



HBV: Current Gaps in Diagnosis and Linkage to Care



Volume 5 Issue 1

In this Issue...

The worldwide burden of chronic hepatitis B infection (CHB) continues to be substantial. As viral eradication is not achievable with current treatments, the focus remains on decreasing the risk of morbidity and mortality by sustained suppression of hepatitis B viral replication. The biggest challenges to reaching this goal are diagnosing CHB and linking those patients to appropriate medical care.

In this issue, Dr. Mindie Nguyen from Stanford University and Dr. Iris Liou from the University of Washington review the current research describing the epidemiology of CHB; point out the gaps in appropriate screening, diagnostic testing, evaluation, and treatment; and highlight some of the long-term benefits of antiviral therapy.

Program Information

- [CME Information](#)
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Length of Activity

- 1.0 hour Physicians
- 1.0 hour Nurses

Launch Date

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Expiration Date

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LEARNING OBJECTIVES

- Identify at-risk patients who should be screened for chronic hepatitis B.
- Describe appropriate screening and diagnostic tests for chronic hepatitis B to identify those in need of hepatitis B treatment.
- Summarize the benefits of early diagnosis and treatment of chronic hepatitis B.

GUEST AUTHORS OF THE MONTH

Commentary & Reviews



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Guest Faculty Disclosure

Dr. Nguyen Dr. Nguyen has indicated that she has received grant research support from Bristol-Myers Squibb, Gilead Sciences, Inc., and Janssen; and advisory board honorarium from Bristol-Myers Squibb, Gilead Sciences, Inc., Intercept Pharmaceuticals, Roche Laboratories, Dynavax Laboratory, and Alnylam Pharmaceuticals.

Dr. Liou has indicated that she has no financial interests or

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relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Unlabeled/Unapproved uses

Dr. Nguyen and Dr. Liou have indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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KEY TAKEAWAYS

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At least 2 billion people have been infected with hepatitis B virus (HBV) worldwide,¹ and more than 240 million remain chronically infected as reported by Schweitzer et al (reviewed in this issue), resulting in more than 750,000 deaths annually related to complications of chronic hepatitis B (CHB).² While HBV vaccinations are available, the prevalence of CHB remains high in certain parts of the world, such as the Western Pacific and Sub-Saharan Africa. Immigration patterns make CHB an active medical issue for industrialized, low-endemic regions as well, including the United States. According to NHANES data from 2007-2012 as described herein by Roberts and colleagues, over 11 million persons in the US have been exposed to HBV, with a steady prevalence of CHB of around 0.3%-0.4% (around 850,000 persons) and even higher prevalence rates reported in non-Hispanic Asians (3.1%) and foreign-born, non-Hispanic blacks (2.5%). The true number of people in the US with CHB is thought to be much higher, though — at least 2.2 million persons, based on screening studies of US immigrants³ and the fact that at least 2% of institutionalized and homeless persons are estimated to have CHB.⁴

For these reasons, the US Preventive Services Task Force (USPSTF) recommends HBV screening for persons born in regions of high and intermediate endemicity (where HBsAg prevalence is $\geq 2\%$) including people in the US not vaccinated as infants whose parents were born in regions with high HBV endemicity ($\geq 8\%$), injection drug users, HIV-positive persons, men who have sex with men, pregnant women, and close contacts with persons known to be HBsAg positive (household, needle-sharing, or sex contacts).⁵ The Center for Disease Control (CDC) also recommends HBV screening for persons needing immunosuppressive therapy, persons with elevated ALT/AST of unknown etiology, donors of human products (blood, plasma, organs, tissues, or semen), hemodialysis patients, infants born to HBsAg-positive mothers, persons who are the sources of blood exposure, and health-care and public safety workers.⁶ Screening starts with an HBsAg test, followed by a licensed, neutralizing confirmatory test, with chronic infection defined as persistence of HBsAg beyond six months. Testing for antibodies to hepatitis B surface antigen (anti-HBs) and hepatitis B core antigen (anti-HBc) provides additional information.

