Hepatitis B virus (HBV) infection has a high worldwide prevalence and is a major contributor to morbidity and mortality. Although its prevalence in the United States overall is low, the existence of high-prevalence areas warrants attention and intervention. With the growth of the Asian American population, the prevalence of HBV infection can also be expected to grow. In this supplement, which presents the proceedings of a symposium, “B-SMART: Hepatitis B,” thought leaders examine and debate the management of HBV infection. In addition to a review designed to update clinicians who are not liver specialists, the authors provide up-to-date commentary and recommendations on the prevention of complications, cultural barriers to treatment, drug resistance, and special patient populations such as pregnant women and those who are coinfected with HBV and human immunodeficiency virus (HIV). Also included is a debate on the question of monotherapy versus multiple-drug therapy.

Objectives
Upon completing this activity, participants will be able to:
• Explain the markers that signal the presence of chronic HBV infection and its resolution
• Develop a treatment plan that minimizes the risk of hepatocellular carcinoma
• Address cultural issues that may prevent patients from seeking and adhering to adequate care
• Assess treatment choices based on the likelihood of resistance
• Describe a rationale for single- or multiple-drug therapy
• Create a treatment strategy for a pregnant patient with HBV infection that will protect her and her baby
• Decide when to begin treatment in a patient coinfected with HBV and HIV.

Target Audience
Gastroenterologists, hepatologists, primary care physicians, and other health care professionals with an interest in hepatitis.

Disclosure
In accordance with the Standards for Commercial Support issued by the Accreditation Council for Continuing Medical Education, The Cleveland Clinic Foundation Center for Continuing Education requires resolution of all faculty conflicts of interest to ensure CME activities are free of commercial bias.

The following faculty have indicated that they may have a relationship which, in the context of their contributions to this supplement, could be perceived as a potential conflict of interest:

Pierre M. Gholam, MD, reported that he has received grant/research support from Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals, Inc., Gilead Sciences, Inc., Roche Pharmaceuticals, and Sanofi-Aventis; and consulting fees and honoraria for teaching and speaking from Gilead Sciences, Inc., Onyx Pharmaceuticals, and Vertex Pharmaceuticals.

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The following faculty indicated that they have no relationships which, in the context of their contributions to this supplement, could be perceived as a potential conflict of interest:

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The prevalence and natural history of hepatitis B in the 21st century

■ ABSTRACT

The prevalence of chronic hepatitis B virus (HBV) infection varies by geographic region. Most of North America is a low-prevalence (< 2%) area. Certain high-prevalence pockets exist, especially areas with a high proportion of Asian immigrants and Alaskan and northern Canadian native populations, where rates of chronic HBV are as high as 5% to 15%. In most low-prevalence areas, HBV infection is acquired mainly during adolescence and midadulthood, whereas perinatal transmission is the main route in high-prevalence (≥ 8%) areas. Up to 40% of patients with chronic HBV infection develop liver complications. Age at acquisition affects the likelihood of chronicity and the development of liver complications. The risk of each is greatest with perinatal transmission; the disease is usually self-limiting when exposure to HBV occurs during adolescence or young adulthood. Viral load predicts progression to cirrhosis and hepatocellular carcinoma; therefore, reducing viral load is the major goal of treatment.

■ KEY POINTS

The prevalence of chronic HBV infection in the United States is expected to increase as Asian immigrants constitute a larger proportion of the US population.

The chance of chronic infection is 90% or greater with perinatal transmission; conversely, the risk of chronic disease is less than 10% with adult-acquired infection.

In addition to viral load, predictors of disease progression include age at onset, male sex, and comorbidities.

Hepatitis B virus (HBV) infection is highly prevalent worldwide and is a major cause of morbidity and death. Two billion people globally have been infected with HBV, 350 to 400 million are chronic carriers, and tens of millions of new cases occur annually. Of those infected, 15% to 40% develop HBV complications, namely cirrhosis or hepatocellular carcinoma (HCC).1–3

The high prevalence of HBV infection represents an enormous failure of public health, considering that HBV immunization has been available for an entire generation, and where it has been employed it has been highly effective at reducing the incidence of HBV infection. Immunization, however, has been underused.

This supplement to the Cleveland Clinic Journal of Medicine, derived from a live symposium, aims to enhance awareness of the natural history of HBV infection and clarify its management recommendations with illustrative case histories. The supplement starts with a brief review of HBV terminology, natural history, and epidemiology.

■ CHRONIC HBV INFECTION TERMINOLOGY

Familiarity with the terms commonly used to describe chronic HBV infection will help clinicians in the management of the disease4:

- **Chronic HBV infection** is defined as presence of hepatitis B surface antigen (HBsAg) for more than 6 months. Those with infection may also express another antigen, HB e antigen (HBeAg), a marker of heightened infectivity. At the same time, those who are HBeAg positive are better responders to antiviral therapy compared with those who are HBeAg negative.

- An **inactive HBsAg carrier** is an individual who is HBsAg positive with a very low level of circulating virus, liver enzyme levels within normal limits, and a low likelihood of having chronic progressive disease.

- **Resolved HBV infection** is defined as previous HBV infection with no remaining evidence of active disease. Such individuals test negative for HBsAg and positive for antibody to HBsAg (anti-HBs) and to HB core antigen (anti-HBC). They also have no detectable viral load, or HBV DNA, in their blood. In most instances, they are protected from reinfection.

- **Reactivation** is the reappearance of HBV infection in someone who is known to be an inactive HBsAg carrier or whose previous HBV infection had resolved (see “Case: Recurrence despite anti-HBs and HBsAg negativity,” page S3).

- **HBeAg seroconversion** is the transition from
HBeAg-positive to HBeAg-negative status and development of antibody to HBeAg (anti-HBe), usually accompanied by less active liver disease and lower viral loads.

- **HBeAg clearance** is disappearance of HBeAg without the development of anti-HBe; reactivation or reversion to HBeAg-positive status can occur.

### Geographic Distribution of Chronic HBV Infection

The global prevalence of HBV varies widely. Regions are divided into areas of low, intermediate, and high prevalence, defined as follows:

- **High prevalence** implies that at least 8% of the population is currently infected, with a lifetime likelihood of active or resolved infection greater than 60%. About 45% of the world’s population lives in regions of high prevalence. Among this group, early childhood infections are common, with the virus usually transmitted from mother to infant during the perinatal period.

- **Intermediate prevalence** is defined as 2% to 7%, with a lifetime risk of infection of 20% to 60%. These regions represent about 43% of the global population. In intermediate-prevalence areas, infections occur in all age groups.

- **Low prevalence** is defined as less than 2% and represents only 12% of the global population. In these regions, the lifetime risk of infection is less than 20%.

North America is a low-prevalence area except for the northern rim, where Inuit and Yupik Eskimos have a high prevalence, and communities that have a substantial immigrant population from high-prevalence areas, such as sub-Saharan Africa and many parts of Asia.

### Chronic HBV Infection in the United States

Approximately 1.25 million individuals in the United States are HBsAg carriers. In Asian Americans and Alaskan natives, the prevalence of HBsAg positivity, or chronic disease, is 5% to 15%. Similarly, US health statistics sources estimate that among those who are chronically infected, approximately half are Asian American. As the Asian American population continues to increase (1.5 million to 7 million from 1970 to 1990; 11.9 million in the 2000 US Census), the total prevalence of chronic HBV infection will increase as well.

### Natural History of Chronic HBV Infection

The progression to chronic HBV infection characteristically starts with an acute infection, indicated by the presence of HBsAg (Figure 1). Serum tests for HBsAg remain positive as long as chronic infection is present. Positivity for HBeAg, a marker of higher viral load and heightened infectivity, also develops, and may remain for months to years. Resolution of infection is heralded by disappearance of HBsAg. In this case, the anti-HBc and anti-HBs are positive.

### Case: Recurrence despite anti-HBs and HBsAg negativity

A 55-year-old man previously treated for lymphoma was referred in March 2008 for evaluation following recent discovery of an abnormality in liver enzyme levels. His lymphoma had been treated successfully in 2002 with a combination of radiation therapy and chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] and rituximab). There is no evidence of residual lymphoma. The patient had been well until 2 weeks before his referral, when he developed abdominal distention found to be ascites.

In 2002, his laboratory values were essentially normal except for a trivial elevation of alanine aminotransferase (ALT). At that time, he was hepatitis B surface antigen (HBsAg) negative and had antibody to HBsAg (anti-HBs), consistent with resolution of chronic hepatitis B virus (HBV) infection.

On presentation in March 2008, the patient was HBsAg positive. IgM anti-HBc, a marker of recent infection or reactivation, was positive. Anti-HBs was not measured. Computed tomography to assess tumor burden showed no tumor; however, ascites was present.

A laboratory evaluation in 2006 had shown marked elevation of transaminase levels; now, in 2008, evaluation shows startlingly elevated levels of ALT (1,023 U/L) and aspartate aminotransferase (472 U/L). The patient is also profoundly jaundiced.

What can explain the recurrence of chronic HBV infection in this patient?

Chronic HBV usually causes microinflammatory changes that evoke a fibrotic response in the liver, and many infected individuals will eventually develop cirrhosis and are at risk for the development of HCC. Inactive HBsAg carriers often bypass the development of cirrhosis but remain at risk for HCC if their viral load is very high. This is particularly true when infection is acquired in infancy.

The age at acquisition of HBV has a large impact on the likelihood of the disease becoming chronic. The chance of chronic infection is 90% or greater among neonates who become infected with HBV through perinatal transmission. Exposure during adolescence or young adulthood is associated with a 95% or greater likelihood that the disease will be self-limiting.

The typical North American patient with HBV acquires the infection as an adolescent or young adult and is not at risk of HCC unless cirrhosis develops. In most patients who acquire the disease in adolescence or adulthood, the infection resolves after weeks or a few months and they are not at risk of either cirrhosis or
FACTORS THAT INFLUENCE THE COURSE
and, in most instances, lifelong immunity. Antibody to HB core antigen (anti-HBc) indicates resolution of infection by its antibody (anti-HBe). The development of immunoglobulin M aminotransferase (ALT). Typically, HB e antigen (HBeAg), a marker of infectivity, also becomes positive; in some instances, HBeAg is replaced by its antibody (anti-HBe). The development of immunoglobulin M antibody to HB core antigen (anti-HBc) indicates resolution of infection and, in most instances, lifelong immunity.

HCC. However, an individual such as the one described in the accompanying case, who becomes immunocompromised, is at risk of reactivation of HBV infection (see “Case revisited”).

HBV MODES OF TRANSMISSION
In low-prevalence areas, such as most of North America, most cases of HBV infection are acquired during adolescence to midadulthood, a period during which behaviors that increase the risk of HBV infection (ie, intravenous drug abuse or unprotected sexual activity) are most likely. Sex workers and homosexuals are at particular risk of sexual transmission of HBV. Intravenous drug abusers and health workers are at risk of parenteral transmission.

In high-prevalence areas, HBV is mostly transmitted during the perinatal period from mother to infant, conferring a high likelihood of chronicity. Mothers who are HBsAg positive, particularly those who are also HBeAg positive, are much more likely than others to transmit HBV to their offspring.

FACTORS THAT INFLUENCE THE COURSE OF HBV INFECTION
Viral load has emerged as the most significant factor implicated in the development of cirrhosis or HCC. Iloeje et al found that viral load predicted progression to cirrhosis among a cohort of nearly 4,000 Taiwanese. Other factors that can influence the course of HBV infection include age at onset, male sex, and comorbidities (ie, alcohol use, human immunodeficiency virus infection, hepatitis C virus infection). Core promoter and precore mutants may affect the likelihood of developing HCC. A genetic signature that predisposes liver cells to proliferate, termed field effects, may also lead to the development of HCC. The influence of smoking and diabetes on the development of HCC in HBV-infected individuals is not well documented.

