NARRATIVE REVIEW

A Review of the Systemic Manifestations of Hepatitis B Virus Infection, Hepatitis D Virus, Hepatocellular Carcinoma, and Emerging Therapies

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Chronic hepatitis B virus (HBV) infection affects about 262 million people worldwide, leading to over 820,000 deaths each year primarily due to cirrhosis and hepatocellular carcinoma. The World Health Organization has pledged to eliminate HBV as a health threat by 2030, but currently, no countries are on track to achieve this goal. One of the barriers to HBV elimination is stigma, causing shame, denial, self-isolation, self-rejection, and depression leading to those with chronic HBV less likely to get tested or seek treatment and more likely to conceal their infection. Other barriers include limited access to care and complicated and restrictive clinical practice guidelines. Increasing public and political efforts are necessary to raise awareness, increase access to care, and change screening and treatment guidelines. The current guidance of the American Association for the Study of Liver Diseases (AASLD) recommends testing only if patients are considered at risk, but this has proven to be ineffective. We propose a simplified "test all and treat all" approach with a 5-line guideline for HBV infection. Universal screening and treatment of adults is cost-effective and can prevent transmission by effectively managing chronic HBV. All patients who are hepatitis B surface antigen (HBsAg) positive with detectable HBV-DNA should receive treatment until HBsAg is undetectable for 12 months, as HBV-DNA transmission via blood transfusion can occur even at low viral loads of 16 copies/mL, and mother-to-child transmission is still a risk even with passive-active immunoprophylaxis. Furthermore, clinical outcomes after HBsAg clearance are significantly better than the clinical outcomes of those who remain HBsAg positive.

Keywords: Hepatitis B Virus; Chronic Hepatitis B; Five-line guideline for HBV; Test all and treat all

Introduction

Chronic hepatitis B virus (HBV) infection is a significant global health issue affecting an estimated 262 million people worldwide with 1.5 million new infections each year.[1,2] It is associated with more than 820,000 deaths per year, and patients face substantial risk of complications, as 15%–40% of patients with chronic HBV (CHB) may develop cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1,3–5] Prevalence of HBV is highest in African, Western Pacific, East Asia, and Southeast Asia regions, with the Western Pacific accounting for approximately 50% of all CHB infections worldwide.[1,4] Unfortunately, the prevalence is underestimated partly due to limited surveillance systems within different countries, reactivation risk of hepatitis B surface antigen (HBsAg)-negative patients, and occult HBV infection.[6]

In 2021, the World Health Organization (WHO) estimated that approximately 15%–25% of people with CHB will require treatment[1]. Based on all the global guidelines, patients who have HBV-DNA ≥2000 IU/mL and elevated alanine aminotransferase (ALT) should begin treatment.[7–11] The goal of the current treatment regimen has 2 targeted end points: suppression of HBV-DNA to undetectable levels

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and the loss of HBsAg or HBsAg seroconversion (ie, functional cure). Studies have shown that these proposed goals for treatment have been associated with improved long-term outcomes.[12,13] Although HBV-DNA suppression occurs in more than 70% of patients, the loss of HBsAg occurs only in a small subset of patients. The loss of HBsAg has been difficult to achieve since the first-line therapies have very little effect on the HBsAg production and do not modify the immune response.[9,14] Because the mortality rate for HBV has not changed in the last 20 years, major research and investments have been made in the development of new medications.

The "test all and treat all" approach within the 5-line guideline of HBV discussed herein will likely increase HBV diagnosis, reduce transmission, extrahepatic manifestations of HBV, stigma, and rates of hepatitis Delta virus (HDV) coinfection, improve quality of life, and be cost-effective overall.[15–25] This will increase the number of patients with HBsAg loss since a far greater number of patients will be receiving treatment especially as advanced treatments become available in clinics. Lower costs for low- and middle-income countries (LMICs) can also help improve access to treatment, and emerging therapies for the treatment of CHB under investigation may increase the number of patients with HBsAg loss (ie, functional cure).[12,13]

Transmission of Hepatitis B

Blood Exposures, Relationship to Viral Load, and Infectivity

The risk of infection from blood exposures, such as blood transfusions, is dependent on the circulating infectious agent, antibodies bound to virions, stage of infection of the donor, blood volume received, degree of immunosuppression in the recipient, and type of blood product received.[26,27] Hepatitis B core antibody (anti-HBc) negativity or low levels of anti-HBc have been related to higher infectivity rates. There was 50% transmission in those without anti-HBc and HBV <100 copies/mL vs 3% transmission in those with anti-HBc and HBV <100 copies/mL.[26,27] In a study involving human hepatocytes transplanted into chimeric mice, low anti-HBc titers were related to ~3% infectivity, whereas those without anti-HBc had 37%–50% infectivity. Therefore, transmission may be higher during the window period and in the acute phase than in the chronic phase.[28]

