Drug Therapy

Hepatitis B Virus Infection
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REPORTS OF SUCCESSFUL ANTIVIRAL THERAPY FOR CHRONIC HEPATITS B virus (HBV) infection appeared three decades ago, and during the past decade, progress has accelerated dramatically. Along with progress, however, has come complexity. So much more is known now than at the dawn of the antiviral era about the protean clinical expressions of HBV infection that determining whom, when, and how to treat has become progressively more challenging.

Virologic and Epidemiologic Factors and Natural History

HBV, a DNA virus transmitted percutaneously, sexually, and perinatally, affects 1.25 million persons in the United States and 350 to 400 million persons worldwide. HBV infection accounts annually for 4000 to 5500 deaths in the United States and 1 million deaths worldwide from cirrhosis, liver failure, and hepatocellular carcinoma.

Viral proteins of clinical importance include the envelope protein, hepatitis B surface antigen (HBsAg); a structural nucleocapsid core protein, hepatitis B core antigen (HBcAg); and a soluble nucleocapsid protein, hepatitis B e antigen (HBeAg). Serum HBsAg is a marker of HBV infection, and antibodies against HBsAg signify recovery. A serum marker of active viral replication, HBeAg, is accompanied by serum levels of HBV DNA that are 100,000 to 1 million IU per milliliter or higher. HBV relies on a retroviral replication strategy (reverse transcription from RNA to DNA), and eradication of HBV infection is rendered difficult because stable, long-enduring, covalently closed circular DNA (cccDNA) becomes established in hepatocyte nuclei and HBV DNA becomes integrated into the host genome (Fig. 1).

Progression from acute to chronic HBV infection is influenced by the patient’s age at acquisition of the virus; age is also related to a dichotomy in the clinical expression of HBV infection between high-prevalence (e.g., Asian) and low-prevalence (e.g., Western) countries (Fig. 2). In the Far East, where HBV infection is acquired perinatally, the immune system does not recognize a difference between the virus and the host, and high-level immunologic tolerance ensues. The cellular immune responses to hepatocyte-membrane HBV proteins that are associated with acute hepatitis do not occur, and chronic, usually lifelong infection is established in more than 90% of persons who are infected. In contrast, in the West, most acute HBV infections occur during adolescence and early adulthood because of behaviors and environments that favor the transmission of bloodborne infections, such as sexual activity, injection-drug use, and occupational exposure. In immunocompetent adults, a strong cellular immune response to “foreign” HBV proteins expressed by hepatocytes results in clinically apparent acute hepatitis, which, in all but approximately 1% of persons infected, affects clearance of the infection.

Immunologic tolerance to HBV established during perinatal infection is profound and lifelong, but not complete; a low level of liver injury occurs and accounts for
up to a 40% lifetime risk of death from liver disease among men.\(^9\) This risk is lower among women.\(^9\) A so-called immune-tolerant phase occurs in the early decades of life, with negligible HBV-associated liver injury despite high-level HBV replication. An immune-clearance phase occurs in the later decades of life with active liver disease. This categorization of phases reflects relatively higher immunologic tolerance early and relatively lower tolerance later in the natural history of chronic HBV infection acquired early in life.\(^5,6,10\) Such categorization, however, does not explain the presence of substantial liver injury and fibrosis during the apparent immune-tolerant period in some
patients or the presence of necroinflammatory quiescence during the immune-clearance phase later in the course of chronic HBV infection.

The HBeAg status distinguishes two additional categories of chronic HBV infection. HBeAg-reactive chronic HBV infection is accompanied by high-level HBV replication, and spontaneous seroconversion from HBeAg-positive to antibody (anti-HBe)-positive infection coincides with a reduction in HBV replication and clinical improvement. HBeAg-negative chronic HBV infection, in which precore or core-promoter gene mutations preclude or reduce the synthesis of HBeAg, accounts for an increasing proportion of cases. Patients with HBeAg-negative chronic HBV infection tend to have progressive liver injury, fluctuating alanine aminotransferase (ALT) activity, and lower levels of HBV DNA than patients with HBeAg-reactive HBV infection; however, they cannot have treatment-induced HBeAg seroconversion, a durable response that may permit the discontinuation of antiviral therapy.

Eight HBV genotypes — and differences in clinical outcome according to genotype — are recognized. For example, patients with genotype A are more likely to undergo interferon-induced HBeAg seroconversion; HBeAg seroconversion and slower disease progression are more frequent in patients with genotype B than in patients with genotype C. These differences, however, are not sufficiently established to guide management.

The progression of liver disease in HBV infection is fostered by active virus replication, reflected by the presence in serum of an HBV DNA level above a threshold of approximately 1000 to 10,000 IU per milliliter. Persons with a serum HBV DNA level below 1000 IU per milliliter and a normal ALT level consistently are considered to be inactive carriers with a low risk of clinical progression, although, rarely, reactivation can occur spontaneously or with immunosuppression. Although perinatal infection can result in high-level HBV replication without substantial liver injury in the early decades of life, ultimately the risk of progression to cirrhosis and hepatocellular carcinoma is proportional to the level of HBV DNA maintained persistently over time.

