

REVIEW ARTICLE

DRUG THERAPY

Hepatitis B Virus Infection

Jules L. Dienstag, M.D.

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.

VIROLOGIC AND EPIDEMIOLOGIC FACTORS
AND NATURAL HISTORY

From the Gastrointestinal Unit (Medical Services), Massachusetts General Hospital; and the Department of Medicine and Office of the Dean for Medical Education, Harvard Medical School — both in Boston. Address reprint requests to Dr. Dienstag at the Gastrointestinal Unit, Jackson 7, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at jdienstag@partners.org.

N Engl J Med 2008;359:1486-500.
Copyright © 2008 Massachusetts Medical Society.

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

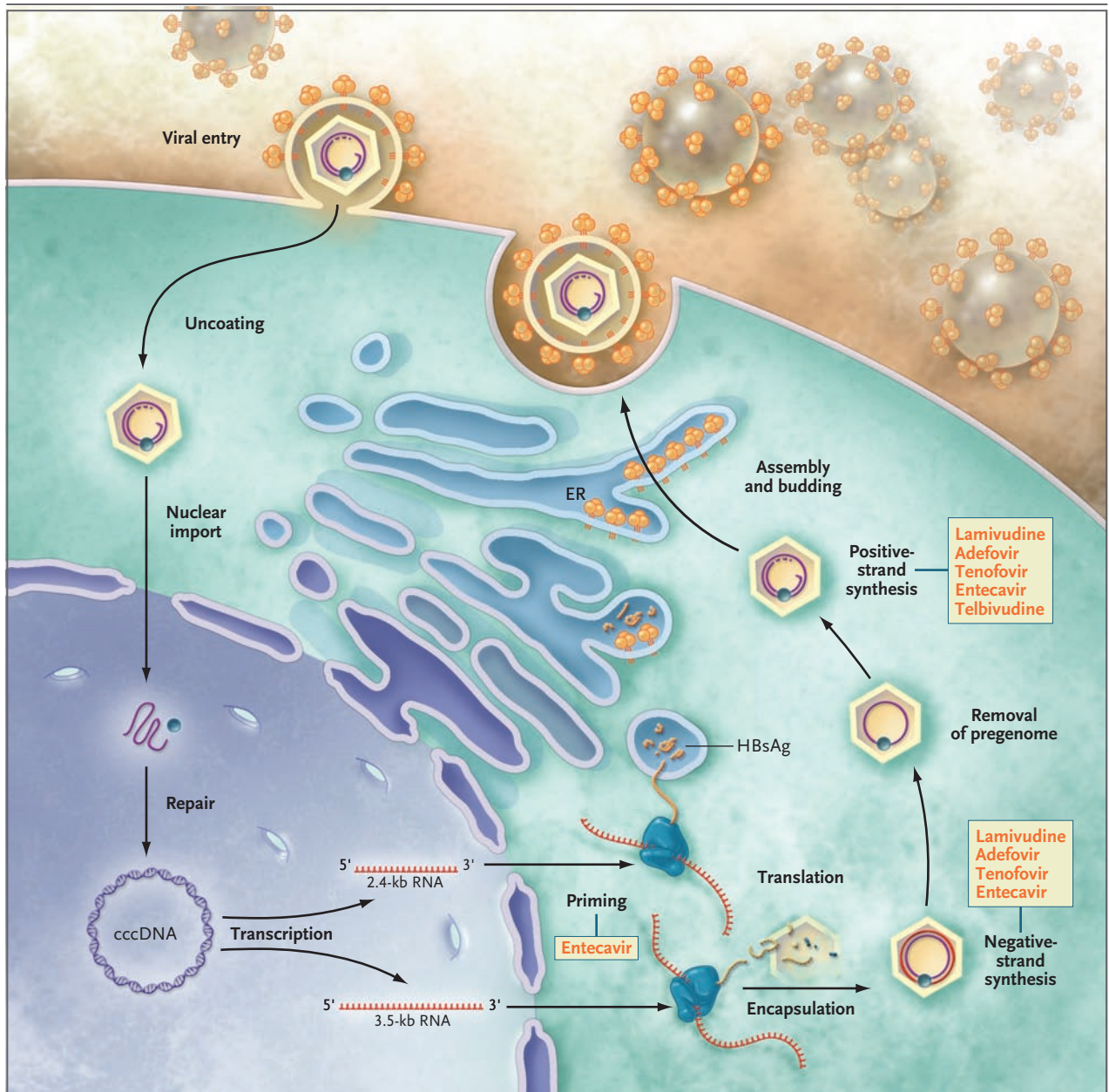


Figure 1. Steps of HBV Replication.

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

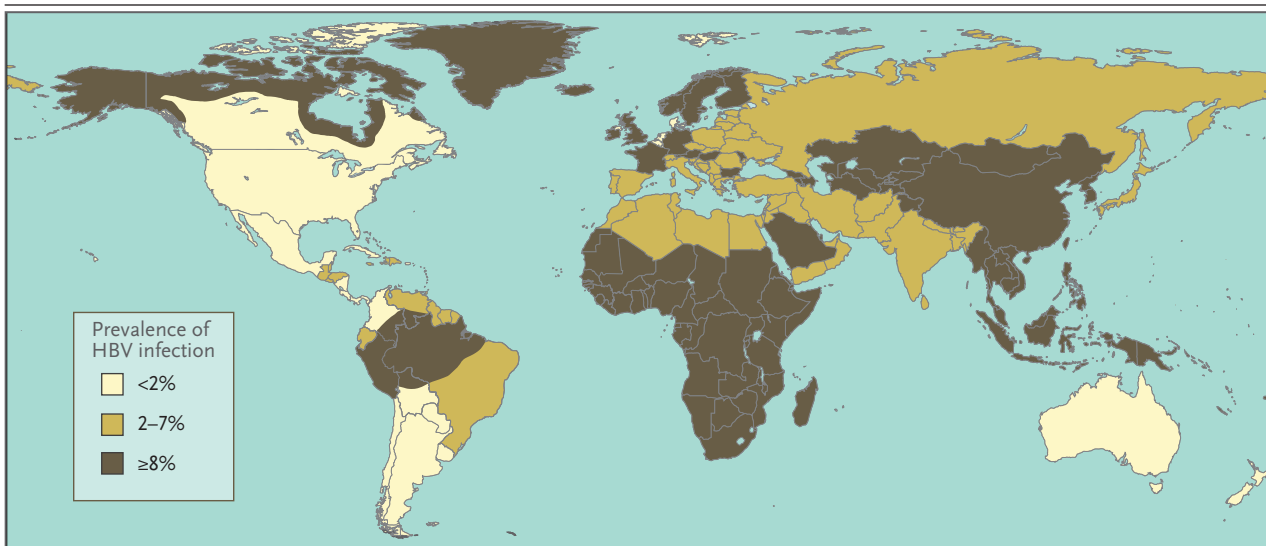


Figure 2. Clinical and Epidemiologic Correlations in HBV Infection.

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 seroconversion²⁰; HBeAg sero-

conversion 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 patients⁵⁶).

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

