatology. 2005;42(suppl 1):267A.