Goals of Antiviral Therapy

Because clinical and histologic improvement accompanies reductions in HBV replication, interventions that reduce HBV replication are expected...
to limit progressive liver disease and improve the natural history of chronic HBV infection. Practically, however, serious outcomes of HBV infection evolve over decades, whereas clinical trials of antiviral therapy are limited to 1 to 2 years and, rarely, up to 5 years. Therefore, surrogate end points that are achievable during time-limited clinical trials are used. These end points are serologic (i.e., HBeAg loss or seroconversion, usually reflecting a transition to inactive HBV carriage, and, more rarely, HBsAg loss or seroconversion, representing a transition to inactive HBV carriage, and, more rarely, HBsAg loss or seroconversion, usually reflecting serologic recovery), virologic (i.e., a log\(_{10}\) reduction in the HBV DNA level or suppression of HBV DNA to an undetectable level [<10 to 100 IU per milliliter]), biochemical (i.e., normalization of the serum ALT level), and histologic (i.e., improvement in the necroinflammatory grade and stage of fibrosis). A course of antiviral therapy may lead to responses that are sustained after treatment withdrawal; more commonly, therapy must be continued to maintain responses achieved during therapy.

**Antiviral Drugs**

Seven drugs are licensed in the United States for the treatment of HBV infection: interferon alfa\(_{20-29}\), pegylated interferon alfa-2a\(_{30,31}\), lamivudine\(_{32-36}\), adefovir\(_{37-41}\), entecavir\(_{42-46}\), telbivudine\(_{47-49}\), and tenofovir\(_{50,51}\) (Tables 1 and 2).\(_{5,6,52}\) The use of interferon, which requires injections daily or thrice weekly, has been supplanted by long-acting pegylated interferon, which is injected once weekly.

As shown in Tables 1 and 2, treatment for 1 year generally results in the reduction of serum HBV DNA levels by 3.5 to 6.9 log\(_{10}\), a level of serum HBV DNA that is undetectable by polymerase chain reaction in 13 to 95% of patients, normalization of the ALT level in 38 to 79% of patients, histologic improvement in 38 to 74% of patients, and HBeAg seroconversion in 12 to 27% of patients; drugs that suppress HBV DNA more profoundly often achieve clinical end points (except perhaps HBeAg seroconversion). Among the oral agents, which differ in resistance profile, the nucleotide analogues adefovir and tenofovir are not cross-resistant with lamivudine, telbivudine, or entecavir. Adefovir resistance is negligible during the first year of therapy but approaches 30% by the end of 4 years. Adefovir is very effective in lamivudine-resistant HBV infection.\(_{37-40,53-55}\) Limiting its appeal among the available drugs, adefovir is the least potent, the slowest to suppress HBV DNA levels, the least likely to induce HBeAg seroconversion, and the most likely to result in “primary nonresponse” (i.e., failure to achieve a reduction in the HBV DNA level of 2 log\(_{10}\) in 20 to 50% of patients).\(_{56}\)

Consolidation treatment for 6 to 12 months or more after HBeAg seroconversion achieves a durable response in approximately 80% of HBeAg-positive patients who have received oral agents,\(_{57-59}\) whereas all but a small minority of HBeAg-negative patients usually have a relapse after therapy. Because responses are not always durable, careful post-treatment monitoring is required to identify relapse (especially rare, severe, and sometimes fatal post-treatment flares in patients with cirrhosis) and to reinstitute therapy. Thus, nearly all HBeAg-negative patients and approximately 80% of HBeAg-positive patients who do not undergo HBeAg seroconversion should continue nucleoside or nucleotide therapy after the first year; in the absence of resistance, such therapy generally maintains clinical effectiveness.\(_{39,40,45,61-63}\)

Successful antiviral therapy retards hepatic fibrosis,\(_{33,37,38,64,65}\) even reverses cirrhosis,\(_{66,67}\) and improves survival.\(_{68-70}\) Unlike pegylated interferon, oral agents are effective in patients who previously did not have a response to interferon\(_{33,35,37,42,44}\) can be used safely and effectively as salvage therapy in patients with hepatic decompensation (delaying or averting liver transplantation),\(_{71-74}\) and, in patients with advanced fibrosis and cirrhosis, may prevent hepatic decompensation.\(_{75}\) Thus, the introduction of oral nucleoside and nucleotide analogues has been lifesaving in HBV infection, paralleling a 30% reduction (from 586 patients in 2000 to 406 patients in 2006) in the number of patients listed for liver transplantation annually in the United States.\(_{76}\)

The side effects of pegylated interferon include flulike symptoms, marrow suppression, depression and anxiety, and autoimmune disorders, especially autoimmune thyroiditis; close medical supervision and laboratory monitoring are required. Most oral agents have an acceptable side-effect profile even after extended use.\(_{39,40,45,77}\) But because adefovir and tenofovir may cause nephrotoxic effects, periodic monitoring of renal function during nucleotide therapy is advisable.\(_{39,40}\)