Patients with occult HBV infection are also HBV-DNA positive, anti-HBc positive, and HBsAg negative. While most patients are found to have HBV-DNA levels around 20,000–90,000 copies/mL (approximately 4000–22,000 IU/mL), much lower titers of HBV-DNA levels can also be observed.[26,29,30] However, there are no data on whether blood products from these patients are infectious.[26] There may be a small relationship between viral load in infectious blood and noninfectious blood in instances where infection was reported with viral copies as low as 2–5 copies/mL and no infection with 200 copies/mL.[27] Some studies have proposed that the minimum infectious dose of HBV may be

as low as 16 copies/mL.[31] Therefore, it is important to treat all those who are HBV-DNA positive as even low levels have the potential to spread HBV infection.[32]

HBV Mother-to-Child Transmission

Mother-to-child transmission (MTCT) of HBV during the perinatal period continues to be a global health issue especially in high-endemic areas.[33–35] Even in low-endemic areas, MTCT accounts for more than one-third of CHB infections.[36–38] If newborns are born to hepatitis B e antigen (HBeAg)-positive mothers and do not receive hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine soon after birth, 70%–90% will develop HBV infection. If the newborns are born to HBeAg-negative mothers and do not receive HBIG and hepatitis B vaccine, 10%–20% will develop HBV infection.[39,40] Also, despite treatment with HBIG and hepatitis B vaccine in neonates, about 9% of newborns will acquire HBV infection if their mother has a CHB infection. This is especially true if the mother is HBeAg positive or she has high HBV-DNA levels.[41] For example, there was 9% transmission rate when mother's viral load was >8 $\log_{10}$ copies/ml (7.3 $\log_{10}$ IU/ml) even after administration of passive-active immunoprophylaxis.[42] Recent studies propose lower levels of HBV-DNA <6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) to reduce MTCT rates.[43,44]

Additionally, newborns have a 90% chance of developing a CHB infection compared to a 50% chance for children younger than 3 year old and only a 5% chance for adults after being infected with HBV.[41] In high-endemic areas such as China, the percentage of women of childbearing age with CHB infection is up to 17.8%.[45] Therefore, we reiterate the importance and the need to "test all and treat all" and vaccinate all who are susceptible. This also recognizes that there are areas of the world where HBV-DNA testing is twice the price of 1 year of tenofovir and other areas where nucleic acid testing is not available for pregnant women.

Sexual Transmission

One of the main modes of transmission for HBV is through sexual contact. In low-prevalent areas, intravenous drug users (IVDUs) and sexual exposure account for most cases of HBV exposure. Historically, men who have sex with men (MSM) are at the highest risk for infection. This has been associated with anal intercourse, increased number of sexual partners, and the number of years of sexual activity.[46] About 70% of MSM were infected after 5 years of activity.[47] However, it is not only limited to MSM. Women and heterosexual men also have an increased risk of HBV infection with an increased number of sexual partners, years of sexual activity, and a history of sexually transmitted diseases.[48]

Hepatocellular Carcinoma

HCC is the leading cause of death in patients with cirrhosis.[25] It was ranked the third-highest cause of mortality due to cancer in 2018,[49] and 90% of primary liver

cancers are due to HCC. Unfortunately, HBV is still a major risk factor for HCC development in East Asian countries.[50] The risk for HCC development is increased for those who have coinfection with hepatitis C virus (HCV), HDV, and or HIV.[50,51] Although there is still a risk for HCC with HBsAg clearance even in the absence of cirrhosis, the risk was significantly lower compared to those who were HBsAg positive.[52] The continued risk in those who are HBsAg negative is likely due to integrated HBV-DNA in the hepatocyte genome.[52]

Although there have been improvements in therapeutic options for HCC, the 5-year survival rate for HCC is lower than 20%.[25] An important factor for HCC prognosis is the tumor stage. The 5-year survival rate can be greater than 60% for those in earlier stages compared to those in advanced stages (median survival of 1–2 years).[25] Surveillance with ultrasound is recommended every 6 months with or without alpha-fetoprotein (AFP) serum testing to reduce mortality due to HCC. Table 1 summarizes HCC surveillance recommendations from different guidelines. Unfortunately, a recent study found that less than 40% of patients underwent annual HCC surveillance.[55]

Ultrasound has a higher sensitivity, specificity, and diagnostic accuracy compared to AFP serum testing, but AFP can be considered for those without ultrasound access.[11,56] However, the accuracy of AFP in detecting HCC may also vary depending on the cutoff value, prevalence of the disease, and patients' virological status. AFP is Food and Drug Administration-cleared as a risk test for HCC and not for diagnosis.

