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Gastroenterology & Hepatology

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Improving HBV Treatment: Early Screening and Sustained Control for Improved Outcomes

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Abstract: Hepatitis B virus (HBV) infection is a disease of global public health concern, affecting more than 2 billion people worldwide. Although the majority of individuals infected with HBV experience acute disease and are able to recover from and clear the infection, chronic HBV infection occurs with incidence estimates ranging from 1.2 million to 2 million individuals in the United States alone. Global migration of individuals from regions with high rates of incidence play a part in escalating US prevalence. Chronic HBV infection confers increased risk for liver diseases, including cirrhosis and hepatocellular carcinoma (HCC). Disease occurs as a result of the immune response directed against the HBV infection, which triggers an ongoing wound-healing process and leads to tissue scarring and the development of fibrosis. HBV infection status can be determined by assaying for the presence of HBV DNA, indicative of active, replicating virus, the presence of HBV viral proteins (HBeAg, HBsAg, HBcAg), or the antibodies generated in response to these proteins (anti-HBe, anti-HBs, anti-HBc). The main treatments for chronic HBV infection include oral nucleoside or nucleotide analog antiviral drugs and interferon-based therapy. The aim of therapy is to effectively manage the disease and limit liver complications by suppressing HBV DNA, preferably to undetectable levels.

Target Audience: This activity has been designed to meet the educational needs of gastroenterologists and hepatologists involved in the management of patients with chronic hepatitis B virus infection.

Statement of Need/Program Overview: Both in the United States and worldwide, chronic hepatitis B is a major public health concern. An estimated 400 million people are chronically infected with the virus worldwide, including 1.25 million in the United States. The typical mode of transmission varies based on geographic location, but in areas of high prevalence transmission is primarily perinatal, whereas in areas of lower prevalence transmission is predominantly sexual and parenteral. Although hepatitis B is 100 times more infectious than the AIDS virus, it may be prevented via vaccination. Left untreated, chronic hepatitis B may result in cirrhosis, liver cancer, liver failure and death. According to the Centers for Disease Control, death from chronic liver disease occurs in 15–25% of those chronically infected with the virus. Worldwide, chronic hepatitis B is the leading cause of liver cancer as well as the sixth leading cause of liver transplantation. Management of hepatitis B is complex, particularly because the presentation of symptoms varies among patients. Approximately 30% of infected individuals have no signs or symptoms. For those experiencing symptoms, the most common include jaundice, fatigue, abdominal pain, loss of appetite, nausea and vomiting, and joint pain. Although vaccination can prevent the disease, for those currently infected with chronic hepatitis B, and for the 10 to 30 million individuals who will become infected annually worldwide, early detection and effective management are necessary.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Cite high serum levels of hepatitis B DNA as a strong predictor of disease progression and treatment resistance.
2. Explain methods for rapid and sustained suppression of viral loads in order to reduce the risk of cirrhosis and hepatocellular carcinoma.
3. Describe ways to increase motivation and awareness among the Asian-American population to promote early screening and treatment
4. Review options for combination therapy in the treatment of patients with hepatitis B.
5. Outline the treatment options of HBV/HIV co-infection

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Natural History of Chronic Hepatitis B Infection

Ira M. Jacobson, MD

Progression of HBV Infection and Potential Associated Illnesses

Patients with chronic hepatitis B present in one of four phases of infection.¹ Phase 1, termed the “immune tolerance” stage, is characterized by high levels of serum HBV DNA levels, HBeAg-positive status, and normal alanine aminotransferase (ALT) levels, accompanied by little to no liver inflammation. Among patients infected with HBV via perinatal transmission, the length of this phase can vary greatly, ranging from 10 to 40 years. Phase 1 is short or absent in patients who acquire HBV later in childhood or as an adult. Despite the fact that these patients exhibit high levels of HBV DNA, chronic hepatitis B in the immunotolerant phase is associated with minimal disease progression. A 5-year follow-up of 57 patients diagnosed with chronic HBV infection in the immunotolerant phase found that 15.8% developed elevated levels of ALT, and that those patients who had persistently normal ALT levels showed no disease progression.² Another study with a longer follow-up (median 10.5 years) of 240 patients with phase 1 chronic HBV reported that only 5% progressed to cirrhosis. None of these patients were diagnosed with HCC.³

The second phase of chronic HBV infection has traditionally been termed the “immune clearance” stage. As in phase 1, patients in this phase are HBeAg-positive and have high levels of HBV DNA. However, these patients additionally exhibit elevated ALT levels, along with signs of active liver inflammation. A hallmark of phase 2 infection is flaring levels of ALT, caused by the immune-mediated lysis of HBV-infected hepatocytes. Thus, phase 2 may be more accurately termed the “immune active” phase.^{4,5} Second-phase chronic HBV infection frequently results in seroconversion of HBeAg to anti-HBe antibodies within the patient serum.

