REVIEW ARTICLE

DRUG THERAPY

Hepatitis B Virus Infection

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Reports of successful antiviral therapy for chronic hepatitis B virus (HBV) infection appeared three decades ago,[1] 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.

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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.[2-6]

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),[7] 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.[5,6,8]

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

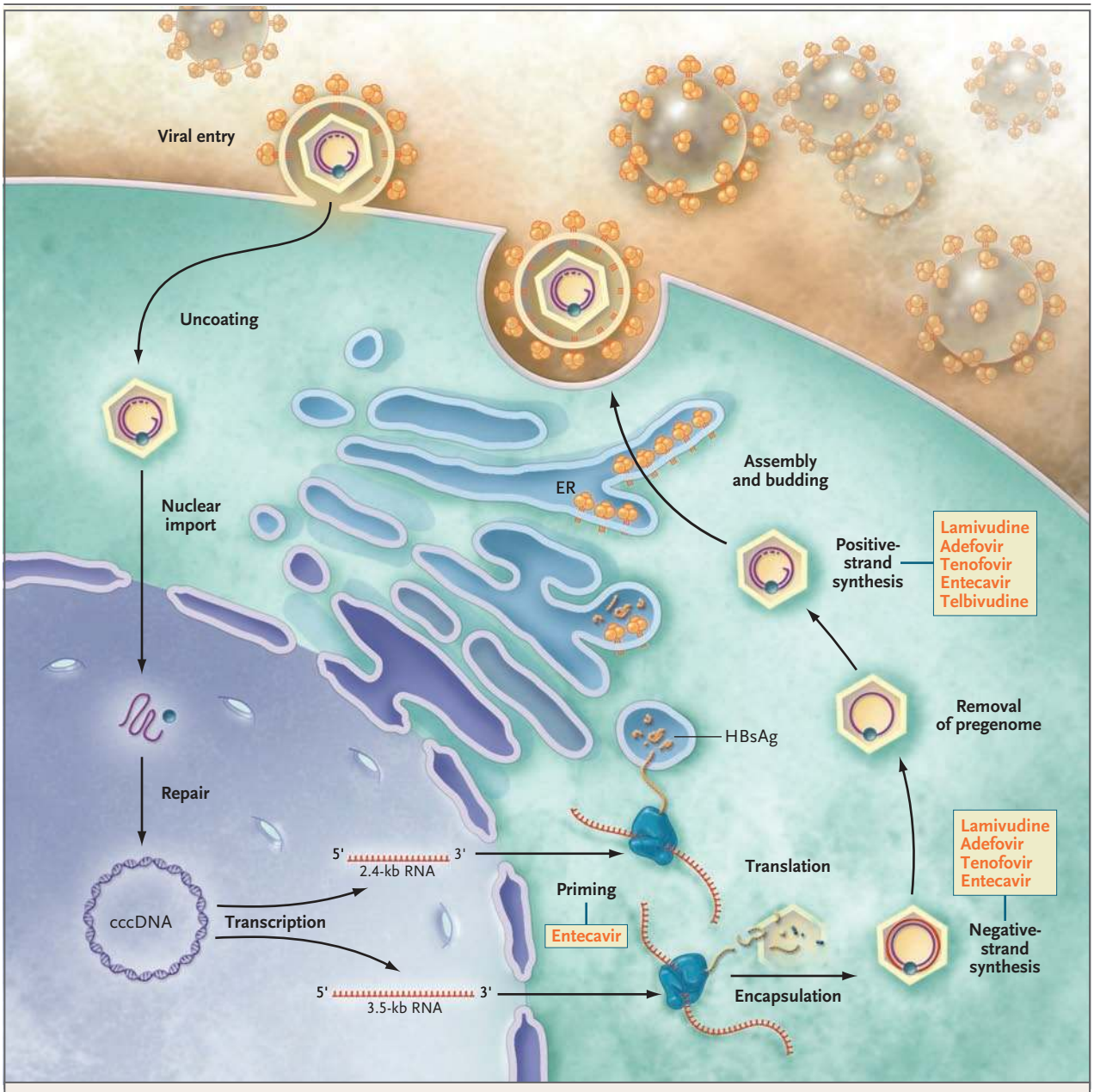

Figure 1. Steps of HBV Replication.

The hepatitis B virus (HBV) establishes covalently closed circular DNA (cccDNA) as a durable miniature chromosome in the host nucleus and relies on a retroviral strategy of reverse transcription from RNA to negative-strand DNA. The steps of HBV replication targeted by nucleoside and nucleotide analogues that are used to treat chronic HBV infection are shown. ER denotes endoplasmic reticulum, and HBsAg hepatitis B surface antigen.