In preclinical rodent-toxicology studies, doses of entecavir that were 30 to 40 times higher than those that were used in humans were associated with lung, brain, and liver tumors, which have not been observed in higher species (e.g., rabbits and...
<table>
<thead>
<tr>
<th>Variable</th>
<th>Pegylated Interferon Alfa-2a (Pegasys)†</th>
<th>Lamivudine (Epivir)</th>
<th>Adefovir (Hepsera)</th>
<th>Entecavir (Baraclude)</th>
<th>Telbivudine (Tyzeka)</th>
<th>Tenofovir (Viread)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose</td>
<td>180 µg/wk</td>
<td>100 mg/day‡</td>
<td>10 mg/day‡</td>
<td>0.5 mg/day‡</td>
<td>600 mg/day‡</td>
<td>600 mg/day‡</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>— wk§</td>
<td>48</td>
<td>48 to ≥52</td>
<td>≥48</td>
<td>≥52</td>
<td>≥48</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Well tolerated, but creating monitoring advisable</td>
<td>Well tolerated</td>
<td>Well tolerated, but creating monitoring advisable</td>
<td>Well tolerated</td>
<td>Well tolerated, but creating monitoring advisable</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>HBeAg seroconversion — %‡‡</td>
<td>At 1 yr 27 (32 at 72 wk)</td>
<td>16–21</td>
<td>12</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>At &gt;1 Yr</td>
<td>At 1 yr 26 (32 at 72 wk)</td>
<td>16–21</td>
<td>22</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Serum HBV DNA reduc. in log_{10} copies/ml at 1 yr</td>
<td>25</td>
<td>5.5</td>
<td>3.5</td>
<td>13–21</td>
<td>48–61</td>
<td>48–61</td>
</tr>
<tr>
<td>ALT normalization at end of 1 yr — %</td>
<td>—</td>
<td>NA</td>
<td>72</td>
<td>72</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>Virologic response after 1 yr</td>
<td>None</td>
<td>3</td>
<td>1</td>
<td>&lt;1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Approximate cost for 1 yr of treatment — $§§</td>
<td>18,000</td>
<td>2,500</td>
<td>6,500</td>
<td>8,700</td>
<td>6,000</td>
<td>6,000</td>
</tr>
</tbody>
</table>

* Data were derived from assessment of these drugs versus placebo or versus an active control or in registration clinical trials; in most cases, these comparisons were not based on head-to-head testing of the different drugs. In addition, the sensitivity and dynamic range of virologic assays differed across trials, as did definitions of and criteria for drug resistance. ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; NA, not applicable.

† Standard interferon alfa is also an approved therapy for chronic HBV infection, but unlike pegylated interferon, which is administered subcutaneously, standard interferon is administered 3 times a week. The dose should be adjusted downward for patients with reduced creatinine clearance, per the manufacturer’s recommendation. Recommendations for weight-based dosing of pegylated interferon alfa-2b are found in the product brochure.

‡ The dose should be adjusted downward for patients with reduced creatinine clearance, per the manufacturer’s recommendation. Recommendations for weight-based dosing of pegylated interferon alfa-2b are found in the product brochure.

§§ The costs of therapy were derived from Hoofnagle et al. 6

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Telbivudine, too, appears to cause few major toxic side effects, although grade 3 and 4 elevations in levels of creatine kinase were more common in patients treated with telbivudine than in patients treated with lamivudine after 2 years of therapy, and peripheral neuropathy has been attributed to telbivudine.

Treatment with pegylated interferon for 1 year is more likely to result in HBeAg seroconversion than is treatment with an oral agent for 1 year; however, oral agents are usually administered for more than 1 year and achieve similar rates of HBeAg seroconversion (approximately 30%) by the end of 2 years, approaching approximately 50% at 5 years. Similarly, earlier studies suggested that rates of HBsAg seroconversion at 1 year are higher for interferon-based therapy than for oral agents. However, rates of HBsAg loss are similar between pegylated interferon and some of the newer, more potent oral agents (Tables 1 and 2).

Two other oral agents that appear to be efficacious against HBV but are not yet approved by the Food and Drug Administration are emtricitabine and clevudine. Emtricitabine, which is similar in structure, efficacy, and resistance profile to lamivudine, appears to confer no advantage over lamivudine. Clevudine is distinguished from other oral agents by its sustained suppression of HBV DNA.
Resistance does not appear to emerge during pegylated interferon therapy. L-nucleosides (e.g., lamivudine and telbivudine) are associated with the emergence of mutations in the YMDD motif (tyrosine, methionine, aspartate, aspartate) of HBV DNA polymerase domain C and with upstream compensatory mutations in polymerase domains A and B that, collectively, reduce treatment efficacy. The nucleotide analogues (adefovir and tenofovir) are associated with mutations in polymerase domains B and D. Although resistance to lamivudine is sufficiently high to limit its clinical impact, resistance to the cyclopentyl guanine analogue entecavir and tenofovir remains low (Tables 1 and 2). Ultimately, drug resistance reduces drug effectiveness and may precipitate hepatic decompensation in patients with advanced cirrhosis and after liver transplantation. In addition, because of cross-resistance between several of the oral agents, the emergence of resistance to one drug (e.g., lamivudine) eliminates the option for subsequent treatment with others (e.g., telbivudine and entecavir [see below]). Because of 1-to-2-year treatment-emergent resistance, telfibuvudine has not been widely used for the treatment of chronic HBV infection. The nucleotides are effective in nucleoside resistance and vice versa. Entecavir, at a dose of 1 mg, is approved for lamivudine-resistant HBV; however, entecavir resistance emerges in 7% of patients at the end of year 1, in 16% of patients at the end of year 2, in 35% of patients at the end of year 3, and in 43% of patients at the end of year 4. Specialized assays are available to detect these mutations. However, the emergence of resistance can usually be detected by an increase in HBV DNA of greater than 2 log10 after an initial virologic response (in the absence of nonadherence, which accounts for breakthrough in 30% of patients treated in clinical trials), especially when accompanied by an elevation in the ALT level. More detailed overviews of antiviral resistance in HBV infection appear elsewhere.