Phase 3 of chronic HBV infection is also known as the “inactive HBsAg carrier state.” Patients with phase 3 chronic HBV infection typically are HBeAg-negative and anti-HBe-positive. ALT levels in these patients are normalized, and they have low or undetectable levels of HBV DNA. Mild liver disease may be present, and inactive cirrhosis may be apparent as a result of the liver insult during phase 2. The duration of phase 3 varies and may be indefinite, but the prognosis during this phase is favorable. A long-term follow-up study of 296 healthy phase 3 chronic HBV-infected patients showed no difference in survival compared to uninfected controls over a 30-year mean follow-up period.⁶ However, other studies, including a recent follow-up to the landmark REVEAL study, which included over 10 years of follow-up of a very large cohort of HBV carriers, have indicated an excess risk of HCC, even in inactive carriers, compared to healthy controls.⁷

The final phase of chronic HBV infection, phase 4, is the “reactivation phase.” During this period, patients experience a reactivation of HBV replication, either spontaneously or resulting from immunosuppression, such as that caused by cancer chemotherapy or biologic therapies. Some patients can undergo seroreversion to the HBeAg-positive state but most patients in phase 4 remain HBeAg-negative and anti-HBe-positive, and have detectable levels of HBV DNA (> 2000 IU/mL) with signs of active liver disease such as elevated ALT levels and progressive liver inflammation. The basis for HBeAg-negative chronic hepatitis B is the presence of precore and/or core promoter mutations that render the virus incapable of producing HBeAg or downregulating its production to the extent that it cannot be detected. When interpreting data from natural history studies, it is important to consider that the majority of these reports do not distinguish between HBeAg-negative patients in phase 3 and phase 4.

Liver fibrosis is a major HBV-associated morbidity, which may progress to cirrhosis and, ultimately, liver failure. Several long-term studies following HBeAg-positive chronic HBV patients suggest that the 5-year cumulative incidence of cirrhosis ranges from 7% up to 20%.⁸⁻¹⁰ Another study showed that as many as 54% of these patients developed active cirrhosis over a mean follow-up of 4.5 years.¹¹ A 10-year follow-up of HBV-related cirrhosis revealed that the risk of liver decompensation is approximately 40%. In decompensated patients, 1-year survival ranges from 55-70%; the 5-year survival is reduced to 14-28%.¹²⁻¹⁵ Importantly, HBsAg-positive chronic HBV patients with detectable HBV DNA levels have a higher risk for liver decompensation than HBV DNA negative patients (RR: 4.05, 95% CI=1.09-15.1).¹³ This same study also reported that the 5-year cumulative incidence of HBV-related liver decompensation was 16% in these individuals. In patients with end-stage liver disease, the only remaining treatment strategy is liver transplantation.

Worldwide, chronic HBV infection is a major risk factor for HCC, with recent data showing that nearly 80% of all HCC cases occur in patients with chronic HBV.^{16,17} The exact mechanism by which HBV infection induces HCC is unknown, but is thought to be related to cell turnover in response to HBV-induced hepatocyte necrosis. Mutations within these rapidly dividing cells may select for cells with cancerous characteristics, leading to the development of HCC.¹⁸ Cirrhosis is a major risk factor prior to the development of HCC, and 70-90% of HBV-related HCC occurs in patients with cirrhosis.^{16,19} The capacity for HBV DNA to integrate into that of host-cell chromosomes is another potential factor in hepatic carcinogenesis, although the pre-

cise mechanisms have yet to be fully elucidated. Given the seemingly important role hepatic inflammation plays in the development of HCC, treating the underlying HBV infection and associated liver disease is an important strategy to prevent progression to HCC.²⁰

Prognostic Factors in HBV Progression

One of the key prognostic factors in chronic HBV infection is HBV viral load. Recently published results of the REVEAL-HBV Study Group were key in providing evidence that HBV DNA levels have a significant impact on liver disease progression.²¹ In this prospective study of 3653 HBsAg-positive Taiwanese patients, the incidence of HCC was found to increase with the serum HBV DNA level at baseline, in a dose-dependent relationship. The cumulative incidence rate of HCC was 1.3% in patients with HBV DNA levels less than 300 copies/mL and 1.4% in patients with viral loads between 300 copies/mL and 10,000 copies/mL. At 10,000–100,000 copies/mL, the cumulative incidence of HCC rose to 3.6%. The cumulative incidence of HCC was 12.2% in patients with 100,000–1 million copies/mL, increasing to 14.9% in patients with HBV DNA levels greater than 1 million copies/mL. A similar relationship was observed between HBV viral load and risk of cirrhosis.²² Patients with low HBV DNA levels (<300 copies/mL) had a cumulative cirrhosis incidence of 4.5%, which was increased to 36.2% in patients with the highest HBV DNA levels (1 million copies/mL). Current treatment guidelines, which recommend initiating anti-HBV therapy only in patients with elevated ALT levels may change with the confirmation of these data, to reflect the need, as many experts perceive it, to treat many patients with normal ALT levels and elevated HBV DNA.^{23,24} Recently, the data from the REVEAL study were reanalyzed using a more sensitive real-time polymerase chain reaction assay.²⁵ This updated analysis revealed that a significantly elevated risk of both cirrhosis and HCC existed even in patients who had the lowest category of measurable HBV DNA (300–10,000 copies/mL), compared to patients with undetectable HBV DNA levels.²⁵