Reduction or elimination of measurable virus is the current holy grail of treatment; available antiviral therapies are potent tools that lower viral load with the hope of reducing the likelihood of either cirrhosis or HCC.

HBV genotypes may be implicated in the progression of liver disease or the risk of development of HCC. HBV genotypes differ by region and may correlate with ethnicity and disease progression. In a study of 694 US patients with chronic HBV, Chu et al found that genotypes A and C were associated with a higher prevalence of HBsAg positivity than other genotypes. Genotypes B and C were the most common among Asian American patients, while genotype A was the most common among Caucasian and African American patients. The authors suggested that HBV genotypes may explain the heterogeneity in the manifestation of the disease.

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Dr. Carey reported that he has no financial interests or relationships that pose a potential conflict of interest with this article.

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Risk of hepatocellular carcinoma in hepatitis B and prevention through treatment

**ABSTRACT**

Risk factors for the development of hepatocellular carcinoma in patients with chronic hepatitis B virus (HBV) infection are being elucidated. An HBV DNA concentration greater than $10^4$ copies/mL is an especially strong predictor of risk in individuals aged 30 years or older, independent of the level of serum alanine aminotransferase (ALT). Other predictors of cancer are HBV genotype, with genotype C imparting an increased risk, and serum ALT values at least two times the upper limit of normal. Viral suppression with continuous lamivudine therapy reduces the risk of complications and delays progression of liver disease as long as response is maintained.

**KEY POINTS**

- A high viral load is a significant predictor of the development of hepatocellular carcinoma in patients aged 30 years or older with chronic HBV infection.
- The risk of developing liver complications from chronic HBV infection increases with increasing concentrations of alanine aminotransferase.
- Continuous antiviral therapy to suppress viral load dramatically reduces the risk of complications from HBV infection and reduces the rate of disease progression, as long as patients maintain a therapeutic response.

The role of hepatitis B virus (HBV) as a risk factor for the development of hepatocellular carcinoma (HCC) is well established. Not every patient with HBV infection develops HCC; yet, the current guidelines issued by the American Association for the Study of Liver Diseases recommend screening all patients who have HBV infection when they reach certain ages associated with increased risk. Improved identification of risk factors specifically associated with the likelihood of developing HCC may spare some patients the burden of unnecessary testing. This article reviews up-to-date information that will help identify patients who are at risk of HCC based on factors with more specificity than age, and considers whether treatment can alter their risk.

**ASSESSING RISK**

Several factors are associated with increased risk of developing HCC (see “Case: Hepatocellular carcinoma in a young woman,” page S7):

- **An elevated serum alanine aminotransferase (ALT) level** signifies the presence of active disease and increases risk, particularly if the ALT is persistently or intermittently elevated over years.
- **Persistently elevated alpha-fetoprotein** level is a reflection of enhanced regenerative state in the liver; the increased rate of cell division increases the risk of mutation, leading to increased risk of HCC.
- **A low platelet count** suggests the presence of cirrhosis, which itself increases the risk of HCC.
- **Histologic risk factors** revealed at biopsy include dysplasia, geographic morphologic changes that suggest clonal populations of cells, and a positive stain for proliferating cell nuclear antigen.
- **Viral load** (HBV DNA) is a significant predictor of HCC; two recent large, prospective studies—the Haimen City study and the REVEAL-HBV (Risk Evaluation of Viral Load Evaluation and Associated Liver Disease/Cancer-Hepatitis B Virus) study—support the importance of this risk factor.

**Haimen City study**

The Haimen City study involved 83,794 subjects aged 25 to 64 years at entry. The 2,763 subjects who were positive for hepatitis B surface antigen (HBsAg) were tested at baseline for viral load and followed for 11 years. The relative risk of mortality associated with a high viral load (HBV DNA $\geq 10^5$ copies/mL) was 11.2; low viral load (HBV DNA $< 10^5$ copies/mL) had no significant association with mortality (Figure 1). Nearly 20% of the study subjects with high viral load died of HCC.

**The REVEAL-HBV study**

The REVEAL-HBV study was a multicenter observational cohort study of 23,820 Taiwanese individuals aged...
30 to 65 years old who were free of HCC at baseline. Of these, 3,653 were seropositive for HBsAg and seronegative for antibodies to hepatitis C virus. Some 1,619 men and women had serum HBV DNA levels greater than or equal to $10^4$ copies/mL at study entry. A direct correlation was observed between baseline HBV DNA levels and the incidence of HCC. During a mean follow-up period of 11.4 years, there were 164 new cases of HCC. In a model that integrated baseline and follow-up HBV DNA levels, the cumulative incidence of HCC ranged from 1.3% of those with undetectable levels of HBV DNA to 14.9% of those with HBV DNA levels of $10^6$ copies/mL or greater. The same association between viral load and incidence of HCC was evident in patients who upon study entry had normal ALT levels and were hepatitis B e antigen (HBeAg) negative, a group previously considered to be inactive carriers of HBV.

The incidence of HCC was higher in the subjects with persistent viremia than in those whose viral load decreased over time, representing a biologic gradient of risk. Compared with the reference group (baseline HBV DNA < $10^4$ copies/mL), the adjusted relative risk was nine times greater in those who maintained HBV DNA levels of $10^5$ copies/mL or greater.

**Genotype further defines risk**

In addition to viral load, genotype may further define the risk of HCC in HBV carriers aged 30 years or older. In a nested case-control study, genotype C was associated with fivefold increased risk of HCC compared with other genotypes. Consistent with other studies, the risk of HCC increased with increasing viral load.

**Caveats to the viral load–HCC link**

The association between viral load and the development of HCC applies to patients aged 30 years or older, the subjects of the aforementioned studies. Younger patients who present with a high viral load and are HBeAg positive are likely to be in an immune-tolerant phase of HBV infection. Among patients aged 30 years or older, the association between viral load and HCC applies to HBeAg-positive as well as HBeAg-negative status. The longer the HBeAg-positive state is maintained, the greater the risk of developing cirrhosis and HCC, which is a reflection of active disease over a prolonged period. The association applies equally to patients with normal or elevated ALT levels. A risk nomogram is being developed that will help identify patients at highest risk of HCC.

### ALT AS PROGNOSTIC DETERMINANT

The risk of developing liver complications from chronic HBV infection increases with increasing concentrations of ALT. Yuen et al. followed 3,233 Chinese patients with chronic HBV infection for approximately 4 years. The risk of developing complications from liver disease increased as ALT concentration increased from less than 0.5 times the upper limit of normal (ULN) to two to six times the ULN; ALT levels one to two times the ULN...
were associated with the highest risk of development of complications. Interestingly, an ALT level greater than six times the ULN was associated with a significantly lower risk of liver complications. The speculation is that this phenomenon represents inactivation of disease following HBcAg seroconversion.

**Viral Load Suppression Limits Disease Progression**

Disease activity may flare during the natural course of chronic HBV infection, and repeated episodes may lead to progressive fibrosis, cirrhosis, and end-stage liver disease, as well as HCC. Patients whose cirrhosis has progressed to end-stage liver disease are candidates for transplant.

Continuous antiviral therapy with lamivudine has been shown to dramatically reduce the risk of complications and disease progression in patients with chronic HBV infection. In a placebo-controlled trial of 651 patients with chronic HBV infection and advanced fibrosis or cirrhosis, those randomized to lamivudine who remained sensitive to the drug had a 7.8% risk of complications over approximately 3 years, compared with a 17.7% risk in the patients randomized to placebo. The difference was significant and sizeable enough that the study was terminated after a mean duration of 32.4 months. Patients who developed resistance to lamivudine, caused by a mutation in HBV (YMDD mutation, a sign of lamivudine resistance), lost the protection provided by viral suppression.

The risk of disease progression to cirrhosis or HCC was also significantly lower among HBcAg-positive patients without cirrhosis who were treated with lamivudine for a median of 89.9 months compared with placebo, Yuen et al found. As in other studies, patients in whom the YMDD mutation developed lost the protection of viral suppression.

In a retrospective study, Di Marco et al also found that a loss of response to lamivudine was associated with higher risk of development of HCC, whereas patients who maintained a response to lamivudine were much less likely to develop progressive disease. The authors found that cirrhosis and loss of antiviral response were independently related to mortality and development of HCC.

**Summary**

Patients with HBV are at risk for cancer, and the risk factors can be identified. Although not yet fully evaluated, awareness of these factors will make the screening process more efficient and less burdensome than current guidelines recommend. The publication and eventual validation of a risk nomogram will facilitate the determination of risk. An especially strong predictor of adverse outcomes, including HCC, is HBV DNA concentration higher than $10^6$ copies/mL, as shown by two recent large studies; further, investigators observed a correlation between HBV DNA level and incidence of HCC.

Antiviral therapy has dramatically reduced the risk of complications and progression of HBV infection. Those who develop resistance to therapy lose the protection provided by viral suppression.

**Discussion**

William D. Carey, MD: Does biopsy of nontumorous portions of the liver have value, either by showing dysplasia or perhaps through a staining technique, in predicting the development of liver cancer?

Morris Sherman, MD, PhD: I believe that you're referring to a recent study in which microarray technology was used to identify patients at risk for the development of a de novo tumor after a resection of the first tumor. Liver tissue surrounding the tumor was analyzed by microarray technology, and gene expression profiling accurately predicted the development of a new tumor in another part of the liver more than 2 years later. This discovery suggests the presence of a field defect, or a propensity for the development of new tumors in a damaged organ. Patients who have a field defect identified by the microarray technique are at much higher risk of developing a subsequent cancer. These patients might be candidates for liver transplant despite apparent surgical cure of their HCC. However, because the subsequent liver malignancy occurs some time later and is a new primary tumor, the need for transplant is less urgent than it is for a patient with a progressive hepatoma, for example.

Pierre M. Gholam, MD: Do you consider ethnicity in addition to age, viral load, and other factors in your decision to screen patients for HCC?

Dr. Sherman: We traditionally think of ethnicity as a major factor because HBV is concentrated in Asian and African populations. I'm not entirely sure whether ethnicity or the viral genotypes are more important, because the viral genotypes are distributed along ethnic lines. We know that genotypes B and C, which are common in the Far East, are associated with a high rate of progressive liver disease. Genotype D, observed mainly in Middle Eastern and Greek populations, is associated with a much higher rate of progressive liver disease than genotypes common in Western Europe and most of North America. I believe that genotype should be a factor in decisions to screen.

Robert G. Gish, MD: In your case presentation you described the aspartate aminotransferase (AST) and ALT as being normal. New criteria define an AST/ALT...
of 20 as being “healthy” for a woman. I like the word “healthy” better than “normal.” How would you have described those test results to the patient?

Dr. Sherman: I would have told her that although her AST and ALT levels were within the laboratory reference range, ideally for a young woman the ALT should be closer to 20 U/L. Her actual levels were at least twice the upper range of ideal, and therefore, I believe a biopsy to determine the extent of injury in the liver would be important.

Tram T. Tran, MD: Are there any new serum markers for liver cancer that have promise?

Dr. Sherman: The problem with serum markers, or biomarkers in general, is the confusion over their intended use, such as for screening, risk stratification, or diagnosis.

I assume that your question refers to their potential use in screening, and so far none of the existing biomarkers is adequate to find small tumors. For screening purposes, you ideally want to find tumors that are 2 cm or smaller, and none of the biomarkers is efficient with those small tumors. A biomarker is not needed to identify tumors that are 5 or 6 cm.

■ DISCLOSURES

Dr. Sherman reported that he has received consulting fees and honoraria for teaching and speaking from Bristol-Myers Squibb Company, Gilead Sciences, Inc., and Roche Laboratories, Inc.