Factors that are most predictive of a response include a high ALT level, a low HBV DNA level, and mild-to-moderate histologic activity and stage. The genotype is associated with higher frequencies of spontaneous (B>C) and pegylated interferon alfa-2b–related (A>B>C>D) HBeAg and HBsAg seroconversion, but it does not correlate with the degree of HBV DNA suppression associated with the oral agent. In clinical trials of oral agents, numbers of events were too small to determine the influence of the genotype on HBeAg seroconversion. The rapidity and profundity of HBV DNA suppression during oral-agent therapy is predictive of the virologic, serologic, biochemical, and histologic benefit at the end of 1 year of therapy. Three oral agents have low genetic barriers to resistance — lamivudine, telbivudine, and, to a lesser degree, adefovir. In lamivudine and telbivudine, the level of residual HBV DNA at the end of the first half-year of therapy is inversely proportional to the frequency of drug resistance by the end of the year of therapy. In adefovir, the level of residual DNA at the end of a full year is inversely proportional to the frequency of drug resistance by the end of the second year. Other factors favoring resistance to lamivudine, telbivudine, and adefovir include high baseline HBV DNA and treatment of long duration.

Combinations of available antiviral drugs for HBV infection in patients who have not received treatment do not increase efficacy. Although combinations of pegylated interferon and lamivudine yielded a reduction in HBV DNA of an extra 1 to 2 log10 during therapy, the combination did not result in a durable post-therapy benefit. Similarly, telbivudine and lamivudine combined did not achieve additional antiviral activity over that of telbivudine alone. Combination therapy with agents of differing resistance profiles should limit the emergence of resistance; however, resistance is so negligible during the early years of treatment with entecavir or tenofovir that demonstrating the superiority of preemptive combination therapy over initial monotherapy will be challenging. Indeed, adding a second, complementary drug after the emergence of resistance has been a very difficult task.
successful strategy. Because of the lack of data to provide support for the efficacy of combination therapy over monotherapy in patients who have not received treatment, current treatment guidelines do not recommend combination therapy except for patients in whom drug resistance can precipitate or aggravate hepatic failure, as in decompensated cirrhosis or after liver transplantation. Among patients with drug-resistant HBV who have received treatment, available data provide support for adding, rather than switching to, a second drug with a different resistance profile.

**HIV and HBV Coinfection**

Antiviral therapy for patients with human immunodeficiency virus (HIV) and HBV coinfection has been reviewed recently in the *Journal.* In such patients, durable responses are rare, and indefinite but continuing therapy is usually required. Many of the drugs for HBV infection are effective against HIV, and HIV and HBV resistance to monotherapy with these drugs emerges rapidly. Thus, monotherapy with most of the approved drugs for HBV infection should not be used in HIV and HBV coinfection. In patients with coinfection requiring treatment for HIV or for both HIV and HBV infection, the use of two HBV drugs is recommended. For patients with coinfection who require therapy for HBV but not HIV infection, the antiviral agent should have little or no activity against HIV; however, except for interferon, the available agents are effective against HIV (i.e., lamivudine, entecavir, tenofovir, and emtricitabine) or, theoretically, can promote HIV mutations with cross-resistance to the drugs (i.e., adefovir and telbivudine). Therefore, simultaneous combination antiretroviral therapy is advisable.

**Indications for Antiviral Therapy**

Recommendations for antiviral therapy in patients with chronic HBV infection have been issued by several professional societies and by a group of U.S. hepatologists supported by an unrestricted grant from a pharmaceutical company. The most updated, authoritative, and influential of these recommendations is the practice guideline of the American Association for the Study of Liver Diseases (Table 3).

For HBeAg-reactive chronic HBV infection, antiviral therapy is indicated for patients with an ALT level that is more than two times the upper limit of the normal range and HBV DNA that is greater than 20,000 IU per milliliter; patients with an elevated level of ALT are more likely to have potentially durable HBeAg, biochemical, and histologic responses. Without antiviral therapy, fibrosis progresses in approximately one quarter of such patients followed for 1 year. The indication for therapy is so clear-cut that a pre-treatment liver biopsy is optional, and therapy should be instituted urgently in patients with jaundice or other evidence of hepatic decompensation. For HBeAg-positive patients with an HBV DNA level that is greater than 20,000 IU per milliliter but an ALT level that is two times the upper limit of the normal range or less (a pattern common among young Asian patients with perinatally acquired infection), progression is limited during the early decades when high HBV DNA levels are accompanied by biochemical quiescence, the baseline histologic grade and stage tend to be low, and ALT levels are already normal or near normal. Although controversy surrounds the treatment of such patients, the opportunity for biochemical and HBeAg serologic responses in these patients is so low that committing them to antiviral therapy rarely achieves any near-term clinical benefit; clinical monitoring should suffice to identify the emergence of active liver disease in time to intervene therapeutically. Therefore, antiviral therapy is not recommended routinely in these patients unless they have risk factors for progression (i.e., they are older than 40 years of age, they have a family history of hepatocellular carcinoma, or they have an ALT level in the high-normal range [up to two times the upper limit of the normal range]). In these circumstances, liver biopsy should be considered and treatment should be initiated for moderate-to-severe necroinflammatory activity or fibrosis.