A key study that evaluated the role of ALT levels in predicting liver disease progression included 3233 chronic HBV-infected Chinese patients that were followed for up to 15 years (median 46.8 months).²⁶ This follow-up showed that the cumulative risk for development of complications was highest in patients with ALT levels of 1–2 times the upper limit of normal (ULN). Even patients with ALT levels of 0.5–1 times the ULN had a significantly increased risk of complications, compared to patients with ALT levels less than 0.5 times the ULN ($P=.0071$). These data show that current guidelines for therapy initiation may require further adjustment to reflect the correlation that different levels of elevated ALT have with liver disease progression. Indeed, based on population studies of ALT distribution and correlation of serum ALT with liver-related mortality, at least

one HBV treatment algorithm has proposed a reduction in the normal cutoff for ALT to 30 U/L in men and 19 U/L in women.²⁴ Other prognostic factors for chronic HBV disease progression include older age, male gender, genotype C infection, family history of liver cancer, and existence of core promoter mutations.^{26–28} Environmental factors, such as alcohol consumption, diabetes, obesity, and co-infection with hepatitis C virus and HIV also significantly increase the risk of liver disease progression.^{29,30}

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Hepatitis B Treatment Strategies to Maximize Positive Outcomes

Paul J. Pockros, MD

Administration of Therapy Early in Disease Course

The treatment guidelines from the AASLD for the management of chronic HBV were recently updated to reflect an increased understanding of the biology of the disease, as well as the approval of new anti-HBV therapies.¹ Using these guidelines, treatment of chronic HBV is indicated only in patients with a high risk of developing liver-disease-related morbidities or mortality in the foreseeable future, and in whom treatment is likely to achieve and maintain HBV viral suppression. Recently, a panel of expert chronic HBV physicians published a revised treatment algorithm, to help determine the best point at which to begin anti-HBV therapy.² The guidelines of this panel were stratified for HBeAg-positive or HBeAg-negative status. For HBeAg-positive patients, treatment is only recommended when HBV DNA levels are $\geq 20,000$ IU/mL and ALT levels are abnormally elevated (defined as > 19 U/L for women and > 30 U/L for men). Treatment is also recommended in patients with normal ALT levels if a biopsy reveals liver disease. For HBeAg-negative patients, treatment is reserved for patients with HBV DNA levels of 2,000 IU/mL or higher and elevated ALT levels. Again, treatment is also considered for patients with liver disease, in spite of normal ALT levels. In both HBeAg groups, patients who do not initially require therapy should be carefully monitored to assess both HBV DNA levels and ALT levels every 6–12 months.

The original standard front-line therapy, lamivudine monotherapy, is no longer recommended in this setting, due to its high rate of resistance. Lamivudine resistance is detected in up to 32% of patients after the first year of therapy, and develops in 65–67% of patients after 5 years of treatment.³⁻⁷ Importantly, many of the resistance mutations selected by lamivudine display cross-resistance to other anti-HBV agents, and limit the efficacy of these drugs as second-line agents. Therefore, the current guidelines recommend three other anti-HBV agents, adefovir, entecavir, and telbivudine, as front-line therapy for chronic HBV.¹

Efficacy and Safety of Small Molecule Agents

Adefovir is an attractive alternative to lamivudine for the treatment of chronic HBV, due to its activity against

lamivudine-resistant HBV as well as its slower rate of resistance mutation development. Two placebo-controlled phase III trials established the efficacy of 1 year of adefovir therapy in treating chronic HBV, showing histologic response rates between 53–64% and normalization of ALT levels in 48–72% of patients.^{8,9} Additionally, HBV DNA levels were undetectable in 51% of patients receiving adefovir, compared to 0% of control patients ($P < .001$).⁹ No adefovir-induced resistance mutations were found after 1 year of therapy in these phase III trials, but patients had a cumulative probability of 29% of developing resistance after 5 years. More recently, the cumulative probability of adefovir resistance was found to be 22% after 2 years of adefovir monotherapy.^{10,11} The majority of adefovir mutations in these studies occurred in lamivudine-resistant patients.