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■ REFERENCES


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ABSTRACT

The prevalence of hepatitis B virus (HBV) infection in the Asian American population is disproportionately high compared with the US population as a whole. Effective management is difficult because of cultural barriers, which can be better understood with recognition of the diversity of the Asian continent in terms of language and spiritual beliefs. Barriers to care among the Asian American population include educational deficits, low socioeconomic status, lack of health insurance, noncitizenship, inability to communicate in English, negative perceptions of Western medicine, and underrepresentation among health care professionals. Given the diversity of the population, some subpopulations may be more directly affected by certain barriers than others. The resulting delays in seeking care can lead to poor outcomes and risk of HBV transmission to household members. Health care providers are obligated to educate themselves regarding cultural sensitivity and to advocate for improved access to care.

KEY POINTS

- Some Asian Americans have limited proficiency in English and are isolated linguistically, limiting their ability to communicate with health care providers.
- Asian Americans may view Western medicine with suspicion, causing delays in seeking care and making it difficult to successfully manage chronic HBV infection.
- Sensitivity to cultural attitudes may enhance communication and the likelihood that immigrant patients will accept health care providers’ recommendations; cultural sensitivity training may be helpful.

Asian Americans represent 4% of the population in the United States, and their share of the US population is projected to grow to 9% by 2050.¹ These numbers are significant because of the high prevalence of hepatitis B virus (HBV) infection in this community and the cultural barriers to its effective management.

Appreciating the impact of cultural barriers on health care among Asian Americans requires an understanding of the diversity of the Asian continent, which is composed of 52 countries where 100 languages and dialects are spoken. Within each region are religious, cultural, and societal differences. Asians have immigrated to the United States over the course of several generations, and the era in which they immigrated may affect their ability to understand English, integrate into American culture, and navigate the US health care system. Successful integration into American life favors those whose families immigrated several generations earlier.

The overall prevalence of HBV infection in the United States is 0.4%; however, estimates of prevalence range from 5% to 15% in Asian American populations, and are as high as 20% in some Pacific Rim populations.²,³ The prevalence of HBV infection in Asian Americans differs by subpopulation, with the highest prevalence among immigrants from Vietnam, Laos, and China, and the lowest among those from Japan.

Of the approximately 1 million Americans estimated to be infected with HBV as of 2005, more than 750,000 had access to health care; of these, 205,000 were diagnosed with HBV infection,³ suggesting substantial underdiagnosis. Referrals to specialists were even fewer (175,000), and only about 31,000 patients chronically infected with HBV received antiviral treatment, a figure that has likely increased with greater awareness of HBV and the availability of new antiviral medications.

BARRIERS TO DIAGNOSIS AND TREATMENT

The barriers to effective management of HBV infection in Asian Americans include cultural, socioeconomic, and accessibility issues (see “Case: Stigma and cultural barriers lead to inadequate care,” page S11).

Language and linguistic isolation

Limited proficiency in English is a large, if not the largest, barrier to effective management of chronic HBV infection. According to the US Census Bureau, a person with limited English proficiency is one who does not speak English “very well.”⁶ This terminology...
Lack of health insurance and its correlates

The high percentage of Asian immigrants without health insurance is a challenge to providing adequate health care. Health insurance coverage is lacking for about one-third of Korean immigrants, about one in five immigrants from Southeast Asia and South Asia, and about 15% of Filipino and Chinese immigrants. Only half of Asian immigrants become naturalized compared with 38% of US residents.8

One reason for the large proportion of uninsured among these groups is the high rate of small business ownership among Asian Americans and the difficulty that small business owners have in obtaining affordable health insurance coverage. In addition, although Asian Americans are as likely as other US residents to be employed full time, their employment options may be less likely to include health insurance benefits.

Poverty affects the ability to acquire health insurance. Although the popular image of the Asian immigrant is an educated person with high earning potential, the reality is that poverty strikes immigrants from Southeast Asia at a high rate. Almost 40% of the Hmong population, for example, lives below the poverty level, and poverty rates among the Cambodian, Bangladeshi, Malaysian, and several other Asian subpopulations are nearly as high.5

Citizenship correlates with the ability to obtain health insurance; it is estimated that 42% to 57% of noncitizens lack health insurance, compared with 15% of citizens.8 Only half of Asian immigrants become naturalized citizens, with wide variability among subgroups. Two-thirds of Filipinos who immigrate to the United States eventually become naturalized compared with less than one-third of Malaysian, Japanese, Indonesian, and Hmong immigrants.8

Educational achievement is associated with attainment of financial security and health insurance. The vast majority of Taiwanese, Japanese, Filipino, and Korean Americans obtain a high school education or higher, with correspondingly higher rates of health insurance coverage. Among those from Southeast Asia (Hmong, Cambodians, Laotians, and Vietnamese), whose immigration to this country is relatively recent, fewer than half complete a high school education.8

Has implications for allocation of federal government resources; ie, the percentage of a community’s residents with limited English proficiency is a criterion for receipt of governmental grants and other forms of assistance, including translation services.5

Linguistic isolation, another barrier to medical care, is lack of an English-speaking household member who is older than 14 years.7 By this definition, more than one-third of Korean, Taiwanese, Chinese, Hmong, and Bangladeshi households, and almost half of Vietnamese households, are linguistically isolated, with limited ability to communicate with health care providers.8

Case: Stigma and cultural barriers lead to inadequate care

During a routine examination, a 55-year-old woman is found to have liver abnormalities; screening reveals that she is hepatitis B surface antigen (HBsAg) positive. The patient, who immigrated from Vietnam in 1982, speaks limited English but is accompanied by her daughter, who acts as translator. She has no complaints, has no history of intravenous drug or alcohol abuse, and reports feeling well. Her only medication is an antihypertensive drug. Her laboratory results include bilirubin 0.8 mg/dL, aspartate aminotransferase 92 U/L, alanine aminotransferase 126 U/L, albumin 3.8 U/L, international normalized ratio 1.2, and a platelet count of 166 × 10^4/L. Her HBsAg-positive status is confirmed, and her viral load is 1,100,000 IU/mL. Hepatic ultrasonography reveals a slightly nodular appearance. She is diagnosed with chronic hepatitis B virus infection, but despite extensive discussion with the patient and her daughter, she refuses further testing or workup. She says that she fears ostracism if friends and family know about her infection.

The patient is lost to follow-up for 2 years. When she is next seen, she reports using herbal medications daily in an effort to “clean her liver,” but now notices “yellow eyes” and a 10-pound weight loss. Her liver enzymes remain elevated, her bilirubin is now 3.4 mg/dL, and imaging studies reveal a 4-cm mass consistent with hepatocellular carcinoma.

Health care workforce representation

Certain Asian subgroups are underrepresented in the racial composition of the US health care workforce; this imbalance may affect accessibility to the health care system and adherence to medical prescriptions and instructions among underrepresented groups. Racial concordance between patient and health care provider is associated with greater patient participation in care, according to the Institute of Medicine.10 In addition to racial similarity, linguistic similarity enhances communication and adherence to instructions.

Belief systems and attitudes toward health care

An immigrant patient’s religious beliefs and cultural attitudes toward Western medicine may pose difficulties in successfully managing disease. Many Asian Americans are Buddhists, who may believe that suffering is an integral part of life; proactively seeking medical care may not be imperative for them. Confucianism, the worship of ancestors and the subjugation of the self to the well-being of the family, is a common belief system among Asians that may inhibit the desire to seek needed care.
medical care. For example, a family elder may instruct a young man not to seek medical care for his HBV infection because this would jeopardize his siblings’ marriage prospects. Taoism involves the belief that perfection is achieved when events are allowed to take the more natural course. Intervention is therefore frowned upon.

Some belief systems may impede care because they incorporate indifference toward suffering. Many Hmong believe that the length of life is predetermined, so life-saving care is pointless. Cultural value may be placed on stoicism, discouraging visits to health care providers. A belief that disease is caused by supernatural events rather than organic etiologies is another perception that serves as a barrier to seeking medical care.

Distrust of, or unfamiliarity with, Western medicine may delay care, and the resulting poor outcomes may be falsely attributed to Western medicine itself. In some cultures, there is a pervasive belief that a physician can touch the pulse and identify the problem. Some Laotians believe that immunizations are dangerous for a baby’s spirit, and therefore forgo immunization against HBV when it is indicated.

The patient’s relationship with his or her health care provider is an important determinant of quality of care and willingness to continue to receive care. The best possible scenario is concordance in language and culture. Asian cultures emphasize politeness, respect for authority, filial piety, and avoidance of shame. Because Asian patients often view physicians as authority figures, they may not ask questions or voice reservations or fears about their treatment regimens; instead, they may express their agreement with physicians’ advice, but with no intent to return or follow instructions. Infection with HBV carries a stigma about the mode of transmission that can interfere with patients’ daily lives. A study of attitudes about HBV found that HBV-infected patients feel less welcome to stay overnight or share the same bathroom at friends’ or relatives’ houses, that noninfected persons fear that the disease may be passed to them by HBV-positive friends, and that HBV-infected patients are concerned about whether their choices may have led to the infection.11

■ OVERCOMING BARRIERS

Sensitivity to cultural attitudes may enhance communication and the likelihood that patients will accept physicians’ recommendations. Several office visits may be necessary to confirm that a patient is receptive to the health care provider’s instructions and is adhering to them. Referral to access programs can aid communication. For example, most cities have community centers where patients can seek medical advice from physicians who speak the patients’ language; these centers also may provide native-language materials and interpreters.

Offering reassurance to patients in their own language and in a culturally sensitive setting will help break down barriers and improve care. Patients who are educated about HBV transmission and the availability of an effective vaccine may be instrumental in preventing transmission of the disease to household members.

Cultural sensitivity training will benefit health care providers and staffs whose patients include Asian Americans. Educational programs should be specific to the needs of the community, as different subpopulations have different needs. Resource materials are available for such training; for example, the federal government’s Office of Minority Health Web site (http://www.omhrc.gov/) offers links to resources for cultural training. In addition to educating themselves and their staffs, health care providers have a responsibility to advocate for funding and equal access to care, and for the creation of more cultural and community health centers that can serve as resources to overcome cultural barriers.

■ DISCUSSION

Robert G. Gish, MD: How often are herbal remedies tried for chronic HBV infection in the patients you see, especially in the Vietnamese population?

Tram T. Tran, MD: Once patients are diagnosed with chronic HBV infection, the use of herbal remedies is very high; it approaches 80% in my practice. Patients may not admit to it unless you ask them specifically, because they know herbal remedies may be somewhat frowned upon by Western physicians. If you are careful and ask very gently about their use of herasals, they will tell you that they do believe in herbal medicines pretty strongly.

Morris Sherman, MD, PhD: I’d like to emphasize the need to be able to communicate with patients in their own language. In Toronto, 50% of the population was born outside of Canada. We have a huge immigrant population; given the nature of hepatology, we have many patients from Southeast and South Asia, and from all over the world, who don’t speak English. My hospital has a multilingual interpreter service, which we use freely. Scarcely a day goes by without two or three interpreters coming to the clinic to talk to patients, and as a result it’s rare that I can’t make myself understood. Maybe what I’ve said hasn’t been accepted, but patients can at least understand what I’m saying.

William D. Carey, MD: I interview many applicants for our medical school, and many of them are Asians, including Hmong and Vietnamese. With the high value that most of these groups put on education and their success with educational attainment, is their access to care improving? Are we doing a better job of training nurses, allied health personnel, and physicians to deal with this problem?
Dr. Tran: I think so, yes. For instance, the Southeast Asian immigrant population arrived in two different eras. The Vietnamese who immigrated in 1975 have been in the United States longer and in general have been able to attain a higher level of education than those who came later. The group that arrived earlier is therefore more likely to have health insurance, and it has been easier to get them into the health care system. More recent immigrants have had more difficulty navigating the system. In general, their socioeconomic status and therefore access to care is directly related to how long they have been in the country.

DISCLOSURES

Dr. Tran reported that she has no financial interests or relationships that pose a potential conflict of interest with this article.