Patients with HBeAg-negative chronic HBV infection, an ALT level that is more than two times the upper limit of the normal range, and an HBV DNA level that is more than 20,000 IU per milliliter are candidates for antiviral therapy; liver biopsy is optional. If the ALT level is persistently one to two times the upper limit of the normal range or less and the HBV DNA level is greater than 2000 IU per milliliter, antiviral therapy is not recommended routinely; a liver biopsy should
Guidelines are from the American Association for the Study of Liver Diseases.

Interferon and pegylated interferon are contraindicated in decompensated cirrhosis. Because the risk of hepatic deterioration is high when drug-resistant HBV occurs in patients with decompensated cirrhosis, a regimen with a high barrier to resistance — either combination nucleoside (lamivudine and telbivudine) and nucleotide (adefovir or tenofovir) or entecavir monotherapy — is recommended. Future guidelines are likely to favor tenofovir over adefovir. The drafting of this practice guideline was assigned to primary authors by the practice guidelines committee of the association after approval by the governing board. Before publication, the document was subjected to the rigorous review and approval process of the practice guidelines committee of the association. Of the guidelines issued since 2006, this guideline is the only one in which every individual recommendation was subjected to accepted quality-of-evidence hierarchical coding, lending even more rigor and authority to the document. All HBV DNA levels are given as IU per milliliter, the international, universal standard adopted by the World Health Organization to reduce interlaboratory and intertrial differences in the measurement of HBV DNA. In earlier literature and published guidelines, HBV DNA levels are given in copies per milliliter. Because the conversion factor between international units (IU) per milliliter and copies per milliliter is approximately 5.6 (1 IU per milliliter is approximately 5.6 copies per milliliter), treatment thresholds in copies per milliliter are five times higher than international units per milliliter. ALT denotes alanine aminotransferase, HBeAg hepatitis B e antigen, and ULN the upper limit of the normal range.

\[ 1 IU/ml \times ULN \]

be considered and treatment should be advised for moderate-to-severe necroinflammatory activity or fibrosis. Antiviral therapy is not indicated for inactive HBV carriers (i.e., persons with a persistently normal ALT level and an HBV DNA level that is ≤2000 IU per milliliter). Conversion to this status is the clinical end point reached in most successfully treated patients. However, inactive carriers, like other patients with chronic HBV infection, can have severe HBV reactivation during withdrawal of immunosuppressive therapy; thus, preemptive treatment with a nucleoside or nucleotide analogue is recommended before the initiation of immunosuppressive or cytotoxic chemotherapy.\(^{108,109}\)

<table>
<thead>
<tr>
<th>HBeAg Status</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Potential First-Line Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>&gt;20,000</td>
<td>≤2</td>
<td>Do not treat (low efficacy of current therapy)</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;20,000</td>
<td>&gt;2</td>
<td>Treat with interferon, pegylated interferon, adefovir (Hepsera), or entecavir (Baracide)†</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;20,000</td>
<td>&gt;2</td>
<td>Treat with interferon, pegylated interferon, adefovir, or entecavir†</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt;2000</td>
<td>1 to &gt;2</td>
<td>Consider liver biopsy to help in treatment decision</td>
</tr>
<tr>
<td>Negative</td>
<td>≤2000</td>
<td>≤1</td>
<td>Observe</td>
</tr>
<tr>
<td>Positive or negative</td>
<td>Approximately ≥10 to 100</td>
<td>Cirrhosis with ≤1 to &gt;2</td>
<td>If liver function compensated with DNA &gt;2000 IU/ml, treat with adefovir or entecavir†; if DNA &lt;2000 IU/ml, treat if the ALT level is elevated; if decompensated, treat with lamivudine (Epivir) or telbivudine (Tyzeka) plus adefovir, or entecavir†; coordinate with liver-transplantation center</td>
</tr>
<tr>
<td>Positive or negative</td>
<td>Approximately &lt;10 to 100</td>
<td>Cirrhosis with ≤1 to &gt;2</td>
<td>If compensated, observe; if decompensated, refer for liver transplantation</td>
</tr>
</tbody>
</table>

\( \text{Positive or negative Approximately } \text{ <10 to 100 } \text{ Cirrhosis with } \text{ ≤1 to >2 } \text{ If compensated, observe; if decompensated, refer for liver transplantation} \)
After such consolidation therapy, the durability of sustained responses can exceed 80%. In HBeAg-negative chronic HBV infection, the opportunity for HBeAg responses is absent; although sustained virologic responses occur in a small proportion of patients, indefinite therapy is required to maintain clinical benefit.

Patients with compensated cirrhosis and a detectable level of HBV DNA, independent of HBeAg status, are candidates for antiviral therapy to prevent progression; if the level of HBV DNA is greater than 2000 IU per milliliter, therapy is recommended, but if the level of HBV DNA is less than 2000 IU per milliliter, treatment is reserved for patients with an elevated level of ALT. Patients with decompensated cirrhosis and a detectable level of HBV DNA should be treated in coordination with a liver transplantation center. For patients with cirrhosis who have an undetectable level of HBV DNA, observation without therapy is recommended; patients with decompensated cirrhosis should be referred to a transplantation center.