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

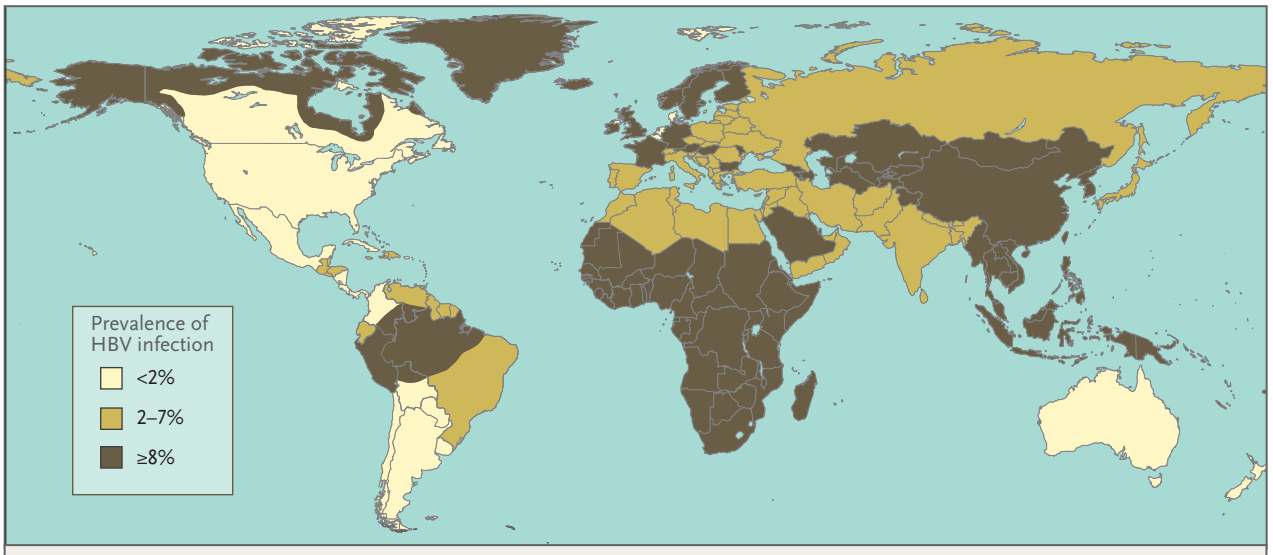

Figure 2. Clinical and Epidemiologic Correlations in HBV Infection.

The clinical expression of HBV infection depends on the time of life when the infection is acquired. In Asian countries with a high prevalence of HBV infection, HBV is acquired perinatally from infected mothers. It is not accompanied by acute hepatitis, but it results in chronic infection in more than 90% of patients. Later in life, cirrhosis and hepatocellular carcinoma account for up to a 40% lifetime risk of death. In contrast, in Western countries with a low prevalence of HBV infection, HBV is rarely acquired perinatally but instead is acquired during adolescence and early adulthood; infections acquired in adulthood usually cause a clinically apparent acute hepatitis, but progression to chronic hepatitis is rare, as is the risk of hepatocellular carcinoma.

patients[11,12] 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.[13-15] 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.[16] 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.[17-19] For example, patients with genotype A are more likely to undergo interferon-induced HBeAg seroconversion[20]; HBeAg seroconversion and slower disease progression are more frequent in patients with genotype B than in patients with genotype C.[19] 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,[21] although, rarely, reactivation can occur spontaneously or with immunosuppression.[22,23] 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.[24,25]

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 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).[5,6] 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,[26-29] 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 more 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.[31,60] 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 1. Currently Used or Approved Antiviral Therapies for HBeAg-Positive Chronic HBV Infection in Patients Who Have Not Received Treatment.*