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Hepatitis B treatment: Current best practices, avoiding resistance

ABSTRACT

All patients who are positive for hepatitis B virus (HBV) DNA should be considered for antiviral treatment. Potency in suppressing HBV DNA is the main factor in the choice of first-line therapy; entecavir and tenofovir constitute the most potent nucleoside and nucleotide analogues to date with the lowest rates of resistance. Viral negativity may reduce the development of liver failure and the need for transplant, although these benefits need to be demonstrated prospectively. Loss of hepatitis B surface antigen, or seroconversion, may represent a new treatment paradigm. The development of resistance to therapy can result in virologic breakthrough and serious clinical consequences. Use of the most potent agents as first-line therapy lowers the risk of resistance; but if resistance develops, adding an additional agent, rather than switching to another therapy, is advised.

KEY POINTS

Consider treatment for chronic HBV infection for all patients who are positive for HBV DNA, as viral load levels as low as 300 copies/mL confer a risk for hepatocellular carcinoma. The goal of therapy is an undetectable level of HBV DNA; initiate therapy with the most potent agent to limit the possibility of resistance.

Preventing resistance to therapy is crucial for successful treatment of chronic HBV infection.

GUIDELINES

Guidelines for the management of hepatitis B virus (HBV) infection can be daunting to clinicians. Further, although established practice guidelines can provide direction, treatment of chronic HBV infection is characterized by uncertainties that can hinder optimal patient care. Reservations about when to initiate and terminate therapy, cost issues, and the development of resistance to therapy are among the factors that impede adequate treatment. This article offers a straightforward roadmap for the management of chronic HBV infection, based on interpretation of recently released guidelines,1–3 and strategies for preventing and managing resistance to antiviral therapy.

DECIDING TO TREAT

Key factors: Viral load and ALT

Two important factors influencing the decision to treat are viral load (HBV DNA) and alanine amino-transferase (ALT) level; although these are relatively straightforward measures, other factors can cause clinicians to avoid or delay treatment.

A simple guideline is to discuss treatment with any patient who is positive for HBV DNA. The most recent guidelines for the treatment of HBV infection, published by the European Association for the Study of the Liver (EASL), recommend an HBV DNA level of 2,000 copies/mL as a threshold for initiating therapy; this recommendation applies to patients who are either positive or negative for hepatitis B e antigen (HBeAg).3

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study investigators used ultrasensitive polymerase chain reaction (PCR) to quantify HBV DNA levels and conducted a time-dependent multiple Cox regression analysis of HBV DNA level and the risk of hepatocellular carcinoma (HCC).4,5 The length of time at a given DNA level was weighted in determining the adjusted hazard ratio. With an HBV DNA level less than 300 copies/mL defined as the reference group, risk of HCC increased commensurate with increasing HBV DNA level; even at levels ranging from 300 to 10,000 copies/mL, longer duration of HBV DNA positivity increased risk. This group also found HBV DNA level to be an independent risk factor for cirrhosis.

Patients who are HBV DNA negative are at much lower risk of cirrhosis and HCC than HBV DNA–positive patients; HBV DNA–negative patients being treated with antiviral drugs are much less likely to develop resistance to treatment, provided that first-line medications such as tenofovir or entecavir are used.

The definition of a “healthy” ALT level is controversial. In my opinion, an abnormal ALT is greater than 19 IU/mL.

See end of article for author disclosures. doi:10.3949/ccjm.76.s3.04
GOALS OF THERAPY:

VIRAL LOAD SUPPRESSION, SEROCONVERSION

Profound suppression of viral load reduces the risk of resistance and is the ultimate goal of therapy for HBV infection. We can infer from recent data that achieving HBV DNA negativity has led to improved outcomes in patients with chronic HBV infection; ie, with the increased use of antiviral drugs in the United States over the past 2 decades, the number of liver transplants for end-stage liver disease has fallen dramatically, suggesting that profound suppression of viral loads has translated into fewer cases of liver failure and less need for transplants.

Over the same period, the number of patients diagnosed annually with HCC has increased by 146%. In discussing treatment duration with patients, I present the ultimate goal of therapy as loss of HB surface antigen (HBsAg), or seroconversion to anti-HBs. At our clinic, we monitor HBsAg at least annually when patients are on long-term therapy.

The cost-effectiveness of treating all patients until they are HBsAg negative needs to be assessed. Incremental cost-effectiveness ratios per quality-adjusted life-year are key to identifying the best course of action.

Case: Viral breakthrough after switching therapy

A 31-year-old man born in San Diego of Asian parents presented in September 2000 with pain in the right upper quadrant, diarrhea, yellow eyes, and dark urine. He was referred for a life insurance policy 2 years previously because of a liver problem, but did not know the details. His mother and brothers are positive for hepatitis B virus (HBV). At first presentation, his alanine aminotransferase (ALT) level was 3,285 U/L, his bilirubin was 21 mg/dL, and his HBV DNA was not especially high: 10^3 copies/mL. He was hepatitis B surface antigen positive. He was diagnosed with probable acute exacerbation of chronic HBV infection.

The patient was followed without treatment, and his bilirubin and transaminase levels soon returned to normal. By February 2001, his transaminase levels were again elevated (ALT, 395 U/L) and his viral load was 10^7 copies/mL. Treatment with lamivudine was initiated in 2002, and his ALT promptly normalized and has remained normal to the present time. His viral load became undetectable and remained undetectable until 2004, when it increased to 10^7 copies/mL; at that point the decision was made to switch therapy from lamivudine to adefovir, after which his HBV DNA again became undetectable and he seroconverted from HBs antigen (HBsAg) positive to HBsAg negative.

His HBV DNA was monitored regularly and remained undetectable until October 2008, when it was 10^3 copies/mL, representing a second virologic breakthrough.

Should we add therapy, switch to yet another agent, or continue the course?

Barriers to optimal treatment

Patient reluctance to undergo invasive tests, concerns about resistance, confusion about when to initiate therapy, cost, and other issues can impede timely and effective treatment of HBV infection.

Invasive studies. Liver histology is a key driver for initiating treatment, but many patients resist undergoing a liver biopsy. Ultrasonography has enabled noninvasive determination of spleen size, portal vein size, and liver tissue and surface heterogeneity; noninvasive assessments such as measurement of aspartate aminotransferase, varices, serum markers of fibrosis, and platelet count may provide clues to advanced liver fibrosis. Eventually, ultrasonographic elastography to measure liver stiffness and magnetic resonance scans may be common in clinical practice for noninvasive evaluation of liver damage. Ultimately, however, liver biopsy remains a valuable tool to motivate patients with chronic HBV infection to initiate and continue antiviral therapy.

Rationales for avoiding or delaying treatment. Concern about the development of resistance to treatment, as with antiviral therapy directed against human immunodeficiency virus (HIV), is one reason not to treat. The absence of clear guidelines regarding the appropriate time to terminate therapy has also led to avoidance or delay of treatment. The lack of risk calculators similar to the Framingham risk score, which estimates the risk of coronary heart disease, has limited the treatment of chronic HBV infection.

Cost. Cost must be examined in relation to the cost of resistance developing and the cost of treating complications. Lamivudine, considered a third-line treatment for chronic HBV infection, is an inexpensive drug. However, up to 70% of patients will develop resistance to lamivudine over 5 years; most will require combination therapy, with its attendant costs, and may eventually require transplants or experience poor clinical outcomes. Although the initial costs of potent first-line therapies (tenofovir, entecavir, and pegylated interferon) are high, cost modeling shows that they are less expensive over the long term when the overall cost of care is considered.

for women and greater than 25 IU/mL for men; in either setting, treatment should be instituted if the patient is HBV DNA positive. This position is supported by a recently published algorithm, a recent National Institutes of Health conference on management of HBV, and other sources.

Although the initial costs of potent first-line therapies (tenofovir, entecavir, and pegylated interferon) are high, cost modeling shows that they are less expensive over the long term when the overall cost of care is considered.
The nucleoside analogues lamivudine, entecavir, and telbivudine, and the nucleotide analogues adefovir and tenofovir, are indicated for the treatment of HBV infection. These agents differ in their capacity to suppress HBV DNA, are associated with differing rates of resistance (Table 1), and therefore have different roles in the management of chronic HBV infection (see “Case: Viral breakthrough after switching therapy,” page S15). Pegylated interferon has also demonstrated utility in certain patients with chronic HBV infection.

**Nucleoside analogues**

**Lamivudine.** The incidence of lamivudine resistance increases with increased treatment duration, reaching a peak of 80% after 5 years of treatment; use of this agent eventually requires combination therapy. For this reason, lamivudine is considered a third-line drug and is not recommended as a first-line therapy.

**Entecavir.** Entecavir induces profound suppression of HBV DNA (to undetectable levels by weeks 24 to 36) in patients who are HBeAg positive or negative, regardless of baseline HBV DNA levels; resistance rates are very low in treatment-naive patients, and entecavir is therefore considered first-line therapy. More than 90% of HBeAg-positive or -negative patients who are adherent to entecavir are HBV DNA negative at 5 years. Loss of HBsAg is 5% in entecavir-treated patients at follow-up of approximately 80 weeks, which is roughly double the rate of HBsAg loss with lamivudine.

**Telbivudine.** Telbivudine has a secondary role in treatment of HBV infection. In a study by Lai et al, the cumulative incidence of telbivudine resistance and virologic breakthrough in HBeAg-positive patients rose from nearly 5% after 1 year to 22% after 2 years of treatment. Although the incidence was lower in HBeAg-negative patients, rates of genotypic resistance with virologic breakthrough rose to 9% in this population.

Since these results report genotypic resistance and virologic breakthrough, the rates of genotypic resistance in these patients may actually be higher than reported. Indeed, genotypic resistance was detected in 6.8% of the entire study population after 1 year of treatment. In this study, it must be remembered that patients with HBV DNA levels that were detectable by PCR (≥ 300 copies/mL) but were less than 1,000 copies/mL were not assessed for resistance.

Because of high rates of resistance associated with telbivudine, its role in the treatment of chronic HBV is secondary. I may use it in pregnant patients because most other nucleoside analogues are category C drugs and telbivudine is a category B agent (see “Management of hepatitis B in pregnancy: Weighing the options,” page S25). There are risks of myositis and neuropathy with telbivudine; although these risks are low, I mention them to patients when discussing a treatment plan.

**Nucleotide analogues**

**Adefovir.** Adefovir is considered second-line or add-on therapy when resistance to lamivudine develops because of its low potency in suppressing viral load. At 48 weeks, only 12% of HBeAg-positive patients are HBV DNA negative when treated with adefovir monotherapy.

In a phase 3 clinical trial, genotypic resistance to adefovir was detected in 29% of HBeAg-negative patients treated for up to 5 years. The probability of resistance with virologic breakthrough was 3%, 8%, 14%, and 20% after 2, 3, 4, and 5 years of treatment, respectively. In patients infected with lamivudine-resistant HBV, the probability of adefovir resistance is reduced by adding adefovir to ongoing lamivudine therapy, according to data from a large retrospective comparative study. In patients treated with adefovir monotherapy, the probability of virologic breakthrough (defined as > 1 log10 rebound in HBV DNA compared with on-treatment nadir) reached 30% over 36 months. In patients treated with add-on adefovir, the probability of virologic breakthrough was reduced to 6%. Similarly, the probability of adefovir resistance over 36 months of treatment was greater in the adefovir monotherapy group (16%) than in the add-on adefovir group (0%). Although adefovir resistance is observed infrequently when adefovir is added to lamivudine, the effectiveness of adding adefovir is still limited by its low potency.