The therapy for patients with a reduction in the HBV DNA level of less than 2 log10 within 6 months after the initiation of treatment (a “primary nonresponse”) should be switched to an alternative drug. For patients with lamivudine resistance, the potential choices are switching to or adding adefovir or switching to entecavir. Because switching from lamivudine to adefovir may result in biochemical flares and can be accompanied subsequently by adefovir resistance, switching is no longer recommended; the nucleotide should be added to the nucleoside. Although a double dose (1 mg) of entecavir is approved for the treatment of lamivudine resistance, entecavir resistance in patients who have received lamivudine is substantial; therefore, entecavir has not been widely used as treatment for lamivudine resistance. Now that tenofovir is approved, it is likely to replace adefovir as a treatment for nucleoside resistance. In patients who do not meet the criteria for antiviral therapy and in patients who have completed successful antiviral therapy, close clinical and laboratory monitoring is indicated to identify potential reactivation.

As noted above, combination therapy is not recommended as the initial antiviral therapy for patients who have not received treatment. However, it is the approach of choice for patients with drug-resistant HBV infection who have received treatment.

Because the 6-month virologic response to some oral agents is predictive of beneficial outcomes and reduced resistance at 1 year, a group of experts supported by an unrestricted grant from Idexx Pharmaceuticals and Novartis recommended a “road-map” approach to managing oral antiviral therapy for chronic HBV infection based on the level of residual HBV DNA at week 24. In patients with a complete virologic response (i.e., no detectable residual HBV DNA) at 24 weeks, the likelihood of the anticipated treatment outcome (i.e., HBeAg seroconversion and maintenance of an undetectable level of HBV DNA) is high and resistance is unlikely; therefore, continued monotherapy with the same drug is recommended. At 24 weeks, in patients with a partial virologic response (i.e., residual HBV DNA of <2000 IU per milliliter) to a drug such as lamivudine, which has a low genetic barrier to resistance, a second drug that is not cross-resistant such as a nucleotide should be added to prevent resistance. For inadequate virologic responses (i.e., a residual level of HBV DNA of ≥2000 IU per milliliter) at 24 weeks, switching to a more effective drug, if available (as recommended in the current guidelines of the American Association for the Study of Liver Diseases), or adding a second drug that is not cross-resistant is suggested.

Because adefovir reduces HBV DNA more slowly than the other drugs, and because the 24-week milestone is not predictive of 48-week outcomes, the recommended timing of the adefovir decision node is week 48 instead of week 24. For entecavir, which has a very high genetic barrier to resistance and a very rapid decrease in the HBV DNA level in almost all patients, interim modifications of the treatment are not recommended.

The most compelling data providing support for this road-map approach, however, were derived from clinical trials of lamivudine and telbivudine; because of their high resistance profiles, these drugs are not preferred as first-line therapy. With the anticipated replacement of lamivudine, telbivudine, and adefovir by the more highly potent, rapidly suppressive, and less resistance-prone entecavir and tenofovir, a 24-week (or a later time point) interim decision may be irrelevant. However, monitoring serum HBV DNA levels during treatment and modifying treatment in patients with an inadequate response is recommended.
Choice of Agents

The availability of so many potential drugs to treat HBV infection presents clinicians with a confusing wealth of choices. Among the oral agents, the high rate of viral resistance to lamivudine and telbivudine limits their appeal (Tables 1 and 2), and, now that it is approved, tenofovir is likely to supplant adefovir. Therefore, among the oral agents, entecavir or tenofovir would be preferable for first-line therapy.

Oral agents are the only option for treating decompensated chronic HBV infection and for preventing hepatic decompensation in patients with advanced fibrosis and cirrhosis. However, for patients with compensated disease who have not received previous treatment, pegylated interferon and oral agents are recommended, and current guidelines do not favor one approach over the other. Whether to treat with a finite course of side-effect–intense pegylated interferon injections or, in most cases, a longer, sometimes indefinite course of a well-tolerated oral agent remains the subject of debate (Table 4). Favoring pegylated interferon as first-line treatment is the value of a 48-week period of therapy, freedom from drug resistance, and the high likelihood of durable HBeAg and HBsAg responses after a course of therapy. In most studies, however, interferon-based therapy is less effective in patients with high-level hepatitis B viremia and, as compared with most oral agents, it suppresses HBV DNA less profoundly. Clinicians who favor oral agents emphasize the direct correlation between the profundity of viral suppression and beneficial serologic, biochemical, and histologic outcomes and the inverse correlation between HBV DNA suppression and the emergence of resistance. As compared with treatment with lamivudine for 1 year, treatment with pegylated