Entecavir is also now indicated as first-line therapy for chronic HBV. When compared to lamivudine in phase III trials, entecavir monotherapy resulted in higher rates of histologic and virologic responses.^{12,13} After 2 years of therapy, HBV DNA levels were undetectable in 80% of patients in the entecavir arm, compared to only 39% of patients receiving lamivudine.¹⁴ Importantly, entecavir has been shown in clinical studies to have activity against lamivudine-resistant HBV, although a higher dosage is necessary.^{15,16} Entecavir has also been suggested to be active against adefovir-resistant HBV in preclinical testing.¹⁷ Entecavir has a high genetic barrier of resistance, due to its rapid, sustained suppression of HBV replication, as well as the requirement of multiple mutations within the virus in order for HBV to become resistant. Therefore, resistance to entecavir monotherapy is rare, occurring in less than 1% of patients after 3 years of treatment.¹⁸

In late 2006, the US Food and Drug Administration (FDA) approved the anti-HBV drug telbivudine. After a phase III clinical trial showed telbivudine to more potently suppress HBV replication than lamivudine, the most recent treatment algorithm was updated to reflect the incorporation of telbivudine as a first-line anti-HBV therapy.^{19,20} A recently published randomized trial showed that telbivudine monotherapy more effectively suppressed HBV DNA than either adefovir monotherapy or adefovir followed by telbivudine.²¹ At 24 weeks, more patients in the

continuous telbivudine group attained undetectable HBV DNA than those patients in the combined adefovir-receiving arms (39% vs. 12%, $P=.001$). The superior efficacy of telbivudine was observed out to 52 weeks. Telbivudine displays a favorable safety profile, with no dose-limiting side effects.²² Although less frequent than lamivudine resistance, significant resistance to telbivudine can occur. The phase III trial of telbivudine revealed resistance rates at year 1 in 2.7% and 4.4% of HBeAg-negative and HBeAg-positive patients, respectively.^{19,20} These rates increased to 8.6% and 21.6% after the second year of therapy.

All of these anti-HBV agents are under investigation in various combinations, as combining agents often offers a greater genetic barrier of resistance. However, thus far, none have been shown to be superior to monotherapy in inducing higher rates of sustained response. For example, although the combination of telbivudine with lamivudine effectively reduced serum HBV DNA levels in chronic HBV patients, it was not superior to telbivudine monotherapy.²³ Another trial showed that initial combination of lamivudine and adefovir in treatment-naïve chronic HBV patients produced improvements in HBV infection that were comparable to lamivudine alone.²⁴ Resistance was less frequently observed in this combination group, although the addition of adefovir did not prevent lamivudine resistance from developing. Evidence suggests that adding adefovir to lamivudine is preferable to switching from lamivudine to adefovir monotherapy in patients with lamivudine-resistant chronic HBV, because the continuation of lamivudine reduces the risk of developing adefovir resistance.^{10,25} Currently, this is the only setting in which the AASLD recommends combination therapy. However, several other combinations are under investigation in clinical trials. The PROACTIV study is currently testing telbivudine in combination with either adefovir or tenofovir in chronic HBV patients, whereas another ongoing trial is comparing the combination of telbivudine and adefovir with adefovir monotherapy.^{26,27}

Interferon-Based Therapies

Interferon therapy is thought to exert multiple effects against chronic HBV, through antiviral, antiproliferative, and immunomodulatory actions. Pegylated interferon-alfa (Peg-IFN) is currently the recommended interferon-based therapy, as it possesses superior pharmacokinetics and a more convenient administration method than standard interferon.

In many European countries, Peg-IFN is considered the front-line standard therapy. However, many patients and clinicians in the United States prefer to avoid its use because of the numerous associated adverse effects, including psychological disorders. In the US setting, Peg-IFN most often used in chronic HBV infected females of child-bearing age, as it limits the need for anti-HBV agents that should be discontinued in pregnancy.

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At-Risk Populations in Chronic Hepatitis B

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HIV Co-Infected Patients

Co-infection of HBV and HIV is quite common, estimated at approximately 4 million people worldwide.¹ One study showed that evidence of past HBV infection was apparent in 50–70% of HIV-infected men who have sex with men, diagnosed by either the presence of core or surface HBV antibodies. Another multi-center French study reported 55% of 477 chronic HBV patients were co-infected with HIV.²

HIV co-infection can have profound effects on the natural history of HBV infection.³ Primary among these is the increased likelihood of HIV co-infected patients to develop chronic HBV. An analysis of 77 homosexual males found that 23% of HIV co-infected patients developed chronic HBV, compared to 4% of patients only infected with HBV ($P=.026$).⁴ Importantly, those HIV co-infected patients who successfully cleared the HBV infection had significantly higher counts of circulating CD4+ lymphocytes ($P<.005$). Additionally, higher levels of HBV replication are noted in patients with HIV co-infection, shown by higher HBV DNA levels and increased activity of HBV DNA polymerase in patients.⁵ This correlates with decreased rates of loss of serum HBeAg, another alteration to the natural course of HBV infection induced by HIV co-infection.