**Tenofovir.** More than 90% of HBeAg-negative

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**TABLE 1**

Rates of viral resistance to drugs for treating HBV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance at year of therapy (% patients)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>23</td>
</tr>
<tr>
<td>Entecavir (naïve)</td>
<td>0.1</td>
</tr>
<tr>
<td>Entecavir (laminudine-resistant)</td>
<td>6</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2.7</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td>4.4</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>0</td>
</tr>
<tr>
<td>Adefovir (naïve)</td>
<td>0</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td>0</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>0</td>
</tr>
<tr>
<td>Adefovir (laminudine-resistant)</td>
<td>0–18</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>0</td>
</tr>
</tbody>
</table>
patients and nearly 80% of HBeAg-positive patients treated with tenofovir have persistent virologic responses and HBV DNA levels less than 400 copies/mL by 72 weeks, with minimal side effects. Marcellin et al reported no development of resistance to tenofovir after 48 weeks of treatment. Although the nucleotide analogues have been associated with renal toxicity, the risk of renal toxicity associated with tenofovir is 1% or less per year; it can be reduced even further by calculating renal function through the use of the Cockroft-Gault equation or the Modification of Diet in Renal Disease equation prior to therapy and adjusting the dosage accordingly.

With profound HBV DNA suppression, HBsAg loss occurs in about 5% of tenofovir-treated patients at 64 weeks.

Treatment with tenofovir in treatment-experienced patients leads to potent suppression of HBV DNA independent of HBV genotype, HBV mutations (YMDD mutations) that signal lamivudine resistance, or HBeAg status at baseline. Patients with genotypic resistance to adefovir at baseline had a lower probability of achieving HBV DNA suppression during treatment with tenofovir.

Pegylated interferon
Pegylated interferon has proven useful in subsets of HBV DNA–positive patients. These include patients with genotype A or B who are young, those with high ALT levels (≥ 2 or 3 times the upper limit of normal) and low viral load (< 10⁷ copies/mL), and patients without significant comorbidities. Pegylated interferon is also an option for patients who require a defined treatment period (eg, a woman wishing to become pregnant in 1 to 2 years). The patients who would benefit from pegylated interferon as first-line therapy must be better defined, and early markers of virologic response need to be identified.

PREVENTING AND MANAGING RESISTANCE
Antiviral drug resistance has a negative impact on the treatment of patients with chronic HBV infection. The development of resistance can result in virologic breakthrough (a confirmed 1 log₁₀ increase in plasma HBV DNA levels); increased ALT levels; and the progression of liver disease, including hepatic decompensation, development of HCC, and need for liver transplant. In addition, resistance mutations may re-emerge, with covalently closed circular DNA representing a genetic archive for development of resistance; this can significantly limit future treatment options. Early detection and regular monitoring are critical to prevention and management of resistance.

Detection
Detecting virologic breakthrough as early as possible increases the likelihood of achieving virologic response. In a study by Rapti and colleagues, patients with lamivudine-resistant chronic HBV were treated with a combination of lamivudine and adefovir. The 3-year cumulative probability of virologic response (< 10⁷ copies/mL) was 99% with the addition of adefovir when baseline viral load levels were less than 5 log₁₀ copies/mL, but only 71% when baseline viral loads were greater than 6 log₁₀ copies/mL.

FIGURE 1. The algorithm used at California Pacific Medical Center for preventing and managing resistance incorporates the use of sensitive assays to measure viral load (HBV DNA), frequent monitoring to detect possible virologic breakthroughs, and a therapeutic plan that includes options to switch or add on to current therapy. Combination therapy is appropriate only for patients in whom therapy has failed to suppress viral load, who are drug resistant, who are posttransplant, and who are coinfected with human immunodeficiency virus.

Algorithm to prevent and manage resistance

<table>
<thead>
<tr>
<th>Preferred treatment options</th>
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<tbody>
<tr>
<td>Tenofvir</td>
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<table>
<thead>
<tr>
<th>Response and resistance monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure HBV DNA with sensitive assays; monitor virologic changes every 3 to 6 months; monitor for breakthrough and adherence</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome</th>
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<tr>
<td>No resistance identified with viral negativity</td>
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<tr>
<td>Resistance identified</td>
</tr>
<tr>
<td>Inadequate virologic response</td>
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<thead>
<tr>
<th>Therapeutic plan</th>
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<tr>
<td>Continue with planned medication</td>
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<tr>
<td>Switch to second medication</td>
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<tr>
<td>Add second medication</td>
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<tr>
<td>Combination therapy</td>
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<td>Combination therapy</td>
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Effective antiviral therapy for chronic HBV includes nucleos(t)ide analogues and pegylated interferon. Nucleos(t)ide analogues are the first-line antiviral agents for patients infected with HBV and include lamivudine, emtricitabine, adefovir, telbivudine, and tenofovir. Pegylated interferon has proven useful in subsets of HBV DNA–positive patients. These include patients with genotype A or B who are young, those with high ALT levels (≥ 2 or 3 times the upper limit of normal) and low viral load (< 10⁷ copies/mL), and patients without significant comorbidities.
Case revisited

The patient is an example of an individual who first had resistance to lamivudine and then to adefovir. A lamivudine-resistant strain of HBV that includes the resistance mutation rtA181T has been described, and also confers resistance to adefovir. In this particular patient, I would switch to tenofovir and add entecavir to manage him over the long term, and defend my action to the insurance company if it denied payment for this treatment approach. Tenofovir alone, based on in vitro data and recent data presented by van Bömmel et al., can be predicted to have a substantial chance of failure; this patient is therefore a candidate for combination therapy.

Monitoring

Patient response must be defined correctly. In adherent patients who show an early favorable response to therapy, I advise HBV DNA testing every 3 to 6 months. For those whose response flattens and whose viral load remains high, switching therapy or adding on should be considered. We continue therapy and monitor regularly after HBV DNA reaches an undetectable level. If the response is suboptimal, the treatment regimen is adapted by adding a new agent or switching to an alternative therapy (see “Case revisited”).

For patients who are being treated with tenofovir or entecavir, I typically extend the interval of measuring DNA levels to every 6 months because rates of resistance with these agents are low. If response is suboptimal but resistance is absent, I consider switching to the opposite drug. In those patients with a resistance mutation, I add the other agent.

Managing resistance

At California Pacific Medical Center, our strategy for limiting the possibility of resistance is to use entecavir or tenofovir as first-line therapy (Figure 1). Combination therapy with these two agents is preferred for any patient with resistance mutations. We do not use lamivudine or adefovir because of their low potency and the availability of tenofovir and entecavir.

Combination therapy has a role in individuals in whom medication has failed to suppress viral load, in the setting of drug resistance, after liver transplant, and in individuals coinfected with HIV (see “Strategies for managing coinfection with hepatitis B virus and HIV,” page S30). If patients demonstrate resistance to their current therapy, we examine viral factors, adherence to therapy, and medication availability (eg, cost and insurance coverage). Switching to entecavir in adefovir-resistant patients produces profound suppression of HBV DNA. Patients in whom entecavir or lamivudine have failed may respond to tenofovir, depending on the resistance mutations.

A POTENTIAL FUTURE OPTION

Clevudine is a nucleoside analogue in phase 3 clinical studies in the United States. Its potential role in therapy is not yet clear. To be determined is whether it will induce a long-term, off-treatment viral response, in which case treatment may be able to be terminated earlier, and whether it will show clinically important cross-resistance with other nucleoside analogues. The availability of more sensitive assays to demonstrate the emergence of early viral resistance would enable earlier changes in treatment for more successful outcomes.

SUMMARY

Preventing resistance is crucial to the success of antiviral drug therapy for treatment of chronic HBV; a persistently high viral load increases the risk of cirrhosis and HCC, and resistance is associated with increased HBV DNA levels. The best chance for long-term success depends on initiating therapy before cirrhosis develops, when viral load is still low; profound suppression of viral load using the most potent agents as first-line therapy; and long-term monitoring of HBV DNA. The development of resistance can result in virologic breakthrough and liver complications. Entecavir and tenofovir represent the most effective first-line options to suppress HBV DNA. Because cross-resistance can occur, adding another agent is preferred to switching agents if resistance to initial therapy develops.

DISCLOSURES

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Powerful antiviral medicines with activity against hepatitis B virus (HBV) have long-term records of potency and safety, supporting the case for monotherapy in treatment-naïve patients. Combination therapy has a limited role in the management of HBV infection; if the approach to treatment is rational from the start, then combination therapy can be reserved for cases of treatment failure or resistance.

THE CASE FOR MONOTHERAPY

Three arguments that favor monotherapy with potent medications are cost, low risk of resistance, and unproven benefit of combination therapy.

Cost
The cost of dual-medication therapy is nearly double that of single-drug therapy, while the benefit is unknown in treatment-naïve patients. My choices for first-line therapy are tenofovir or entecavir, highly potent nucleoside/nucleotide analogues that can cost up to $5,500 and $8,000, respectively, per year of treatment.1 The two in combination would cost nearly $14,000 per year, and benefits have not been proven in the treatment-naïve population.

Low risk of resistance
Potent medications have low rates of resistance, in the range of 1% over 2 to 5 years.2-4 If one starts therapy with the highly potent entecavir, discussions about switching or adding on therapy would be superfluous because of the low rates of resistance and failure associated with entecavir monotherapy. At 5 years, the cumulative rate of entecavir resistance in patients with positive HBV DNA at baseline is 1.2%.5 Tenofovir also produces potent inhibition of HBV DNA and is associated with low rates of resistance,6 although follow-up data with tenofovir extend only to 2 years. Starting therapy with the less potent adefovir, followed by the development of resistance, decreases the probability that tenofovir will achieve HBV DNA suppression during treatment.7 The main driver of resistance is nonadherence with therapy, not treatment failure.

Resistance to pegylated interferon has not been encountered. The therapy is limited in duration (24 to 48 weeks), with durable suppression of HBV DNA and high rates of seroconversion from hepatitis B e antigen (HBeAg)-positive to HBeAg-negative status. Parameters for the use of pegylated interferon as first-line therapy have been established, and include patients with genotype A or B who are young, have HBV DNA levels less than 107 copies/mL, have serum alanine aminotransferase (ALT) levels two to three times the upper limit of normal, and lack significant comorbidities.3,4

Unproven benefit of combination therapy
Perhaps the most convincing argument against combination therapy is that numerous studies of combinations have failed to demonstrate a benefit compared with monotherapy in treatment-naïve patients:

- Interferon in combination with lamivudine has not been shown to be significantly more effective than lamivudine monotherapy.8,9 Further, because of limited information on the safety of interferon in combination with nucleoside or nucleotide analogues, use of the combination is not recommended.4 Neuropathy has been reported with the combination of interferon and telbivudine,4 leading to the release of a warning about its use.10
- A 1-year trial by Lai et al failed to show an improvement in virologic and biochemical responses with the combination of telbivudine and lamivudine.
compared with telbivudine alone.¹¹

- In patients with lamivudine-resistant chronic HBV infection, adefovir reduced serum HBV DNA levels by 4 weeks whether or not lamivudine therapy was ongoing.¹²

- Although more patients taking a combination of adefovir and the nucleoside reverse transcriptase inhibitor emtricitabine had normalization of ALT and suppression of HBV DNA to less than 300 copies compared with adefovir monotherapy, rates of HBeAg seroconversion were comparable in the two arms.¹³

- A recent study that compared tenofovir monotherapy with tenofovir and emtricitabine in combination showed comparable effectiveness for both regimens; the authors concluded that further study is necessary before either choice can be recommended as superior to the other.¹⁴

**RESISTANCE: IDENTIFY EARLY, ADD ON**

To minimize the likelihood of resistance and its impact, HBV DNA levels should be monitored every 3 months; at the first sign of a virologic breakthrough, therapy should be added or switched. Resistance to lamivudine is apparent early; models of treatment response indicate that resistance to lamivudine is likely if HBV DNA does not become undetectable by week 4.

In cases of lamivudine failure, adding adefovir early, when the viral load is less than 10⁷ copies/mL, increases the probability of a virologic response.¹⁵ In the situation of lamivudine failure, I prefer adding on to switching to reduce the risk of resistance—a practice supported by the study just cited.¹⁵ In lamivudine-resistant patients, adefovir monotherapy was associated with virologic breakthrough and resistance to adefovir in 21% of patients, whereas no patient experienced virologic breakthrough or resistance when adefovir was added to lamivudine.