A recent cohort study of 534 patients showed that none of the biomarkers (AFP, AFP-L3, des-gamma-carboxy prothrombin [DCP]) individually or in combination had promising results in risk prediction for HCC.[57] Furthermore, these biomarkers' detection accuracy is also dependent on their cutoff values. Overall, the combination of these serum markers alone or together has shown only marginal improvement in HCC surveillance or diagnosis.

There have been several scoring systems created to help predict the risk of developing HCC in patients with CHB. The PAGE-B model was developed previously to predict 5-year HCC development in Caucasians with CHB receiving nucleos(t)ide analogs. In 2018, a modified PAGE-B model was released, and it showed improved prediction for HCC risk in Asians with CHB infection receiving nucleos(t)ide analogs.[58] Unfortunately, because many of these predictive scoring models are dependent on many factors such as ethnicity, stages of liver disease, and antiviral treatment, their use is limited.

The GALAD scoring system was developed to improve early-stage HCC detection in patients with HBV and HCV. The GALAD scoring system looks at gender, age, AFP level, AFP-L3 level, and DCP level. It has been shown to detect early-stage HCC with 86% sensitivity and 96% sensitivity in a British cohort.[59] In a European cohort study in 2021, the GALAD system was superior at detection of early-stage Barcelona Clinic Liver Cancer stage 0 or A compared to biomarkers AFP, AFP-L3, or DCP alone.[60] However, a recent study found that although GALAD score had significantly higher sensitivity, it also had an increase in false-positive rates.[57]

Treatment of HBV-Associated HCC

The treatment of HCC is dependent on the stage of the tumor, disease burden, patient functional status, and underlying hepatic function. If HCC is found earlier, initial curative

Table 1. AASLD, EASL, and APASL Guidelines for HCC Surveillance

Guidelines	Patients without cirrhosis	Patients with cirrhosis
American Association for the Study of Liver Diseases (AASLD)[11,53] -Every 6 mo with US with or without AFP serum testing every 6 mo if US is not available	*HBsAg seroclearance:* -First-degree relative with HCC -Long duration of infection (> 40 y for males, > 50 y for females) *HBsAg positive:* -Asian males >40 year old -Asian females >50 year old -First-degree relative with HCC -Coinfection with HDV	-Child-Pugh class A and B -Child-Pugh class C, if awaiting liver transplant (due to decreased rate of survival)
European Association for the Study of the Liver (EASL)[54] -Every 6 mo with US	*HBsAg positive:* -Caucasians with PAGE-B score[a] ≥10 precirrhotic with advanced fibrosis (F3)	-Child-Pugh class A and B -Child-Pugh class C, if awaiting liver transplant (due to decreased rate of survival)
Asian Pacific Association for the Study of the Liver (APASL)[51] -Every 6 mo with US + AFP serum testing	*HBsAg seroclearance:* -Receiving antiviral therapy -HBsAg seroclearance >50 year old *HBsAg positive:* -Asian female >50 year old -Asian male >40 year old -Blacks >20 year old -Family history of HCC	-Child-Pugh class A and B -Child-Pugh class C, if awaiting liver transplant (due to decreased rate of survival)

HDV, hepatitis D virus; US, ultrasound.
[a]PAGE-B score: 5-y HCC, risk predictor for Caucasian patients with chronic HBV, receiving nucleos(t)ide analogs.

treatment entails resection and or ablation or liver transplantation. The 5-year recurrence rate is 4%–18% for those treated with liver transplantation vs 50%–75% for those treated with resection or local ablation. In patients with liver transplantation for HBV-associated HCC, the 5-year survival rate is approximately 80%. For those with advanced disease, palliative treatments include local-regional therapies such as transarterial chemoembolization or transarterial radio-embolization followed by systemic therapy.[56]