Variable	Pegylated Interferon Alfa-2a (Pegasys)†	Lamivudine (Epivir)	Adefovir (Hepsera)	Entecavir (Baraclude)	Telbivudine (Tyzeka)	Tenofovir (Viread)
Route of administration	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Dose	180 μg/wk	100 mg/day‡	10 mg/day‡	0.5 mg/day‡	600 mg/day‡	300 mg/day‡
Duration of therapy — wk§	48	48 to ≥52	≥48	≥48	≥52	≥48
Tolerability	Influenza-like symptoms (e.g., fatigue, fever, and myalgias), cytopenias, depression, anxiety, irritability, autoimmune disorders	Well tolerated	Well tolerated, but creatinine monitoring advisable	Well tolerated	Well tolerated	Well tolerated, but creatinine monitoring advisable
HBeAg seroconversion — %¶						
At 1 yr	27 (32 at 72 wk)	16–21	12	21	22	21
At >1 Yr	NA	Up to 50 at 5 yr	43 at 3 yr	39 at 3 yr	30 at 2 yr	ND
Serum HBV DNA — mean or median reduction in $\log_{10}$ copies/ml at 1 yr	4.5	5.5	3.5	6.9	6.4	6.2
Serum HBV DNA undetectable by PCR — %‖	25	36–44	13–21	67	60	80
ALT normalization at end of 1 yr — %	39	41–75	48–61	68	60	77
HBsAg loss — %						
At 1 yr	3	≤1	0	2	<1	3
At 2 yr	NA	3	ND	5	ND	5 at wk 64
Histologic improvement — %**	38 at wk 72	49–62	53–68	72	65	74
Viral resistance — %						
At 1 yr	None	15–30	None	None††	6	0
At >1 yr	NA	70 at 5 yr	ND	<1% up to 4 yr	22	ND
Durability of the HBeAg response after 1 yr — %‡‡	82	70–80	91	82	80	ND
Approximate cost for 1 yr of treatment — $§§	18,000	2,500	6,500	8,700	6,000	6,000
Strength or weakness	Finite duration, no resistance, 1-yr serologic advantage, injectable, low tolerability	Oral, well tolerated, moderate potency, high resistance	Oral, well tolerated, modest potency, moderate resistance	Oral, well tolerated, high potency, low resistance	Oral, well tolerated, high potency, high resistance	Oral, well tolerated, high potency, low resistance

* Data were derived from assessment of these drugs versus placebo or versus an active study drug 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 denotes alanine aminotransferase, HBeAg hepatitis B e antigen, HBsAg hepatitis B surface antigen, NA not applicable, ND no data available, and PCR polymerase chain reaction.

† Standard interferon alfa is also an approved therapy for chronic HBV infection, but unlike pegylated interferon, which is administered once a week, standard interferon is administered daily or three times a week and is less effective. In addition, most clinical trials of standard interferon relied on insensitive assays for HBV DNA levels, which are not comparable to HBV DNA levels reported for the other drugs on the basis of contemporary HBV DNA assays. Since pegylated interferon has replaced standard interferon, standard interferon is not included in this comparison of antiviral agents. Pegylated interferon alfa-2a is the only pegylated interferon approved in the United States for use in patients with HBV infection; however, pegylated interferon alfa-2b is approved for the treatment of HBV infection in several other countries. 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.

§ The duration shown is the duration of therapy in clinical efficacy trials.

¶ The frequency of HBeAg seroconversion (loss of HBeAg and acquisition of anti-HBe) is reported at the end of 1 year of therapy in registration trials and at the end of additional years of therapy, when data are available. For pegylated interferon, 32% HBeAg seroconversion was recorded at week 72 (24 weeks after the discontinuation of therapy). For adefovir, HBeAg seroconversion after year 1 was based on a Kaplan–Meier estimate in a subgroup of study subjects.

‖ Serum HBV DNA was considered to be undetectable by PCR if there were less than 300 to 400 copies per milliliter (<1000 copies per milliliter for adefovir) at the end of year 1.

** Histologic improvement is defined as a reduction of 2 or more points in the histologic activity index at year 1.

†† In lamivudine-resistant patients, viral resistance was 7% during year 1 of therapy and up to 43% at year 4. If entecavir is to be used in such patients, the approved dose is 1 mg per day.

‡‡ For HBeAg responses to oral agents, durability is shown after a period of additional consolidation therapy. The duration of consolidation therapy and the time when durability was assessed differ widely among studies; therefore, caution is warranted in interpreting these data. In patients treated for 48 weeks with pegylated interferon alfa-2a, 72 of 271 subjects (27%) had HBeAg seroconversion at week 48; in 13 of these 72 subjects (18%) followed for 24 weeks after therapy, HBeAg seroconversion responses were lost, so the durability frequency was 82%.