Successful management involves choosing the best medication up front and educating patients about the importance of taking their medication as instructed. For example, entecavir should be taken without food to maximize its bioavailability. With tenofovir, the risk of renal toxicity is low (1%),¹⁶ and can be reduced even further with a pretreatment assessment of the patient.

**Multiple-drug therapy is the wave of the future**

*By Pierre M. Gholam, MD*

A concise rationale for multiple-drug therapy is that resistance to monotherapy will occur eventually, with serious consequences in some patients and grave public health implications over the long term. Data from France and Australia indicate that multidrug-resistant HBV is a reality in individual cases. Resistance may be less likely when combinations are used, although little evidence exists at present to support this contention.

**COMBINATION THERAPY IS COMMON SENSE**

Much of the evidence supporting combination therapy for HBV is common sense:

- Most patients with HBV infection require treatment indefinitely, and duration of therapy that is not finite will inevitably lead to resistance.

- Your first shot is your best shot. Once resistance develops, treatment response will eventually decline.

- Sometimes the stakes are too high to risk breakthroughs. In particular, in patients who have cirrhosis and in those awaiting or following liver transplant, flares and recurrences can have disastrous consequences.

**Treatment duration and resistance**

As Dr. Gish demonstrated, tenofovir and entecavir are highly potent drugs that suppress viral loads effectively and have high genetic barriers to resistance. On an intent-to-treat basis, HBV DNA levels below the threshold level of detection are achieved at impressive rates with tenofovir and entecavir at 2 years in patients who are either HBeAg negative or positive.⁵,⁶,¹⁷ When the analyses are limited to patients who actually received the drugs, suppression of HBV DNA to undetectable levels exceeds 90%. Resistance to tenofovir is 0% at 2 years,³ and resistance to entecavir is 1.2% at 5 years.⁷

Although such data appear to favor monotherapy, most HBV-infected patients who commit to treatment will be treated indefinitely; this applies to patients who are HBeAg negative, who constitute most HBV-infected individuals in the United States and worldwide, or HBeAg positive. There are no established end points for treatment termination in HBeAg-negative patients. The only treatment termination end point that is deemed acceptable in HBeAg-positive patients is a period 6 to 12 months after the loss of HBeAg and the development of antibody to HBeAg, or e antigen seroconversion. Even after many years of treatment that includes the first-line agents tenofovir and entecavir, the likelihood of achieving this end point is fairly low.⁵,⁶,¹⁸
Adherence is also a consideration. Studies of patients with hypertension, heart disease, and other chronic diseases have shown that strict adherence to therapy over decades is unlikely. The same adherence pattern probably applies to the treatment of chronic HBV infection.

Antiviral drugs used in the treatment of chronic HBV infection are associated with certain resistance mutations that confer additional risk of developing resistance to a subsequent drug. Furthermore, with indefinite duration of therapy, it is realistic to expect that resistance will develop.

Other factors play roles in the development of resistance:

- **Mutant viruses.** We do not fully understand the potential problem of transmission of mutant viruses. This phenomenon is becoming apparent in endemic areas where treatment-naive patients harbor mutant viruses acquired through sexual contact with HBV-infected patients who have been treated and in whom the virus has subsequently mutated.

- **Barriers to resistance.** The genetic barrier to resistance for a single drug will eventually be overcome. It may take longer than it took for adefovir, which is associated with a 30% rate of resistance at 5 years.3 It may take a much longer time for entecavir or tenofovir, but resistance is a biological certainty and we need to contend with it. With human immunodeficiency virus (HIV) infection, we are able to genotype for mutations and tailor treatment accordingly. This strategy is not currently recommended for HBV infection, partly because it is expensive and not routinely available.

- **Misuse of therapy.** Finally, wider use of antiviral agents for the treatment of HBV may lead to wider misuse, and therefore more resistance. Realistically, not every practitioner will start therapy with entecavir or tenofovir; many of the less potent agents have associated rates of resistance, and these in turn may confer an additional risk of resistance if tenofovir or entecavir is eventually used.

**Declining response**

Colombo et al19 studied the likelihood of entecavir resistance developing in patients with existing lamivudine resistance. The likelihood of resistance to entecavir at 3 years was 1.2% among patients who had never been exposed to lamivudine. Among patients in whom lamivudine resistance had developed and who were subsequently started on entecavir, resistance to entecavir was 32% at 3 years.19 Resistance has consequences; 25% of lamivudine-resistant patients develop viral breakthrough.

Dr. Gish and I agree that the addition of adefovir to lamivudine is better than switching to adefovir monotherapy in the case of lamivudine failure. Compared with switching, the adefovir-lamivudine combination leads to a lower incidence of virologic breakthrough, a lower likelihood of adefovir resistance over time, a greater probability of achieving undetectable levels of HBV DNA (< 35 copies/mL), and a lower cumulative rate of resistance.20 The superiority of combination therapy in achieving undetectable levels of HBV DNA confers a lower risk of developing resistance over time; by year 4, the likelihood of adefovir resistance is only 4% among lamivudine-resistant patients treated with the combination of adefovir and lamivudine.20

In a study of nucleoside analogue–experienced patients who did not achieve viral suppression, response to tenofovir, defined as HBV DNA less than 400 copies/mL at month 12, was 85% overall and only 30% in adefovir-resistant patients.7 These data demonstrate that, if not starting with combination therapy, it is preferable to initiate treatment with a potent drug that is highly successful at HBV DNA suppression. A second monotherapy will be less successful than the initial attempt.

**Consequences of resistance**

The consequences of resistance in patients with cirrhosis are significant, prompting strong consideration of combination therapy as a potential means to avoid resistance.

One consequence is a well-documented potential for decompensation in the setting of new-onset resistance as a result of flares. Another is post-transplantation recurrence of HBV, leading to poor outcomes. These risks converge in the patient who is awaiting liver transplantation, in whom combination therapy seems to make the most sense to prevent the development of a flare and a recurrence of HBV infection after transplantation.

**WHO SHOULD RECEIVE MULTIPLE-DRUG THERAPY?**

The American Association for the Study of Liver Diseases recommends combination therapy as the preferred rescue therapy for primary failure of a first-line agent, citing the possibility of resistance with switching in some circumstances and the superiority of adding on as opposed to switching.2 No data clearly support de novo multiple-drug therapy. Although a number of studies have failed to show an advantage of combination therapy over monotherapy, they were of relatively short duration and focused primarily on viral suppression rather than the occurrence of resistance over time. Long-term studies are needed to determine whether combination therapy is an option de novo.

De novo multiple-drug therapy might be reasonable...
if a patient is at high risk for resistance—for example, for patients with extraordinarily high levels of HBV DNA or in whom resistance can lead to dire consequences, such as patients with cirrhosis or pretransplant patients. The HIV pandemic serves as a paradigm for combination therapy. Many agents used to treat HBV infection also have anti-HIV effects; their use as monotherapy should be avoided in order to prevent the development of HIV drug resistance. HIV regimens that include only one HBV antiviral agent with a low genetic barrier to resistance (eg, lamivudine) should also be avoided in order to minimize the risk of HBV drug resistance.

I agree with Dr. Gish that cost and potential toxicity, especially renal toxicity, may limit the widespread use of combination therapies.

Discussion

William D. Carey, MD: I hear more agreement than not between the debaters. Are there any comments from the panel?

Morris Sherman, MD, PhD: I'll comment on the guidelines for the treatment of HBV infection. Tong et al recently examined whether a group of HBV-infected patients who developed cirrhosis and hepatoma would have qualified for treatment under four current sets of guidelines. A startlingly large proportion of patients who developed adverse consequences from their liver disease would not have met the criteria for treatment under any of these major guidelines. As many as one-fourth of patients with chronic HBV infection die as a consequence of their liver disease, and in order to prevent these deaths up to one-half of the patients have to be treated. In the long run, overtreatment may be preferable to undertreatment to reduce the incidence of hepatitis-related deaths. My point is that the treatment guidelines probably exclude many patients who should be treated.

The factors I consider important in my decision to treat are a high viral load, which is indicative of active viral replication, and evidence of liver injury. Patients who have a high viral load and no liver injury won't experience complications. What do I consider evidence of liver injury? Prolonged elevation of ALT is suggestive, although not necessarily as high as 200 or 300 U/L; it could be in the range of 50 to 80 U/L if fibrosis is significant, which I define as stage 2 or greater on the biopsy. If a high viral load and evidence of significant liver injury are present, I treat the patient regardless of the precise level of the viral load or the ALT.

Dr. Carey: Can you clarify your position? Some of our earlier discussion emphasized the importance of treating when the viral load is high, regardless of other factors. A high viral load by itself may be associated with increased risk of cirrhosis or hepatocellular carcinoma without cirrhosis, so why would a biopsy make a difference?

Dr. Sherman: We can’t predict which younger HBeAg-positive patients with a very high viral load are going to run into trouble down the road. Many will seroconvert spontaneously and never have problems thereafter. In contrast, a patient in his 40s with a high viral load, even if HBeAg positive, and without major fibrosis should be considered for therapy. I tell my patients and the physicians who refer them that once I’m finished with the evaluation, it’s not good-bye. They have to be followed for life because things change.

Tram T. Tran, MD: In the paper by Tong et al, all of the patients who subsequently had poor outcomes had low platelet counts. I therefore recommend considering the entire picture in the decision to treat. If physicians followed the treatment guidelines strictly, they would not have treated those patients, but had they noticed thrombocytopenia they would have considered the possibility of advanced fibrosis and considered screening or a biopsy.

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ABSTRACT

Maternal screening and active and passive immunoprophylaxis have reduced the perinatal, or vertical, transmission of hepatitis B virus (HBV) dramatically. Without immunoprophylaxis, chronic HBV infection occurs in up to 90% of children by age 6 months if the mother is positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Even with immunoprophylaxis, perinatal transmission is possible when the mother is highly viremic and HBeAg positive. Antiviral therapy during the third trimester of pregnancy in high-risk women with chronic HBV infection reduces viral load in the mother and may decrease the risk of perinatal transmission, although data are lacking. Safety data in pregnancy are most robust with lamivudine and tenofovir compared with other therapies. Careful discussion with the patient regarding the risks and benefits of therapy is warranted. Prophylaxis remains the best method of prevention of perinatal transmission.

KEY POINTS

- Hepatitis B immune globulin at the time of birth plus three doses of the recombinant hepatitis B vaccine over the first 6 months of life is up to 95% effective in preventing perinatal transmission.

- Despite successful screening and vaccination, perinatal transmission of HBV is still possible if maternal viral load is high.

- Antiviral treatment during the third trimester of pregnancy may reduce perinatal transmission of HBV; the benefit appears most pronounced with high maternal viremia.

The management of hepatitis B virus (HBV) infection in pregnancy is complex. Because infection with HBV in infancy often leads to chronic disease, prevention of perinatal, or vertical, transmission is a worthy goal; yet, prophylactic therapy during pregnancy is not well studied. This article explores the consequences of HBV infection during pregnancy, the specific risks imposed by high viral load, the evidence to support preemptive antiviral therapy, and the timing of therapy during pregnancy.

PERINATAL TRANSMISSION

Perinatal transmission is the most common mode of HBV transmission worldwide; however, the maternal screening programs and universal vaccination in newborns with active and passive immunoprophylaxis have dramatically reduced HBV transmission rates. According to recent data from the US Centers for Disease Control and Prevention, prenatal screening for hepatitis B surface antigen (HBsAg) in the United States is nearly universal; 97% of pregnant women undergo screening before delivery. Further, among infants at risk of acquiring HBV infection, 92% complete the three-dose vaccination series by the time they are 3 years old. There is some nationwide variation, however, in the appropriate administration of immunoprophylaxis to infants exposed perinatally, ranging from 78% in Louisiana to 99.8% in one California health maintenance organization.

Perinatal transmission of HBV infection has declined steadily in the United States over the past 2 decades, consistent with the successful implementation of universal screening of pregnant women and vaccination policies. Outside the United States, however, many high-prevalence countries lack vaccination coverage and perinatal transmission is common. In 87 countries with a prevalence of HBV infection that exceeds 8%, the infant vaccine coverage was only 36%.