A major morbidity associated with HIV-HBV co-infection is a higher risk of progressive liver disease. HIV co-infection leads to an increased risk of cirrhosis development, as high as 30–40%, compared to a 25–30% risk in Asian patients with only HBV infection and only 7% among Europeans with adult-acquired HBV. Recently, a study of 132 homosexual men with chronic HBV, 49% of whom were co-infected with HIV, reported that HIV co-infection carried a significantly increased risk of cirrhosis development (RR=4.2, 95% CI=1.3–13.8, $P=.03$).⁶ Likewise, a second study showed a similar increased risk (RR=4.57, $P=.007$), which was most notable in HIV-HBV patients with low CD4+ cell counts.⁷ In addition to cirrhosis, HIV co-infection can also increase the likelihood of patients developing HCC, although the precise increase in risk has yet to be determined.⁸ HIV-HBV co-infected patients may also exhibit an elevated risk of developing fulminant HBV infection, particularly in the event of treatment failure.^{9–11} Recently, a large multicenter prospective cohort study of 5,293 men who had sex with men was performed to determine the impact of HIV/HBV co-infection on liver disease-related mortality.¹² This study confirmed that these mortality rates were highest in HIV-HBV co-infected men (14.2 per 1000 person-years), compared to rates in HIV mono-infection (1.7 per 1000 person-years, $P<.001$) or HBV

mono-infection (0.8 per 1000 person-years, $P<.001$). Again, these rates were particularly high in patients with low CD4+ cell counts. Other studies have confirmed these results, finding that liver-disease-related deaths are considerably higher in HIV-HBV co-infected individuals compared to HIV mono-infected patients.^{13,14}

Treatment of HBV infection in HIV-HBV co-infected patients is initiated only after careful consideration of several factors, including the necessity of also treating the HIV infection, progression of liver disease, and the likelihood of attaining a response.¹⁵ The goals in treating HIV-HBV co-infected patients are similar to treatment of HBV-mono-infected patients: virologic suppression, normalization of ALT levels, and improvement in liver pathology. For all patients with evidence of liver disease, anti-HBV therapy is recommended, regardless of the progression of HIV infection.¹ Additionally, anti-HBV therapy is called for in patients with active HBV infection, indicated both by detectable HBV DNA levels and elevated ALT levels.^{16,17}

Currently, co-infected patients who only require anti-HBV therapy are treated with standard anti-HBV therapies, including peg-IFN, adefovir, or telbivudine. These agents have moderate to high activity against HBV, but not HIV. For patients who require concomitant treatment of both infections, the introduction of agents with activity against both HBV and HIV has dramatically improved prognosis. Recently, an analysis of the baseline characteristics of the COinfection and Liver Disease (COLD) cohort, a group of patients on active anti-HBV regimens, showed that 45% of co-infected patients had HBV DNA levels lower than 20 IU/mL, an encouraging suggestion that these patients will have reduced risks of future liver disease (Figure 1).¹⁸

Lamivudine achieves undetectable HBV DNA levels at rates up to 87% in multiple studies of co-infected patients.^{19–21} However, there is a high rate of emergence of resistant virus when lamivudine monotherapy is administered, and it is therefore most often given in combination with other agents. After 1 year, between 15–20% of patients develop lamivudine resistance, and this increases to 70% after 5 years of continuous therapy.²² Mutations within the HBV polymerase are primarily responsible for lamivudine resistance.²³ Recently, tenofovir was also shown to effectively treat HBV in HIV-HBV co-infected patients. Retrospective data found that tenofovir was active in both treatment-naïve patients and individuals with demonstrated lamivudine resistance.²⁴ Another multicenter trial reported that 76% of co-infected patients achieved sustained undetectable HBV

DNA levels after receiving tenofovir in combination with lamivudine.²⁵ Importantly, this same study showed that 84% of lamivudine-resistant co-infected patients administered tenofovir alone achieved undetectable HBV DNA levels. Other studies show lower rates of virologic suppression, although tenofovir was still shown to be an effective therapy in these reports.^{24,26} Tenofovir is not currently approved for HBV monoinfection, and severe acute flares of hepatitis B have been observed in cases where HIV-HBV co-infected patients discontinued tenofovir. Adefovir is also used in the setting of HIV-HBV co-infection, but should never be given in combination with tenofovir, due to overlapping renal toxicities and resistance patterns. Adefovir is also active against HBV in the setting of lamivudine resistance, and significantly reduces HBV DNA levels in HIV-HBV co-infected patients.²⁷ The anti-HIV agent emtricitabine has also been investigated as an anti-HBV agent in the setting of co-infection. Several studies have revealed that emtricitabine can successfully improve HBV infection.²⁸⁻³⁰ Despite its structural similarity to lamivudine, resistance to emtricitabine is documented to occur at a lower rate.^{15,31} As a result of these and other studies, the current front-line standard therapy for treating both HBV and HIV in co-infected patients is either tenofovir plus lamivudine, or tenofovir plus emtricitabine.³²