Despite these screening guidelines, only 400,000-600,000 persons in the US have received CHB diagnoses, leaving two-thirds unaware of having the infection.^{7,8} Community-based programs have been trialed in several US metropolitan cities with large Asian-Pacific Islander communities, who account for half of the CHB population in the US. These studies highlighted barriers to CHB diagnosis including lack of CHB knowledge, financial constraints, preference for traditional medicine, and fear of HBV and liver cancer-associated social stigma.^{9,10} Culturally appropriate educational programs with comprehensive care packages in community-based settings have been the most successful, but these programs typically run into problems providing ongoing care because patients have no or inadequate insurance coverage.¹¹ Primary care providers and subspecialists should be targeted for HBV screening training and advocacy, as well.¹²

Beyond the diagnosis of CHB, patients need successful referral to medical care and retention in that care. Moreover, primary care providers and specialists need to know about the up-to-date CHB management guidelines. The initial evaluation of CHB should include laboratory testing for hepatitis B e antigen (HBeAg), HBV DNA, and ALT, and a liver ultrasound should be considered for hepatocellular carcinoma (HCC) screening in higher-risk individuals.^{12,13}

Incomplete laboratory evaluation limits the ability to determine treatment eligibility, as shown in the studies by Wu et al and Kim et al (reviewed in this issue). The two most common guidelines used in the US for treatment eligibility criteria include the American Association



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for the Study of Liver Diseases (AASLD) and US Panel algorithms, which were first issued in 2001 and 2004, respectively, and the most recently updated versions were issued in 2016¹³ and 2015.¹⁴ Both guidelines consider that serum ALT values of 30 IU/L for men and 19 IU/L for women are used as the ULN (upper limit of normal). The AASLD guidelines recommend considering antiviral therapy in patients with immune-active CHB who have an elevation of ALT > 2 ULN or evidence of significant histological disease plus elevated HBV DNA > 2,000 IU/mL if HBeAg negative or > 20,000 IU/mL if HBeAg positive, as well as in persons with immune-active CHB with cirrhosis and HBV DNA > 2,000 IU/mL. The US Panel, on the other hand, recommends that all CHB patients regardless of HBeAg status with HBV DNA > 2,000 IU/mL and ALT > ULN or if they have any degree of hepatic fibrosis should be treated.

Optimal identification of those in need of treatment and initiation of antiviral therapy are important as antiviral therapy has been associated with decrease in the risk of decompensated liver disease, progression to cirrhosis, HCC development, and possibly even mortality risk, particularly in those with more advanced liver disease. There is even some evidence supporting possible benefit in lower-risk populations and patients not currently meeting treatment criteria, as described by Lin et al (reviewed in this issue).¹⁵⁻¹⁷ Even with the positive impact of antiviral therapy, the risk of development of HCC remains, thus routine HCC screening should be continued.

The cascade of care of CHB starts with HBV screening and diagnosis and progresses to engagement in medical care, identification of treatment eligibility and HCC screening, initiation of antiviral therapy, and retention in medical care. There are significant deficiencies in the delivery of care at all levels and across all practice settings. Culturally appropriate patient and provider education efforts should be promoted to close these gaps, as suggested herein by Zhou and colleagues. The ability to provide affordable medical care is critical to the success of these interventions.

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CHB Prevalence Worldwide

Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015; 386:1546-1555.

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This systematic review of 1800 reports from 161 countries estimated that the global prevalence of hepatitis B surface antigen (HBsAg) has been 3.61%, which in 2010 equated to 248 million persons worldwide. Most countries in sub-Saharan Africa were of higher-intermediate endemicity (HBsAg prevalence of 5-7.99%) or high endemicity ($\geq 8\%$), leading to an overall prevalence of 8.83% and a total disease burden of 75 million infected persons from that region. Countries in the Western Pacific region were of high-intermediate endemicity (5%-7.99%), with an overall prevalence of 5.26%, encompassing the largest number of individuals with chronic hepatitis B infection worldwide (95 million persons). Low (< 2%) to lower-intermediate (2%-4.99%) endemicity was generally noted in the Americas, Eastern Mediterranean, Europe, and Southeast Asia, although some countries had higher values. Over time, there was a decrease in the prevalence of HBsAg in most countries, particularly in industrialized countries; however, this downward trend was not noted in some very resource-poor areas, such as some African nations, where the prevalence remained consistently high.

This study is limited by the overall paucity of data, with variable quality of the reports and limited information on infection in children. Resource-limited regions with high hepatitis B endemicity rates are not well studied, and the local estimates used may not be an accurate reflection of national prevalence.

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Thus, worldwide, there is still a large burden of disease attributable to chronic hepatitis B infection. It is important to remember that all migrants from regions of higher-intermediate endemicity to high endemicity ($\geq 2\%$ prevalence) should be screened for chronic hepatitis B infection.^{1,2}

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CHB Infection in the US

Roberts H, Kruszon-Moran D, Ly KN, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988-2012. *Hepatology*. 2016;63(2):388-397.



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The authors assessed the trends of prevalence of past and present chronic hepatitis B infection and hepatitis B vaccination-induced immunity in the United States across a more than 20-year time frame (as previous estimates have been quite variable). Since the implementation of universal hepatitis B vaccination for infants in 1991, the incidence of acute hepatitis B has declined, but these numbers are offset by the new immigration of persons with chronic hepatitis B infection.