Table 4. Advantages and Disadvantages of Pegylated Interferon and Oral Nucleoside and Nucleotide Analogues as Treatment for Chronic HBV Infection.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pegylated Interferon</th>
<th>Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Multiple side effects, dose reductions, discontinuations</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Cytopenias, TSH, depression</td>
<td>Serum creatinine for nucleotides</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>Finite (48 wk)</td>
<td>&gt;1 yr in &gt;80% of patients</td>
</tr>
<tr>
<td>Reduction in HBV DNA log_{10} (copies/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg-positive patients</td>
<td>4.5</td>
<td>3.5–6.9</td>
</tr>
<tr>
<td>HBeAg-negative patients</td>
<td>4.1</td>
<td>3.9–5.2</td>
</tr>
<tr>
<td>HBeAg seroconversion during therapy (%)</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>HBeAg seroconversion with longer therapy (%)</td>
<td>NA</td>
<td>30 at 2 yr; 40–50 at 3–5 yr</td>
</tr>
<tr>
<td>Durability of HBV DNA suppression after treatment in HBeAg-negative patients (%)</td>
<td>13–18 at 3 yr</td>
<td>7 at 24 wk (lamivudine)</td>
</tr>
<tr>
<td>Loss of HBsAg (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg-positive patients</td>
<td>3 at 1 yr</td>
<td>0–3 at 1 yr, 3–5 at 2 yr</td>
</tr>
<tr>
<td>HBeAg-negative patients</td>
<td>4 at 1 yr, 8 at 3 yr after completion of 1 yr of therapy</td>
<td>≤1 at 1 yr, 5 at 4–5 yr (adefovir)</td>
</tr>
<tr>
<td>Antiviral resistance (%)</td>
<td>None</td>
<td>Lamivudine, adefovir, and telbivudine: 0–30 at 1 yr and 3–40 at 2 yr; entecavir and tenofovir: 0 at 1 yr; entecavir: ≤1 at 4 yr</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensated</td>
<td>Contraindicated</td>
<td>Can be lifesaving</td>
</tr>
<tr>
<td>Compensated</td>
<td>Not recommended</td>
<td>Shown to prevent decompensation</td>
</tr>
</tbody>
</table>

* HBeAg denotes hepatitis B e antigen, HBsAg hepatitis B surface antigen, NA not applicable, and TSH thyroid-stimulating hormone.
interferon for 1 year is more likely to achieve durable HBeAg, HBsAg, and HBV DNA responses. However, longer treatment with oral agents can achieve the same responses and the newer, more potent oral agents can achieve similar HBSAg responses at 1 year without the side effects associated with interferon, injections, or the need for more costly laboratory monitoring and medical supervision. In addition, the newer oral agents are associated with no or negligible resistance over several years of therapy. Moreover, in HBeAg-negative patients, HBV DNA suppression is sustained after interferon therapy in a minority of patients and degrades gradually over time.

Because pegylated interferon tends to be more effective in patients with a low level of HBV DNA, a high ALT level, and genotype A, some authorities favor first-line pegylated interferon for such patients; however, oral agents are also more effective in patients with a low HBV DNA level and a high ALT level. In addition, in definitive clinical trials, genotype A favored HBeAg responses to pegylated interferon alfa-2b but not pegylated interferon alfa-2a, and the trial of pegylated interferon alfa-2b did not include a nucleoside-only group. In all likelihood, genotype A would favor HBeAg seroconversion independent of the type of therapy. Finally, because of a modest advantage in achieving clinical end points during a finite treatment period, some authorities advocate pegylated interferon as first-line therapy for younger patients to avoid committing them to many years of treatment. However, only a small proportion of patients will be spared the need for long-duration oral therapy by an initial course of pegylated interferon, and tolerability issues are just as important, if not more so, in younger persons. Ultimately, cogent arguments provide support for both injectable and oral agents, and the choice is often dictated by physician and patient preference.

**CONCLUSIONS**

Recently, more effective and less resistance-prone antiviral agents have become available to treat HBV infection. Substantial data provide support for the link between high-level HBV replication and the late consequences of chronic HBV infection, and there is increasing evidence of the importance of profound, durable therapeutic HBV DNA suppression in slowing and reversing the progression of chronic HBV infection. In the future, we can expect antiviral drug regimens to improve in efficacy without engendering resistance, and combination drug therapy may contribute to this evolution. The challenge will be to develop shorter treatment regimens with more durable clinical outcomes and treatments targeted more accurately to the time during HBV infection when the most substantial, injurious disease activity occurs, especially in patients with perinatal infection.

Dr. Dienstag reports serving as a member of scientific advisory boards for Vertex Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, Metabasis, SciClone, and Nucleonics and as an ad hoc consultant for Achillion Pharmaceuticals, Amgen, Biogen, Cubist Pharmaceuticals, Oxzon Therapeutics, CombinatoRx, Pharmasset, Wyeth, ViroPharma, AstraZeneca, and Avant Immunotherapeutics; receiving research support from Vertex; holding stock options from Achillion Pharmaceuticals, Metabasis, and Nucleonics; and serving on clinical trial data monitoring and adjudication committees for Schering-Plough Research Institute, Genzyme, Human Genome Sciences, and Gilead Sciences. No other potential conflict of interest relevant to this article was reported.

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CORRECTION

Hepatitis B Virus Infection

To the Editor: In his review article on drug therapy for hepatitis B virus (HBV) infection, Dienstag (Oct. 2 issue)1 does not mention the use of prophylactic antiviral drugs in patients treated with chemotherapy, stem-cell transplantation, or immunosuppressive agents. Reactivation of hepatitis B (including death2) has been described in patients who were anti–hepatitis B core–positive and hepatitis B surface antigen (HBsAg)–negative.3 Several guidelines and discussions4,5 on this topic have been published, recommending lamivudine as prophylaxis. This is an important issue that should have been included in the review article because there is an increasing population of patients who are at risk for this threatening complication.