Asian and Asian-American Populations

Asian-Americans are 2.7 times more likely to develop liver cancer than Caucasian Americans.³³ One of the major reasons for this dramatically increased risk is a disproportionate prevalence of chronic HBV infection in Asian-Americans. The prevalence of chronic HBV infection in many Asian and Western Pacific countries is particularly high, ranging from 2.4% to 16.0%, and similar high rates of chronic infection occur in Asian-Americans, documented to be as high as 10%.^{34,35} Infection in Asian-Americans is due to Asian immigration as well as transmission within the population, both vertical (mother-to-child during the perinatal period) and horizontal (between individuals during early childhood).

A large number of Asian-Americans are unaware of their HBV infection status, as several recent studies have shown. One 5-year study of 3163 adult Asian-Americans in the San Francisco area revealed that 8.9% were infected with chronic HBV. Importantly, 65.4% of these infected individuals did not know that they were HBV-positive.³⁶ Another evaluation of 199 adults in the same region reported that less than 60% had been tested for HBV, and only 31% reported having been vaccinated against HBV.³⁷ Despite the majority of these individuals having a college education, most did not display a satisfactory knowledge of HBV transmission, prevention, and risks. Separately, a screening of 6,130 unvaccinated Korean-Americans living in the eastern United States showed 6.1% were positive for HBsAg, and vertical transmission occurred at a rate of 30.3%.³⁸ In HBsAg-posi-

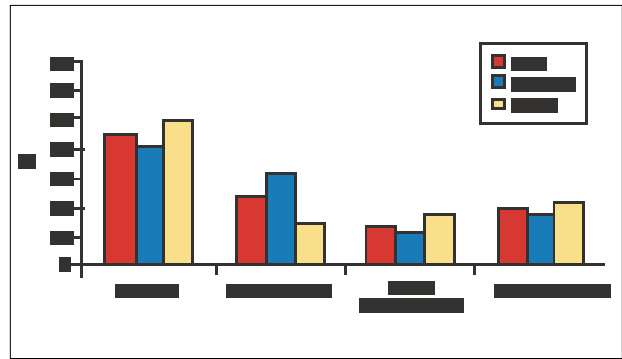


Figure 1. The COLD Study: HBV DNA levels at enrollment.

tive mothers, the rate of vertical transmission was as high as 100%. A survey of 256 Vietnamese-Americans in the greater Philadelphia and New Jersey area found that 46.3% were unaware of the possibility of chronic HBV infection, and 32.6% and 35.5% did not know of the availability of screening or vaccination, respectively.³⁹

One strategy to increase disease awareness in this population is to improve clinician education, especially in areas with high numbers of Asian-Americans. This was shown to be particularly important after a recent study of several primary care clinics within the University of California San Francisco (UCSF) Medical System reported that clinicians were more likely to screen their patients for infection if they were able to effectively communicate with Chinese-speaking patients and they had a greater knowledge of HBV risk factors.⁴⁰ Another strategy to break the cycle of HBV transmission among Asian-Americans is broad-based screening of first and second generation immigrants. Additionally, educating these individuals on the availability of effective treatment options may also lead to increased screening. Vaccination of individuals determined to be at an elevated risk for HBV infection will also aid in preventing chronic HBV infection, as discussed in a recent cost-effectiveness analysis.^{41,42}

Pregnant Patients: Avoiding Perinatal Disease Transmission

Perinatal HBV transmission is the major cause of HBV infection in infants and children, resulting in a 70–90% risk of children developing chronic HBV infection by the age of 6 years.⁴³ Fortunately, immunoprophylaxis with a combination of HBV vaccination and administration of the hepatitis B immunoglobulin (HBIG) can prevent 90–95% of perinatal transmissions.^{44,45} Currently, all pregnant women are recommended to be tested for the presence of the HBsAg, in order to be sure that infection in the infants of HBV-positive women can be effectively prevented.⁴⁵ Preliminary studies have indicated that the higher the HBV viral load is in the pregnant mother, the greater the