Risk of chronic infection

The risk of progression to chronic HBV infection is inversely proportional to the age at which the infection was acquired. Without immunoprophylaxis, up to 90% of infants born to hepatitis B e antigen (HBeAg)-positive mothers become HBV carriers. In comparison, 20% to 30% of children infected between age 1 year and 5 years, and fewer than 5% of immunocompetent adults, become HBV carriers.

If the mother is positive for both HBsAg and HBeAg
Case: Minimizing risk in a 29-year-old woman

Laura is a 29-year-old woman born in Hong Kong who is now living in the United States. She is 34 weeks pregnant and has recently tested positive for hepatitis B surface antigen. She feels entirely well. Her hepatitis B virus (HBV) DNA level is 8 × 10^6 copies/mL. Her aspartate aminotransferase level is 29 U/L and her alanine aminotransferase level is 20 U/L. How would you manage her HBV infection to minimize the risk of maternal-fetal transmission? Is there a role for preemptive antiviral treatment?

and her baby does not receive immunoprophylaxis, the risk of the baby developing chronic HBV infection by age 6 months is 70% to 90%.8,10 Of those exposed in early childhood, 28.8% are HBsAg positive by age 4 years.5 These data underscore the need for early vaccination.

In a study of 402 HBsAg-positive pregnant women in China, Xu et al11 found that 3.7% of their newborn infants were HBsAg positive within 24 hours of birth. Of the women who were HBeAg positive, the intrauterine infection rate was 9.8%. Analysis of placental tissue for HBsAg, hepatitis B core antigen (HBcAg), and viral load (HBV DNA) uncovered an overall placental infection rate of 44.6%.

Transplacental transmission of HBV has been observed in multiple studies, especially when mothers are positive for HBsAg and HBeAg and have high viral loads. Among mothers positive for HBeAg, Burk et al12 found an odds ratio of 147 for a persistently infected infant when the maternal HBV DNA level was at least 1.4 ng/mL compared with less than .005 ng/mL. Among the HBeAg-negative mothers, the odds ratio for a persistently infected infant was 19.2 with high versus low maternal HBV DNA levels.

Importance of maternal viremia

Despite successful screening and vaccination programs, high maternal HBV DNA correlates in some studies with perinatal transmission. Wiseman et al13 studied 298 chronically HBV-infected women and their infants, who were tested for HBV at age 9 months. Interim analysis showed a transmission rate of 8.5% for infants born to mothers with virus levels greater than 8 log_{10} copies/mL. These data suggest that perinatal transmission may still be occurring despite the use of effective active and passive immunoprophylaxis. Additional studies are needed to assess the potential risk reduction associated with treatment of high maternal viremia during pregnancy.

Maternal HBV DNA positivity was associated with a high rate of intrauterine transmission of HBV in a program in India in which 11,524 woman were screened for HBV infection.14 Babies of the 133 women found to be positive at the time of birth were screened for HBsAg, HBeAg, and HBV DNA in serum and cord blood. Of 127 deliveries in which the mothers were positive for HBV DNA, 66% of infants had HBV DNA in their cord blood and 41% had serum markers that were positive at birth. Maternal HBV DNA greater than 1.5 × 10^5 copies/mL was significantly associated with intrauterine transmission (P = .025), whereas mode of delivery and maternal HBeAg status were not. This study adds to the concern that in some cases, the vaccine and hepatitis B immune globulin (HBIG) given at the time of birth may not prevent infection in those born already infected and further supports the need to assess the treatment of pregnant women with high viral titers.

TREATMENT DURING PREGNANCY

The use of active and passive immunoprophylaxis to reduce the risk of perinatal transmission of HBV is well accepted in clinical practice. HBIG given at the time of birth in combination with three doses of the recombinant hepatitis B vaccine given over the first 6 months of life has been up to 95% effective in preventing perinatal transmission. As noted above, however, the risk of perinatal transmission of HBV increases as the mother's viral load increases. In one series of mothers with high viral loads, this risk was as high as 28%.15

It stands to reason that if the mother's viral load can be reduced at the time of birth, the risk of perinatal transmission could also be reduced (see “Case: Minimizing risk in a 29-year-old woman”). In fact, lamivudine treatment of highly viremic HBsAg-positive women during the final months of pregnancy appears safe and may effectively reduce the risk of perinatal transmission of HBV, even in the setting of HBV vaccination plus HBIG.

Evidence for third-trimester treatment

van Zonneveld et al15 studied eight HBeAg-positive women with HBV DNA levels of 1.2 × 10^6 copies/mL or greater who were treated with 150 mg/day of lamivudine after the 34th week of pregnancy, and compared the rates of perinatal transmission between them and 24 matched historical controls who did not receive treatment. All children received standard immunoprophylaxis at birth and were followed for 12 months. In five of the eight treated mothers, viral load declined to less than 1.2 × 10^5 copies/mL. Of the eight infants born to treated mothers, four were HBsAg positive at birth, but only one remained positive at 1 year. This 12.5% rate of perinatal transmission was substantially lower than the 28% rate observed among the controls. No adverse events occurred with lamivudine in this study.
In a multicenter, randomized, double-blind, placebo-controlled study in China and the Philippines, Xu et al\(^1\) assessed outcomes among 114 HBsAg-positive pregnant women who had high viral loads (HBV DNA > 1,000 mEq/mL). The women were randomized to placebo or treatment with lamivudine starting at 32 weeks of gestation and continuing until 4 weeks postpartum. All of the infants received standard vaccine plus HBIG.

The mothers treated with lamivudine were more likely (98%) to have a reduction in their viral loads to less than 1,000 mEq/mL than the controls (31%). This reduction in viral load translated to improved outcomes for the infants of mothers receiving lamivudine. At 1 year, 18% of infants born to mothers treated with lamivudine were HBsAg positive compared with 39% of infants born to mothers randomized to placebo (\(P = .014\)). The rate of HBV DNA positivity at 1 year was reduced by more than half among the infants born to actively treated mothers compared with those who received placebo (20% vs 46%, respectively; \(P = .003\)). There was no difference in the rate of adverse events between the treatment and control groups in either the mothers or the infants.

The Xu study suggests that the use of lamivudine in the third trimester in mothers with high viral loads may effectively reduce the risk of perinatal transmission beyond what can be achieved with active and passive immunoprophylaxis. As this study has been presented in abstract form only, we await the final analysis of these data. This therapy appears to be relatively safe for both mother and infant, although the optimal timing and duration of therapy is still unclear.

### Treatment options during pregnancy

Of the nucleoside and nucleotide analogues and interferons indicated for treatment of chronic HBV infection, all are classified as Food and Drug Administration (FDA) pregnancy risk category C except for tenofovir and telbivudine, which are category B (Table 1).

Most human experience with antiviral drug therapy in pregnancy has been with lamivudine. More than 4,600 women have been exposed to the drug during their second or third trimesters.\(^1\) Even though lamivudine is classified as FDA pregnancy risk category C, it is associated with a risk of birth defects (2.2% to 2.4%) that is no higher than the baseline birth defect rate.\(^1\)

Of the two agents classified as FDA pregnancy risk category B, only tenofovir received this classification based on data collected in human exposure. The experience with tenofovir in pregnant women consists of 606 women in their first trimester and 336 in their second trimester.\(^1\) The rate of birth defects associated with tenofovir ranges from 1.5% (second-trimester use) to 2.3% (first-trimester use), which is similar to the background rate.\(^1\) Telbivudine received its pregnancy risk category B rating based on animal studies; there are few human pregnancy registry data.

Nonpegylated interferon alpha-2b has been shown to have abortifacient effects in rhesus monkeys at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60-kg adult). Peginterferon alpha-2b should therefore be assumed to also have abortifacient potential, as there are no adequate and well-controlled studies in pregnant women. Peginterferon alpha-2b is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is recommended for use in fertile women only when they are using effective contraception during the treatment period. Peglated interferon alpha-2a is approved for treatment of chronic HBV infection, but is not recommended for use during pregnancy.

### MANAGEMENT STRATEGY

Decisions regarding treatment of HBV infection during pregnancy are based on the assessment of HBsAg, antibody to HBcAg, and antibody to HBsAg in the first trimester (Figure 1).\(^8\) If the mother is HBsAg negative, then the maternal HBV vaccination series is initiated and the infant is vaccinated at birth.

If the mother is HBsAg positive in the first trimester, history of perinatal transmission and an assessment of viral load at week 28 guide further management decisions. All children of HBsAg-positive mothers receive HBIG in addition to vaccination at birth.

Women with high viral loads can be considered for treatment with antiviral therapy, but a comprehensive discussion of risks and benefits needs to take place before opting for treatment as the data are too limited at this time to advocate therapy. One strategy for therapy is the use of lamivudine, tenofovir, or telbivudine starting at 32 weeks of pregnancy; the HBV DNA level that warrants treatment depends on the presence or absence of a history of perinatal transmission. If a previous child was HBV positive, concerns about the risk of perinatal transmission may be higher, so the threshold for treatment may be

### TABLE 1

<table>
<thead>
<tr>
<th>Antiviral drug</th>
<th>Pregnancy category</th>
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<tr>
<td>Adefovir</td>
<td>C</td>
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<tr>
<td>Entecavir</td>
<td>C</td>
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<tr>
<td>Interferon alpha-2b</td>
<td>C</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>C</td>
</tr>
<tr>
<td>Pegylated interferon alpha-2a</td>
<td>C</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
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<tr>
<td>Tenofovir</td>
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Pregnancy classification of antiviral therapy

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1. Xu et al. 2016

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2. Management strategy

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3. Table 1
lower (HBV DNA > 10^6 copies/mL) than if the previous child were not positive for HBV. If the previous child was not HBV positive, treatment might be considered with HBV DNA levels greater than 10^8 copies/mL.

**Algorithm for management of HBV infection during pregnancy**

1. **Pregnant woman**
   - First trimester: Check HBsAg, anti-HBc, anti-HBs

   - **HBsAg (-)**
     - Anti-HBc (-)
     - Anti-HBs (-)
     - **Initiate maternal HBV vaccination series**
     - **Infant receives vaccine at birth**

   - **HBsAg (+)**
     - **Confirm HBsAg (+)**
     - Check baseline quantitative HBV DNA
     - Check quantitative HBV DNA at 28 weeks

   - **Previous child HBV (+)**
     - **No**
       - **HBV DNA < 10^6−10^8 copies/mL**
         - Monitor
         - Consider treatment with lamivudine, tenofovir, or telbivudine at 32 weeks
       - **Infant receives HBlg + vaccine at birth**

     - **Yes**
       - **HBV DNA > 10^6−10^8 copies/mL**
         - Consider treatment with lamivudine, tenofovir, or telbivudine at 32 weeks
       - **Infant receives HBlg + vaccine at birth**

   - **HBV DNA > 10^8–10^9 copies/mL**
     - Monitor

2. **SUMMARY**
   Although a case can be made for treatment of HBV infection during pregnancy, the risks and benefits must be weighed carefully. The benefits of treatment appear to be most pronounced in cases with high maternal viremia; in such instances, treatment should be considered and discussed with the patient at the start of the third trimester. Viable treatment choices are limited to lamivudine, tenofovir, and telbivudine. Of these, lamivudine and tenofovir appear to be the therapeutic options with reasonable human exposure and safety data in pregnancy.