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

Table 2. Currently Used or Approved Antiviral Therapies for HBeAg-Negative Chronic HBV Infection in Patients Who Have Not Received Treatment.*

Variable	Pegylated Interferon Alfa-2a (Pegasys)†	Lamivudine (Epivir)	Adefovir (Hepsera)	Entecavir (Baraclude)	Telbivudine (Tyzeka)	Tenofovir (Viread)
Serum HBV DNA — mean or median reduction in $\log_{10}$ copies/ml at 1 yr	4.1	4.2–4.7	3.9	5.0	5.2	4.6
Serum HBV DNA undetectable by PCR — %‡	63	60–73	51–64	90	88	95
ALT normalization at end of 1 yr — %	38	62–79	48–77	78	74	79
HBsAg loss — %						
At 1 yr	4	≤1	0	<1	<1	0
At >1 yr	8 at 3 yr after completion of 1 yr of therapy	ND	5 at 4–5 yr	ND	ND	ND
Histologic improvement — %§	48 at wk 72	61–66	64	70	67	72
Viral resistance — %						
At 1 yr	None	15–30	None	None	4	0
At >1 yr	NA	70 at 5 yr	29 at 5 yr	<1 up to 4 yr	9	ND
Durability of the HBV DNA–ALT response after 1 yr — %¶	18	<10	<10	ND	ND	ND

* Data were derived from assessment of these drugs versus placebo or versus an active study drug in registration clinical trials; in most cases, these comparisons were not based on head-to-head testing of the different drugs. ALT denotes alanine aminotransferase, HBeAg hepatitis B e antigen, HBsAg hepatitis B surface antigen, NA not applicable, ND no data available, and PCR polymerase chain reaction.

† Standard interferon alfa is also an approved therapy for chronic hepatitis B, but unlike pegylated interferon, which is administered once a week, standard interferon is administered daily or three times a week and is less effective. In addition, most clinical trials of standard interferon relied on insensitive assays for HBV DNA that are not comparable to HBV DNA levels reported for the other drugs based on contemporary HBV DNA assays. Therefore, and because pegylated interferon has replaced standard interferon, standard interferon is not included in this comparison of antiviral agents. Pegylated interferon alfa-2a is the only pegylated interferon approved in the United States for use in patients with HBV infection; however, pegylated interferon alfa-2b is approved for the treatment of HBV infection in several other countries. Recommendations for weight-based dosing of pegylated interferon alfa-2b are found in the product brochure.

‡ Serum HBV DNA undetectable by PCR is defined as less than 300 to 400 copies per milliliter (<1000 copies per milliliter for adefovir) at the end of year 1.

§ Histologic improvement is defined as a reduction of 2 or more points in the histologic activity index at year 1.

¶ The durability of the HBV DNA–ALT response is shown after a period of additional consolidation therapy. The duration of consolidation therapy and the time when durability was assessed differ widely among studies; therefore, caution is warranted in interpreting these data.

dogs).[42,44,45] 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,[48] 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[30]; 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.[45,49,61,63] Similarly, earlier studies suggested that rates of HBsAg seroconversion at 1 year are higher for interferon-based therapy than for oral agents.[26,30,31] However, rates of HBsAg loss are similar between pegylated interferon and some of the newer, more potent oral agents (Tables 1 and 2).[45,51] In addition, after successful HBeAg seroconversion and cessation of therapy in Western (not Asian) patients, patients who have received lamivudine appear to have rates of HBsAg seroconversion (20% at 3 years in one small study) that are similar to those achieved after interferon therapy.[58,68,78,79] Reductions in cccDNA are similar in patients with spontaneous, interferon-induced, or oral-agent–induced HBeAg seroconversion.[80]

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,[81] appears to confer no advantage over lamivudine. Clevudine is distinguished from other oral agents by its sustained suppression of HBV

DNA for several months after cessation of therapy.[82-84] However, preliminary clinical trials suggest that clevudine is less potent than other oral agents in suppressing HBV DNA and inducing HBeAg seroconversion.[83,84]

RESISTANCE TO ANTIVIRAL DRUGS

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[66,75] 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,[49] telbivudine has not been widely used for the treatment of chronic HBV infection. The nucleotides are effective in nucleoside resistance and vice versa.[54,55,85] 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.[86,87] 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 1 $\log_{10}$ after an initial virologic response (in the absence of nonadherence,[88] which accounts for breakthrough in 30% of patients treated in clinical trials[5]), especially when accompanied by an elevation in the ALT level. More detailed overviews of antiviral resistance in HBV infection appear elsewhere.[6,89-92]

PREDICTORS OF RESPONSE

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.[93,94] The genotype is associated with higher frequencies of spontaneous (B>C)[19,95] and pegylated interferon alfa-2b–related (A>B>C>D) HBeAg and HBsAg seroconversion,[20,96] but it does not correlate with the degree of HBV DNA suppression associated with the oral agent.[97] 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.[5,48,52,98,99] 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.[6,89-92]