risk of perinatal transmission.^{46,47} Importantly, high HBV DNA levels are also associated with the occasional failure of HBV immunoprophylaxis in infants.⁴⁸ Strategies to reduce HBV DNA levels in pregnant women may further decrease perinatal transmission.⁴⁹ One clinical study in 8 pregnant women, all with high HBV viral loads (HBV DNA $\geq 1.2 \times 10^9$ genome Eq/mL), administered 150 mg lamivudine daily during the last month of pregnancy.⁵⁰ All infants received immunoprophylaxis at birth, and were followed for up to 12 months. Of the 8 children, only 1 was HBsAg and HBV DNA-positive at 1 year, indicating that lamivudine may be an effective adjunct means to avoid the risk of childhood vaccination breakthrough. Lamivudine was further shown to be safe and more effective than immunoprophylaxis alone when administered during the third trimester of pregnancy.⁵¹ In a randomized, double-blind, and placebo-controlled trial of 120 HBV-infected pregnant women with high HBV DNA levels (>1000 mEq/mL), mothers were administered either lamivudine or placebo beginning at gestational week 32 and continuing through 4 weeks after giving birth. HBV DNA levels were decreased to less than 1000 mEq/mL in 98% of the women in the lamivudine group, compared to only 31% in the control group. The infants, all administered immunoprophylaxis and born to mothers with reduced HBV viral load, were also less likely to be HBsAg-positive (18%, $P=.014$) and had a lower incidence of viremia (20%, $P=.003$) than controls (39% and 46%, respectively).

Investigation of the safety of anti-HBV therapy in pregnant women is relatively limited. Most agents used to treat HBV are listed as either category B or C by the FDA. Based on preclinical animal experiments, tenofovir, emtricitabine, and the newly approved agent telbivudine are all considered category B drugs.⁵²⁻⁵⁴ Lamivudine is listed as category C in HBV, due to a preclinical study in rabbits showing early embryolethality with doses similar to that recommended for humans⁵⁵ and but category B in HIV infections where data are more extensive and show an excellent safety profile. The safety of lamivudine in humans during pregnancy has been investigated in one study which included 38 chronic HBV-infected women who became pregnant while receiving lamivudine and elected to continue therapy during pregnancy.⁵⁶ No pregnancy complications were observed, and no developmental abnormality was noted in the newborns. Importantly, none of the newborns tested positive for HBV. Adefovir and entecavir are also pregnancy category C drugs, based on preclinical animal studies.^{57,58}

Immunosuppressed and Liver Transplant Patients

It is well documented that patients with inactive HBV infection can experience a reactivation of hepatitis B as a result of immunosuppressant therapy, ranging from cancer chemotherapy to biologic agents.⁵⁹ The recently updated guidelines from the AASLD for managing HBV infection recommends that all patients be tested for the presence of

HBsAg prior to initiating immunosuppressives.⁶⁰ Patients found to be HBV-positive should then be administered prophylactic anti-HBV therapy to decrease the risk of a hepatitis flare. This anti-HBV therapy should be given throughout the course of immunosuppressant treatment, and up to 6 months following the end of treatment. It is also important to note that some patients who have inactive HBV infection, but test negative for the presence of HBsAg, can also exhibit a resurgence of hepatitis B. These patients are often only positive for antibodies to the hepatitis B core antigen (anti-HBc).^{61,62}

Liver transplant has evolved as a more favorable treatment for HBV-associated liver disease, thanks to improvements in immunoprophylactic strategies as well as the addition of more effective anti-HBV agents. Several clinical investigations have shown that pre-transplant administration of an anti-HBV drug to lower HBV viral load, followed by a combination of the agent with HBIG, leads to favorable response rates and low risk of HBV recurrence.⁶³ Although lamivudine is commonly used in this setting, adefovir is being increasingly used due to its lowered risk of developing resistance. The largest study of adefovir to prevent HBV recurrence in pre- and post-liver transplant patients showed that 81% of lamivudine-resistant patients achieved undetectable HBV DNA levels with adefovir administration prior to liver transplant.⁶⁴ Further evidence of the important role of antiretroviral therapy in reducing the need for liver transplant was presented at the 2007 AASLD meeting, in a study reporting that the number of patients registered for a liver transplant as a result of HBV-related decompensated liver disease has dramatically declined since 2000.⁶⁵ The number of HBV registrants in 2006 was 409, a 30% decline since 2000. Conversely, the number of registrants with liver disease due to hepatitis C infection did not change over the same time period.

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Improving HBV Treatment: Early Screening and Sustained Control for Improved Outcomes

CME Post-Test: Circle the correct answer for each question below.