According to the National Health and Nutrition Examination Survey (NHANES) data collected between 1988 and 2012, the estimated prevalence of hepatitis B core antibody (indicating past or present infection) in the United States declined from 5.5% between 1998 and 1994 (over 12 million persons) to 3.7% between 2007 and 2012 (almost 11 million persons). However, the prevalence of active chronic hepatitis B infection remained constant during the entire time frame at approximately 0.3%-0.4%. Higher rates of infection were noted in foreign-born persons (1.1%) and non-Hispanic blacks (0.6% – among those foreign-born, 2.5%). In 2011-2012, with intentional oversampling of non-Hispanic Asians, the estimated prevalence of chronic hepatitis B in non-Hispanic Asians was 3.1% (approximately 427,000 persons), encompassing half of those in the United States with chronic hepatitis B infection (approximately 850,000 persons); the majority (> 90%) of those Asians were foreign-born. This prevalence is notably lower than estimates from prior studies, which reported prevalence of approximately 12% for CHB in non-Hispanic Asians and was derived mostly from large US cities.¹ The presence of anti-hepatitis B core antibody was found in 20.5% of non-Hispanic Asians, indicating a significant number of individuals who have been exposed to hepatitis B virus in this ethnic group. The prevalence of vaccine-induced immunity in the United States increased from 16% to 21.7%, with the highest numbers found in those age 20-49 years.

Despite these findings, the true prevalence of chronic hepatitis B infection in the United States is still thought to be even higher,¹ as many at-risk persons remain untested — such

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as institutionalized and homeless persons, many of whom (2% or higher) are infected with hepatitis B²—and are not included in these estimates. Thus, despite the implementation of universal hepatitis B vaccination in the United States, a notable number of individuals with chronic hepatitis B still need to be engaged in medical care.

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2. Weinbaum C, Lyerla R, Margolis HS; Centers for Disease Control and Prevention. [Prevention and control of infections with hepatitis viruses in correctional settings](#). *Centers for Disease Control and Prevention*. *MMWR Recomm Rep*. 2003;52(RR-1):1-36.

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Poor Adherence to AASLD Guidelines for CHB Management

Wu Y, Johnson KB, Roccaro G, et al. Poor adherence to AASLD guidelines for chronic hepatitis B management and treatment in a large academic center. *Am J Gastroenterol*. 2014;109(6):867-875.

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This retrospective analysis of nearly 1,000 patients with chronic hepatitis B infection (~ 40% inactive carriers), evaluated in an academic medical center and satellite community health clinics between 2005 and 2012, demonstrated poor adherence to American Association for the Study of Liver Diseases (AASLD) guidelines¹ by both gastroenterologists (following 65% of patients) and primary care providers (following 26% of patients) caring for these individuals. Almost 30% of the inactive carriers did not undergo at least annual laboratory assessment (ALT and HBV DNA), although gastroenterologists were twice as likely to order testing than were primary care providers. Of the 21% of the patients in whom liver biopsy was indicated, only 40% underwent the procedure, attributed to physician nonadherence in almost 80% of the cases. Of the 31% of treatment-eligible patients, almost all (99%) were started on treatment, but the actual treatment rate may be lower, as 12% of the patients had unclear treatment eligibility because they had not had a liver biopsy. Hepatocellular carcinoma screening was recommended in over 70% of the population, but 45% of this group did not receive adequate screening (at least annual liver imaging or serum alpha fetoprotein monitoring); again, physician nonadherence was the primary reason for this failure to screen. There was also insufficient screening for coinfection and immunity, including 35%, 24%, and 54% of the population not tested for hepatitis A, hepatitis C, and HIV infections, respectively.

The authors proposed that further efforts to improve provider education, increased use of electronic order sets for decision support, as well as better delineation of ownership of management of inactive carriers between primary care providers and specialists, can improve guideline adherence and outcome of these patients with chronic hepatitis B infection.

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CHB Evaluation and Management: Primary Care vs Specialty Care Clinics

Ku CK, Li J, Ha NB, et al. Chronic hepatitis B management based on standard guidelines in community primary care and specialty clinics. *Dig Dis Sci*. 2013;58(12):3626-3633.