3. **DISCUSSION**
   - William D. Carey, MD: Referring to your case patient, assume that you treat her with tenofovir and her viral load declines. She delivers her baby and then undergoes a thorough workup, including a liver biopsy, that shows no particular liver damage. What would you do?
   - Tram T. Tran, MD: There are two separate issues: treating the baby and treating the mother. When you’re treating a mother in her third trimester, your goal is to prevent perinatal transmission of HBV. Once the baby is delivered, treated with HBlg, and vaccinated, then your attention turns to the mother. You can then decide based on treatment guidelines and your clinical judgment whether you want to treat the mom.
   - The period immediately after birth is a time of treatment uncertainty in mothers who choose to breastfeed, because the nucleoside analogues are likely passed in breast milk to some unknown degree, and it’s probably unwise to expose the child this way. In a mother who chooses to breastfeed, I would stop the medication after the delivery, by which time the baby will have received HBlg and the vaccine. When treatment is stopped, you have to think about the potential for a flare; although clinically significant flares are uncommon, the mother should be monitored after stopping treatment. After she stops breastfeeding, you can decide whether to treat her.
   - Robert G. Gish, MD: What are the effects of tenofovir on bone? Do you talk to your patients about it, and is it an issue during pregnancy or after the baby is delivered?
   - Dr. Tran: Some data show a decrease in bone mineral density with tenofovir in the human immunodeficiency virus patient population. I definitely talk to my patients about all the potential risks associated with these medicines as, naturally, pregnant women will be very sensitive to any possible risk to their unborn child. Lamivudine probably has the safest profile in pregnancy, given its large body of human experience; however, it is now classified as an FDA pregnancy risk category C drug, whereas tenofovir is classified as category B. This may make a difference to some clinicians.

**FIGURE 1.** Management of hepatitis B virus (HBV) infection during pregnancy starts in the first trimester with assessment of hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and antibody to HBsAg (anti-HBs). Treatment decisions are based on viral load (HBV DNA) levels at week 28 and presence or absence of a history of perinatal transmission. HBlg = hepatitis B immunoglobulin

DISCLOSURES

Dr. Tran reported that she has no financial interests or relationships that pose a potential conflict of interest with this article.

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ABSTRACT

Hepatitis B virus (HBV) infection is more aggressive in individuals coinfected with human immunodeficiency virus (HIV): in the presence of HIV, HBV carrier rates and viremia levels are higher, episodes of activation are more frequent, cirrhosis progresses more quickly, and hepatocellular carcinoma occurs more often than with HBV infection alone. As in HBV monotherapy, the objective of treatment is suppression of viral replication. Standard or pegylated interferon may be appropriate treatment for chronic HBV infection for patients who have not yet started highly active antiretroviral therapy (HAART) for their HIV. When treatment is required for both diseases, the use of a combination of nucleoside and nucleotide analogues is prudent, with careful selection of therapy to reduce the risk of antiviral resistance—a particular concern for patients receiving antiretroviral therapy for both HIV and HBV. HBV DNA levels should be monitored every 3 months; the frequency can be extended to every 6 months once the viral load becomes stable or undetectable.

KEY POINTS

Patients with HBV/HIV coinfection are at relatively high risk of frequent HBV activation, progression to cirrhosis, and death from liver-related causes.

If the patient does not yet require HAART but requires treatment for HBV, this is itself an indication for HAART, since monotherapy for HBV is associated with development of resistance to HIV therapy.

Nucleoside and nucleotide analogues should not be used as monotherapy in the HBV/HIV-coinfected patient because of the risk of inducing HIV resistance.

In North America and Europe, the highest prevalence of HBV/HIV coinfection is in men who have sex with men. Approximately half of HIV-positive men who have sex with men have evidence of prior or active HBV infection, and 5% to 10% have chronic HBV infection. Among those who acquire HIV through injected drug use or through heterosexual transmission, the coinfection rate is much lower.

Coinfection with HBV and HIV is associated with a different natural history. For example, in Africa and Asia, HBV is usually acquired first through neonatal or childhood infection, with either vertical or horizontal transmission after birth. In parts of Africa, ritual scarification is likely a major player in the adolescent transmission of HBV. (Ritual scarification is the practice of creating small incisions in the skin of adolescents and rubbing black ash in the wounds to form scars; the cutting instruments are not sterilized between rituals.)

NATURAL HISTORY

In general, HBV tends to be more aggressive in HIV-positive individuals than in monoinfected individuals, with higher HBV carrier rates, higher levels of HBV viremia, more frequent episodes of activation, and faster progression to cirrhosis.

Hepatocellular carcinoma occurs more often, its onset is earlier, and its course is more aggressive in coinfected individuals than in monoinfected individuals. Using data from a prospective cohort study, Thio et al found that among men coinfected with HIV and HBV, liver-related mortality was almost 19 times greater compared with men infected with HBV only and more than seven times greater compared with those infected with HIV only.

In an observational longitudinal cohort study, the risk of death from liver disease in HIV-positive persons was nearly three times greater among those also infected with HBV (P < .0001).

ASSESSING WHEN TO TREAT

The objectives of HBV therapy in individuals coinfected with HIV are similar to those in the population infected with HBV alone. Suppression of viral replication is the major goal. Ideally, the viral load should be reduced to...
an undetectable level, which will result in normalization of alanine aminotransferase (ALT) level, improved liver histology, reduced risk of progression to cirrhosis and liver failure (although supportive evidence from controlled clinical trials is lacking), and likely reduced incidence of hepatocellular carcinoma.

For those who are hepatitis B e antigen (HBeAg) positive, seroconversion may be a convenient end point for treatment, although for many patients seroconversion is not associated with remission of disease activity or viral replication.

Treatment decisions depend on whether or not the patient requires highly active antiretroviral therapy (HAART) for HIV infection. If HAART is indicated, then HIV agents that have HBV activity are incorporated into the regimen. If the patient does not yet require HAART for HIV but requires treatment for hepatitis B, this is itself an indication for HAART, since monotherapy for HBV is associated with the development of HIV resistance.

**Viral load and ALT**

As with treatment of chronic HBV infection, the approach to the patient coinfected with HBV and HIV starts with an assessment of HBV DNA level (Figure 1). Those with HBV DNA levels less than 2,000 IU/mL, indicating the absence of active replicating disease, do not require anti-HBV therapy as long as their viral load remains low. These patients should have their HBV DNA levels monitored regularly for a change in status. If the HBV DNA level is 2,000 IU/mL or higher, the treatment decision should be based on the ALT level. If the ALT is elevated, even intermittently, anti-HBV treatment should be instituted.

**Liver biopsy**

If the ALT is normal in the presence of a high HBV DNA level, a liver biopsy is recommended, partly because the ALT level is an inadequate indicator of the severity of liver disease. If significant fibrosis is present, treatment is recommended. No treatment is required if fibrosis is mild, but liver biopsies should be repeated every 3 to 5 years in this group because a hallmark of HBV infection is its variability in time to progression. The extent of fibrosis may influence the choice of therapy.

Often in the coinfected patient, HBV-related liver injury must be distinguished from other forms of liver injury. For instance, some of the drugs used to treat HIV infection can induce nonalcoholic fatty liver disease and lipodystrophy. Because the risk of advanced fibrosis is higher in the coinfected patient than in the patient infected only with HBV, the threshold for biopsy in the coinfected patient should be lower.

At present, noninvasive tools to assess the extent of liver injury have not been validated in chronic HBV infection, unlike in hepatitis C virus infection.

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**Case: HIV/HBV with resistance to tenofovir**

A 43-year-old man who is coinfected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) presents to your office. In 1998, he was treated with lamivudine for his chronic HBV infection and with tenofovir for his HIV infection. In 2006, he was hepatitis B e antigen (HBeAg) negative, and his lamivudine was discontinued, but by 2007 he was again HBeAg positive. In 2007, his HBV DNA level was extremely high, 10^6 IU/mL, and his alanine aminotransferase (ALT) level was 252 U/L. His serum creatinine level ranged from 2.2 mg/dL to 2.5 mg/dL from 2006 to 2008. A drug resistance profile was performed in March 2008, at which time the L180M and M204V resistance mutations were discovered. He had also developed moderate renal insufficiency, presumably from tenofovir. His ALT was 90 U/L at this time. His HIV was under moderately good control at the last visit (HIV RNA: 51 copies/mL). He was still taking tenofovir for his HIV. What HBV therapy should be tried next?
HBV AND HIV COINFECTION

Nucleoside and nucleotide analogues
The nucleoside and nucleotide analogues used for HBV therapy have different degrees of effectiveness against HIV polymerase, but none can be used as monotherapy because of the risk of inducing HIV resistance. Lamivudine and tenofovir are used as part of the standard cocktail for the treatment of HIV (see “Case: HIV/HBV with resistance to tenofovir,” page S31). Entecavir is now recognized as a partial inhibitor of HIV replication. Both lamivudine and entecavir induce the YMDD mutation, an indication of resistance to therapy, in HIV polymerase. Tenofovir also may select for resistance mutations in HIV polymerase.

At dosages used for the treatment of HBV infection, adefovir has weak activity against HIV, and therefore HIV would not be under significant selective pressure to develop resistance mutations. In HIV polymerase, the mutations that confer resistance to adefovir also confer resistance to tenofovir, and therefore use of adefovir may induce tenofovir resistance.

Telbivudine has not been studied in HIV-infected patients, but its resistance profile is similar to that of lamivudine.

Treating both infections
When both HBV and HIV infections require treatment, HAART is necessary for HIV. The treatment strategy for coinfection is to use standard therapy for HIV, selecting two agents that are effective against HBV infection.

Case revisited
Lamivudine and tenofovir are no longer useful for our case patient. Despite uncertainty about whether tenofovir is the cause of his renal dysfunction, he cannot be maintained on tenofovir. The choices then become entecavir or adefovir. Adefovir is associated with a slightly higher risk of renal dysfunction than tenofovir, but tenofovir-induced renal toxicity cannot be assumed to translate to adefovir.

The need to avoid antiviral resistance complicates the selection of active agents. Resistance to HIV therapy limits the choices for treatment of HBV infection. The immediate aim of therapy, an undetectable level of HBV DNA, eliminates use of less potent agents. The best choice for therapy is the most potent agent that can be used, such as tenofovir plus lamivudine or tenofovir plus emtricitabine.

Antiviral resistance
For the coinfected patient who develops resistance to lamivudine, the recommendation is to treat with tenofovir plus entecavir (the preferable choice because of absence of cross-reactivity between the two agents) or tenofovir plus lamivudine or emtricitabine. There is some evidence that lamivudine resistance predisposes to entecavir resistance, but the studies that generated these results were conducted in patients who had very high baseline viral loads; the effectiveness of entecavir in patients with low baseline viral loads is unknown. Presumably, when entecavir is used in combination with another potent nucleoside analogue in coinfected patients, the sensitivity of HBV will be more durable than when entecavir is used as monotherapy.

Long-term monitoring
Long-term monitoring for the coinfected patient is similar to that for the patient infected with HBV only. HBV DNA levels should be monitored every 3 months for signs of resistance until levels have plateaued or become undetectable. Once the HBV DNA level is stable or undetectable, the monitoring interval can be extended. Ultrasonographic screening for hepatocellular carcinoma should be conducted every 6 months. Patients with cirrhosis should be screened for esophageal varices.

■ SUMMARY
HBV in the setting of HIV is more aggressive than in a patient infected with HBV only, and treatment must be comparably aggressive and carefully selected. The primary goal of HBV treatment in a coinfected patient is the same as in a patient with HBV infection only: reduction of viral load to undetectable levels. Treatment decisions are based on viral load, ALT level, findings on liver biopsy, the need for HAART, and the drug’s resistance profile. None of the nucleoside or
nucleotide analogues can be used as monotherapy in the coinfected patient because of the risk of inducing resistance to HIV therapy. When the patient requires HAART, then the general recommendation is to select a combination of two drugs that have activity against HIV. If resistance develops, the preferred strategy is treatment with tenofovir plus entecavir. Monitoring includes measurement of HBV DNA levels every 3 months and ultrasonographic screening for hepatocellular carcinoma every 6 months.

■ DISCLOSURES

Dr. Sherman reported that he has received consulting fees and honoraria for teaching and speaking from Bristol-Myers Squibb Company, Gilead Sciences, Inc., and Roche Laboratories, Inc.

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