1. Patients with _____ chronic HBV are anti-HBe-positive and often have a favorable prognosis, as shown in a study of 296 healthy patients who had no difference in survival compared to uninfected controls.
a. phase 1 b. phase 2
c. phase 3 d. phase 4
2. _____ chronic HBV patients with detectable levels of HBV DNA have an increased risk for liver decompensation compared to patients with undetectable HBV DNA levels.
a. HBsAg-positive b. HBsAg-negative
c. HBeAg-positive d. HBeAg-negative
3. The results of the REVEAL study showed that the cumulative incidence of developing HCC in HBsAg-positive chronic HBV patients was _____ in patients with HBV DNA levels less than 300 copies/mL and increased to _____ in patients with HBV DNA levels greater than 1 million copies/mL.
a. 1.4%; 12.2% b. .3%; 14.9%
c. 1.4%, 14.9% d. 1.3%, 12.2%
4. In a study of 77 homosexual males, _____ of HIV co-infected patients developed chronic HBV, compared to only 4% in patients infected with HBV alone.
a. 12% b. 15% c. 23% d. 34%
5. A multicenter trial reported that tenofovir, in combination with lamivudine, achieved sustained undetectable HBV DNA levels in _____ of HIV-HBV co-infected patients.
a. 24% b. 42% c. 54% d. 76%
6. An important study of 3,163 Asian-Americans in the San Francisco area revealed that _____ of HBV-positive patients did not know that they were positive.
a. 55.3% b. 65.4% c. 72.6% d. 82.3%
7. Immunoprophylaxis of infants born to HBV-positive mothers can prevent _____ of perinatal transmission.
a. 90–95%
b. 80–85%
c. 70–75%
d. 60–65%
8. Two phase III trials showed that patients receiving adefovir for chronic HBV infection have a cumulative probability of _____ of developing adefovir resistance after 5 years.
a. 15% b. 21% c. 29% d. 34%
9. In a phase III trial, entecavir was superior to lamivudine in inducing both histologic and virologic responses. After 2 years of entecavir therapy, _____ of patients had undetectable levels of HBV DNA.
a. 60% b. 68% c. 72% d. 80%
10. After a 24-week follow-up, _____ of chronic HBV patients receiving the newly approved anti-HBV drug telbivudine achieved undetectable levels of HBV DNA.
a. 5% b. 12% c. 24% d. 39%

Evaluation Form: To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

To what extent do you agree with the following statements? Please circle the appropriate number on the scale.
(1 = Strongly Disagree 2 = Disagree 3 = Somewhat Disagree 4 = Somewhat Agree 5 = Agree 6 = Strongly Agree)

- Chronic infection with HBV increases the risk for hepatocellular carcinoma, even for those in the inactive carrier state with low levels of circulating virus.
- Patients found to be HBV-positive by this screening should be placed on prophylactic anti-HBV therapy for the duration of immunosuppressive therapy and up to 6 months following the end of treatment.

Strongly Disagree 1 2 3 4 5 6 *Strongly Agree*

Strongly Disagree 1 2 3 4 5 6 *Strongly Agree*

- In patients with HBV infection the risk of liver complications increases significantly at lower ALT values than previously considered.
- For infants born to HBV-infected mothers, immunoprophylaxis with combination of HBV vaccination and administration of hepatitis B immunoglobulin can prevent 90–95% of perinatal transmissions.

Strongly Disagree 1 2 3 4 5 6 *Strongly Agree*

Strongly Disagree 1 2 3 4 5 6 *Strongly Agree*

- All patients should be tested for presence of HBsAg prior to initiating immunosuppressive therapy for any disease state.

Strongly Disagree 1 2 3 4 5 6 *Strongly Agree*

Evaluation Form: (Continued from previous page.)

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- | | | | | | |
|--|---|---|---|---|---|
| 1. Cite high serum levels of hepatitis B DNA as a strong predictor of disease progression and treatment resistance. | 1 | 2 | 3 | 4 | 5 |
| 2. Explain methods for rapid and sustained suppression of viral loads in order to reduce the risk of cirrhosis and hepatocellular carcinoma. | 1 | 2 | 3 | 4 | 5 |
| 3. Describe ways to increase motivation and awareness among the Asian-American population to promote early screening and treatment. | 1 | 2 | 3 | 4 | 5 |
| 4. Review options for combination therapy in the treatment of patients with hepatitis B. | 1 | 2 | 3 | 4 | 5 |
| 5. Outline the treatment options of HBV/HIV co-infection. | 1 | 2 | 3 | 4 | 5 |

Overall Effectiveness of the Activity

The content presented:

- | | | | | | |
|---|---|---|---|---|---|
| • Was timely and will influence how I practice | 1 | 2 | 3 | 4 | 5 |
| • Enhanced my current knowledge base | 1 | 2 | 3 | 4 | 5 |
| • Addressed my most pressing questions | 1 | 2 | 3 | 4 | 5 |
| • Provided new ideas or information I expect to use | 1 | 2 | 3 | 4 | 5 |
| • Addressed competencies identified by my specialty | 1 | 2 | 3 | 4 | 5 |
| • Avoided commercial bias or influence | 1 | 2 | 3 | 4 | 5 |

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey. No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, Zip _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be: _____

I participated in the entire activity and claim 1.25 credits.

I participated in only part of the activity and claim _____ credits.