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In this retrospective study of 253 consecutive treatment-naïve patients (90% Asians) with chronic hepatitis B evaluated at a community multispecialty medical center in the United States between 2007 and 2009, 190 were managed by specialists and 63 were managed by primary care providers. While optimal laboratory evaluation (ALT, HBV DNA, HBeAg) was underperformed overall (thus limiting the ability to determine treatment eligibility), it was more commonly ordered by specialists than by primary care providers (62% vs 33%, $P < .01$). Of those who had adequate testing, 38% met treatment criteria by the ASLD guidelines¹ and 75% met treatment criteria by an algorithm developed by a group of United States hepatologists (US Panel)², which was comparable in patients followed by specialists and primary care providers. Though not statistically significant, treatment eligible patients followed by primary care providers were less likely to be started on antiviral therapy than those who were followed by specialists (per AASLD guidelines, 67% vs 75%, $P = .68$; per US Panel algorithm, 20% vs 32%, $P = .61$). In addition, while most patients (96%) treated by specialists were prescribed optimal therapy (e.g. entecavir, tenofovir, adefovir, tenofovir/emtricitabine, pegylated interferon alfa 2a), 33% of patients treated by primary care providers were prescribed lamivudine, which is considered an inferior agent because of higher rates of resistance. Among those who were treatment-eligible by US Panel algorithm and not treated, the most common reason for not starting treatment was “further observation” (53%) followed by patient preference (19%); whereas for those who were treatment-eligible by AASLD criteria and not treated, the common reason was patient preference (33%).

This study highlights the need for collaboration between primary care providers and specialists to improve adequacy of optimal laboratory evaluation of patients with chronic hepatitis B to appropriately identify patients who are treatment-eligible. Furthermore, to address patient reluctance to start antiviral treatment, awareness of chronic hepatitis B infection has to be promoted at a community level to overcome poor health literacy and educational levels, true and perceived financial difficulties, language and cultural barriers, and the negative social stigma of viral hepatitis.

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Under-Treatment for CHB Infection Across All Practice Settings

Kim LH, Nguyen VG, Trinh HN, et al. Low treatment rates in patients meeting guideline criteria in diverse practice settings. *Dig Dis Sci*. 2014; 59:2091-2099.

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In this retrospective cohort study of 1976 treatment-naïve chronic hepatitis B patients followed in single- and multispecialty centers in the United States between 2007 and 2011, 17%, 64%, and 19%, respectively, were followed by primary care providers, gastroenterologists, and hepatologists, with the hepatologists following more patients with advanced liver disease. Gastroenterologists and hepatologists were more likely to be following treatment-eligible patients than were primary care providers, per both the AASLD 2009 guidelines¹ (25% and 24% vs 9%) and US Panel 2008 guidelines² (54% and 53% vs 37%). Gastroenterologists and hepatologists also had better treatment rates than primary care providers (per AASLD 2009 guidelines, 68% and 73% vs 50%; per US Panel 2008 guidelines, 45% and 59% vs 25%). For those undertreated per US Panel 2008 guidelines, the most common reason for nontreatment for patients followed by primary care providers and gastroenterologists was “further observation” (35% and 67%, respectively), whereas “perceived normal ALT level” was the most common reason for patients followed by hepatologists (37%). Patient refusal to start treatment ranged from 14%-27% across the groups. For those undertreated using AASLD 2009 guidelines, the most common reason was “further observation” for all groups (42%-52%). Fewer treatment-eligible females than treatment eligible males were treated.

Overall, this study demonstrates that undertreatment of chronic hepatitis B infection occurs in all care settings, highlighting the importance of provider education in all practices. The treatment-eligible rates reported underestimate the true extent of patients in need of treatment because of insufficient laboratory evaluation of patients with known chronic infection, in addition to lack of engagement and retention of care by many.

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Operational Interventions to Improve Engagement and Retention

Zhou K, Fitzpatrick T, Walsh N, et al. Interventions to optimize the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. *Lancet Infect Dis*. 2016;16(2):1409-1422.

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In this systematic review of operational (nonpharmaceutical) interventions in chronic viral hepatitis (HBV or HCV) care, a total of 56 studies were included in the qualitative analysis (15 HBV, 38 HCV, and three both HBV and HCV), and 33 studies were included in the quantitative analyses, with all but one of these studies conducted in high-income countries. The HBV studies targeted high-risk populations, mainly Asians immigrants, and over half were performed in community settings. Single lay health worker educational interventions in culturally appropriate community based programs, including six moderate-quality randomized controlled trials, improved HBV knowledge and testing (RR 2.68, 95% CI 1.82-3.93, I² = 56%, n = 2757). HBV testing rates improved in three studies of new institutional testing protocols for high-risk patients and supplemental provider education (RR 3.77, 95% CI 2.06-6.97, n = 37547), and two randomized controlled trials of HBV education and pretest counseling by health care professionals at health or social services used by high-risk groups (RR 6.20, 95% CI 3.19-12.08, n = 2789) — but the quality of evidence was considered very low or low as well as high in heterogeneity.