COMBINATION THERAPY

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 $\log_{10}$ during therapy, the combination did not result in a durable post-therapy benefit.[30,31] Similarly, telbivudine and lamivudine combined did not achieve additional antiviral activity over that of telbivudine alone.[47] 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

successful strategy.[54,55,100] 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[5] 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.[5,6,100]

HIV AND HBV COINFECTION

Antiviral therapy for patients with human immunodeficiency virus (HIV) and HBV coinfection has been reviewed recently in the *Journal*.[89] 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,[101] tenofovir, and emtricitabine) or, theoretically, can promote HIV mutations with cross-resistance to the drugs (i.e., adefovir and telbivudine).[102] 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[5,103,104] and by a group of U.S. hepatologists supported by an unrestricted grant from a pharmaceutical company.[105] 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).[5]

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.[33,37,38] The indication for therapy is so clear-cut that a pretreatment 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,[106] 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.[107] 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

Table 3. Treatment Guidelines for HBV Infection.*

HBeAg Status	HBV DNA	ALT	Potential First-Line Therapy
	IU/ml	*×ULN*	
Positive	>20,000	≤2	Do not treat (low efficacy of current therapy)
Positive	>20,000	>2	Treat with interferon, pegylated interferon, adefovir (Hepsera), or entecavir (Baraclude)†
Negative	>20,000	>2	Treat with interferon, pegylated interferon, adefovir, or entecavir†
Negative	>2000	1 to >2	Consider liver biopsy to help in treatment decision
Negative	≤2000	≤1	Observe
Positive or negative	Approximately ≥10 to 100	Cirrhosis with ≤1 to >2	If liver function compensated with DNA >2000 IU/ml, treat with adefovir or entecavir‡; if DNA <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
Positive or negative	Approximately <10 to 100	Cirrhosis with ≤1 to >2	If compensated, observe; if decompensated, refer for liver transplantation

* Guidelines are from the American Association for the Study of Liver Diseases.[5] 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.

† Although lamivudine and telbivudine are also available as first-line therapy, the high rate of resistance to these agents limits their appeal; therefore, they are not a preferred choice. After the publication of these guidelines, tenofovir (Viread) was shown to be more effective than adefovir, and future recommendations are likely to favor tenofovir over adefovir as first-line therapy. Although interferon is approved therapy, pegylated interferon, which is more effective and more convenient, has supplanted standard interferon.

‡ Although lamivudine and telbivudine are also available as first-line therapy, the high rate of resistance to these agents limits their appeal; therefore, they are not a preferred choice. After the publication of these guidelines, tenofovir (Viread) was shown to be more effective than adefovir, and future recommendations are likely to favor tenofovir over adefovir as first-line therapy. Interferon and pegylated interferon are not recommended for patients with cirrhosis.

§ 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.

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]

During oral-agent therapy of HBeAg-positive chronic HBV infection, HBeAg loss — preferably seroconversion — can serve as a milestone, after which treatment can be discontinued. Therapy should be continued for at least 6 months. In patients with perinatally acquired HBV infection, therapy should be continued for 1 year or longer.

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,[60,70,110,111] in the vast majority 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 $\log_{10}$ 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[55] and can be accompanied subsequently by adefovir resistance,[100] 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[87]; 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 Idenix 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.[99] 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[48]; 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.[5]

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

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

* HBeAg denotes hepatitis B e antigen, HBsAg hepatitis B surface antigen, NA not applicable, and TSH thyroid-stimulating hormone.

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.[72,75,112,113] 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).[114,115]

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[93] 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.[48,99,116] As compared with treatment with lamivudine for 1 year, treatment with pegylated

interferon for 1 year is more likely to achieve durable HBeAg, HBsAg, and HBV DNA responses.[30,31] However, longer treatment with oral agents can achieve the same responses[39,40,45,49,61,63,87] and the newer, more potent oral agents[51] 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.[87] Moreover, in HBeAg-negative patients, HBV DNA suppression is sustained after interferon therapy in a minority of patients and degrades gradually over time.[60,111]

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[114,115]; however, oral agents are also more effective in patients with a low HBV DNA level and a high ALT level.[94] In addition, in definitive clinical trials, genotype A favored HBeAg responses to pegylated interferon alfa-2b[20] but not pegylated interferon alfa-2a,[30] and the trial of pegylated interferon alfa-2b did not include a nucleoside-only group.[20] In all likelihood, genotype A would favor HBeAg seroconversion independent of the type of therapy.[117] 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.[114] 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, Oxxon 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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