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References


To the Editor: We believe it would be relevant to stress that nucleotide and nucleoside analogues can prevent HBV reactivation in patients undergoing immunosuppression who have either inactive disease (HBsAg-negative, with markers of previous HBV contact [i.e., isolated hepatitis B core antigen]).1 HBV reactivation is a known and feared complication in patients who are undergoing immunosuppressive regimens that favor viral replication and, consequently, widespread hepatocyte infection. After immunocompetence is regained, immunomediated hepatic damage develops, leading to acute hepatitis or hepatic failure.2 Reactivation has also been described in patients receiving immunosuppressive agents such as glucocorticoids, azathioprine, and infliximab in various clinical settings (gastroenterology, dermatology, oncology, and rheumatology).3 Preemptive treatment with nucleotide and nucleoside analogues effectively reduces the risk of HBV reactivation in hematology patients,2 even if protocols and the issue of treating occult carriers are still debated.4 The search for inactive or occult HBV infection should be mandatory in all patients undergoing immunosuppression, since effective prophylaxis is now available.

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References


To the Editor: We believe it would be relevant to stress that nucleotide and nucleoside analogues can prevent HBV reactivation in patients undergoing immunosuppression who have either inactive disease (HBsAg-positive, hepatitis B e antigen [HBeAg]–negative, anti–HBe–positive, normal aminotransferase levels, HBV DNA of <20,000 IU per milliliter, and anti–hepatitis B core IgM–negative) or occult disease (HBsAg-negative, with markers of previous HBV contact [i.e., isolated hepatitis B core antigen]).1 HBV reactivation is a known and feared complication in patients who are undergoing immunosuppressive regimens that favor viral replication and, consequently, widespread hepatocyte infection. After immunocompetence is regained, immunomediated hepatic damage develops, leading to acute hepatitis or hepatic failure.2 Reactivation has also been described in patients receiving immunosuppressive agents such as glucocorticoids, azathioprine, and infliximab in various clinical settings (gastroenterology, dermatology, oncology, and rheumatology).3 Preemptive treatment with nucleotide and nucleoside analogues effectively reduces the risk of HBV reactivation in hematology patients,2 even if protocols and the issue of treating occult carriers are still debated.4 The search for inactive or occult HBV infection should be mandatory in all patients undergoing immunosuppression, since effective prophylaxis is now available.

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References


To the Editor: In his report on the worldwide prevalence of HBV infection, Dienstag places Italy among countries with a medium endemic level (defined as a prevalence of HBsAg of >2%). Actually, the epidemiology of HBV infection has changed markedly in Italy during the past three decades. In the early 1980s, Italy was a country with a medium endemic level, with an HBsAg prevalence of 3.4%. The prevalence dropped to 1.6% in 1990.1 Currently, Italy is at a very low endemic level, with an HBsAg prevalence of less than 1%, as clearly stated by some surveys, which were performed from 1994 through 2008 (Table 1).2,3 At the same time, a decrease in the prevalence of

HBeAg and hepatitis delta positivity was observed among HBV carriers.

Since 1991, HBV vaccination has been mandatory in Italy for all newborns and adolescents, and coverage of 94% has been reached. According to the National Surveillance System, the incidence of acute HBV infection per 100,000 inhabitants declined from 5.1 in 1991 to 1.3 in 2005.4

Table 1. Prevalence of Hepatitis B Surface Antigen (HBsAg) in Italy, According to Recent Surveys.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Subjects</th>
<th>Prevalence of HBsAg</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>1540</td>
<td>0.9</td>
<td>Da Villa et al.2</td>
</tr>
<tr>
<td>2008</td>
<td>965</td>
<td>1</td>
<td>Fabris et al.4</td>
</tr>
</tbody>
</table>

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References


The author replies: Bergua et al. and Marignani et al. point out the importance of beginning antiviral therapy preemptively in patients with HBV infection (whether active, inactive, or even recovered) who undergo immunosuppressive chemotherapy, without which HBV reactivation can result in substantial morbidity and mortality. My brief review of antiviral therapy for HBV infection had space constraints, which prevented me from addressing the topic of patients with renal failure or extrahepatic disease. For a thorough overview of antiviral therapy in these specific populations in general and in immunosuppressed patients in particular, readers should consult comprehensive practice guidelines issued by national organizations,1,2 as well as the October 2008 proceedings of the National Institutes of Health Consensus Development Conference on Management of Hepatitis B.3

I thank Milazzo and Antinori for pointing out the declining prevalence of HBV infection in Italy, a pattern evolving in other countries with either a low or moderate prevalence during the contemporary era of HBV vaccination. My intent in showing the world map of HBV prevalence was to emphasize the difference in clinical expression of HBV infection on the basis of the time in life when the infection is acquired. This factor, in turn, is a reflection of the prevalence of the infection in the general population, with a high prevalence in countries in which there is primarily perinatal infection and a low prevalence in countries in which there is primarily adult infection. I was not able to update the current world map on a country-by-country basis and relied instead on data in the public domain derived from the Centers for Disease Control and Prevention (CDC).4 On September 19, 2008, 2 weeks before the publication of my article in the Journal, the CDC published an updated world map showing the prevalence of HBV infection, in which Italy was categorized as a low-prevalence country.5 A corrected version of the world map in my article, which also corrects other areas in western and northern Europe, is available at NEJM.org.

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References