On the other hand, the HCV studies were mostly conducted in established health care or social service facilities and/or targeted health care providers. Clinician reminders prompting HCV testing increased HCV testing, as did HCV education and pretest counseling in facilities used by high risk patients. Guided referral in patients with positive HCV serologic results improved HCV linkage to care. Coordinated psychological counseling and motivational therapy for mental health and substance abuse issues also increased linkage to care but did not necessarily increase HCV treatment uptake. However, there was possible benefit for HCV treatment adherence that was not seen with nurse-led educational sessions about HCV treatment. Overall, coordinated mental health services and nurse-led education seemed to improve rates of achieving sustained virological response but not direct-observed therapy. The overall quality of evidence for these analyses was considered very low to low.

This article focused on viral hepatitis testing and linkage to care and treatment, rather than on patient outcomes, but there is evidence that treatment leads to reduced liver-related complications and reduced development of hepatocellular carcinoma.^{1,2} Given the nature of operational interventional studies, often with nonrandomized designs, there were few high-quality studies to consider, and heterogeneity was high. But despite these limits, this review shows that task-shifting educational programs to lay health workers in a culturally appropriate format can be a simple and inexpensive method to increase HBV testing and may be appropriate for low and middle income countries as well; more studies are needed.

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1. van der Meer AJ, Veldt BJ, Feld JJ, et al. [Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C](#)

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CHB Antiviral Therapy in Low-Risk Patients Associated with Reduction in HCC

Lin D, Yang HI, Nguyen N, et al. Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. *Aliment Pharmacol Ther*. 2016;44(8):846-855.



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While many studies have shown a reduction in the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B infection who are on antiviral therapy,¹⁻³ the risk reduction has been more prominent and consistent in patients with cirrhosis.⁴⁻⁵ The authors of this study described the impact of antiviral therapy in a large retrospective clinical US cohort (n = 2255) and also in comparison to the Risk of Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in Hepatitis B Virus (REVEAL-HBV) population-based cohort of untreated persons from Taiwan⁶ (n = 3653). REVEAL-HBV data was the basis for an externally validated Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) scoring system that has been demonstrated to be a useful HCC-predictive tool in Asian patients.⁷ Particular attention was paid to subjects historically considered to be at lower risk for HCC (female gender, younger age, lack of cirrhosis, HBeAg negativity, normal to minimally elevated ALT levels, and low-to-middle REACH-B scores.) The majority (> 90%) of persons in these lower-risk cohorts did not have cirrhosis. In the US cohort, most the patients were of Asian ethnicity and 43% were treated with antiviral therapy, mostly with the newer agents (e.g. entecavir and tenofovir), with over 80% achieving continuous virological suppression. To account for background risk differences between the cohorts, the investigators used REACH-B score risk adjustment. For those in the US cohort who received antiviral therapy, the risk of developing HCC decreased by 69% compared to the untreated group (HR 0.31; 95% CI 0.15-0.66; *P* = .002) and by 78% when compared to the REVEAL cohort (HR 0.22; 95% CI 0.12-0.4; *P* < .001). This HCC risk reduction was present in patients with and without cirrhosis, was independent of age, gender, HBeAg status, ALT level, REACH-B score, or type of antiviral therapy, and was even found in treated patients who had modestly elevated HBV DNA at baseline (≥ 2000 IU/mL).

Thus, even some patients historically considered to be at lower risk of developing HCC may benefit from antiviral therapy. These findings are similar to those of another US study that used propensity-score adjustment method: HCC risk reduction in patients on antiviral therapy was noted across baseline HBV viral levels and stage of fibrosis (based on FIB4 scores).⁸ It is important to remember that while HCC risk can be reduced by antiviral therapy, it is not eliminated — so treated patients should continue to undergo routine HCC screening.

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KEY TAKEAWAYS

- Persons born in regions of high and intermediate endemicity (where HBsAg prevalence is $\geq 2\%$) and US persons who were not vaccinated as infants and whose parents were born in regions with high HBV endemicity ($\geq 8\%$) should undergo hepatitis B screening, which should include HBsAg testing.
- The initial evaluation of a patient with chronic hepatitis B should include laboratory testing for HBeAg, HBV, DNA, and ALT; and AFP and a liver ultrasound should be considered for hepatocellular carcinoma screening in higher-risk individuals.
- Antiviral therapy in chronic hepatitis B decreases the risk of decompensated liver disease, progression to cirrhosis, hepatocellular carcinoma, and possibly even mortality, particularly in those with more advanced liver disease.

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