The 5-year recurrence risk for HCC after curative resection is between 60% and 80%.[61] About 70% of recurrences are within the first 2 years (early recurrence).[62] The recurrence of HBV-associated HCC is independently related to high HBV viral load.[63,64] Therefore, HBV antivirals are used to prevent recurrence for those who received a curative resection. Unfortunately, even with the antivirals, the recurrence rate is between 40% and 60%.[62,65] A 2022 systematic review and meta-analysis showed that HCC recurrence and mortality were lower with tenofovir disoproxil fumarate (TDF) than

with entecavir (ETV). This was mostly in the prevention of late recurrence (after 2 years).[66]

Other Consequences of HBV

Extrahepatic Manifestations of CHB

About 20% of patients with HBV infection develop extrahepatic manifestations[67] as shown in Table 2. Like HCV, many of the extrahepatic manifestations are thought to be due to the deposition of immune complexes (ICs) with an inflammatory response.[77] These ICs consist of HBsAg, again highlighting the importance of treating all who are HBV-DNA positive until HBsAg loss is achieved.

Coinfection With HDV Systemic Manifestations

HDV is the smallest human RNA virus and is considered a defective subvirus that can only propagate with the

Table 2. Extrahepatic Manifestations of HBV

Types of manifestations	Symptoms
Periarteritis or polyarthritis nodosa (PAN)	• Can present in all stages of HBV infection but more commonly within the first 6 mo of acute HBV infection[67–69] • Associated with IC (HBsAg and/or HBeAg) deposition into blood vessels[70,71] • HBV-associated PAN have more frequent relapses of vasculitis and mortality compared to primary PAN,[67–69] until HBV is fully suppressed • ANCAs and complement levels are normal[70,71] • CTA or MRA diagnose HBV-associated PAN when there are multiple aneurysms in the affected organ[72]
Mixed cryoglobulinemia (MC) vasculitis	• 90% of cases are due to HCV infection, and 10% of cases are due to lymphoproliferative disorders, rheumatic disorders, HBV, or HIV infections[73–75] • Like HCV, HBV-mediated MC is due to IC (HBsAg and anti-HBs) depositing into the small-medium blood vessels[76] • CD20-positive B cells are expanded and activated[77]
Rheumatological manifestations	• Symmetric and nondestructive arthralgia or arthritis involves the hands, feet, and sometimes large joints[67,78] • IC containing HBsAg and activated complement deposit into synovium[67] • Anti-cyclic citrullinated peptide antibody (5%), antinuclear antibody (10%), rheumatoid factor (25%) can be positive[67]
Skin manifestations	• Occur in >50% of acute HBV infections[78] ○ Present as maculopapular, pruritic, or petechial lesions[78] • In chronic HBV, sequela of cutaneous vasculitis are from immunoglobulins, complements, and HBsAg depositing into the vessel walls[78] • These deposits can be found on skin biopsies[78]
Renal manifestations	• 3%–5% of chronic HBV infections develop renal involvement[17,79] • Associated with IC deposition in the glomeruli[80] • MN and MPGN are the most common[77] • HBV genotype A is associated with higher incidences of MN and MPGN[77] • HBV-associated MN: ± anti-PLAR, predominantly associated with IgG1 subtype[81] • Idiopathic MN: + anti-PLAR, predominantly associated with IgG4[81]
Hematologic malignancies	• Associated with NHL and DLCL • In a nationwide study in Taiwan of those with HBV infection, the hazard ratio was 2.2 for NHL, 2.7 for DLCL, and 3.1 for the other B-cell lymphoma[18] • Patients with DLCL and chronic HBV had a poorer 2- and 5-y survival rate and progression-free survival rate[82]

ANCAs, antineutrophil cytoplasmic antibodies; anti-PLAR, antiphospholipase A2 receptor antibodies; CTA, computed tomography angiography; DLCL, diffuse large B-cell lymphoma; Ig, immunoglobulin; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephropathy; MRA, magnetic resonance angiography; NHL, non-Hodgkin lymphoma.

existence of HBV. It envelopes within the HBV surface proteins and uses HBV as a helper for hepatocyte entry, intrahepatic spread, and host dissemination.[83] Modes of transmission occur via simultaneous coinfection with HBV or superinfection with a CHB carrier.[84] A simultaneous infection occurring with HBV can cause severe to fulminant hepatitis with a high mortality rate; however, individuals who are able to achieve recovery typically have clearance of both viruses.[85] Superinfection with CHB usually causes HDV persistence, which can cause rapid progression to cirrhosis and increased risk of HCC, making it one of the most severe forms of CHB.[83,86] Approximately 50%–70% of patients with HBV-HDV coinfection develop cirrhosis within 5–10 years of diagnosis, a 3-fold increase compared to HBV monoinfection.[86]

A systematic review and meta-analysis from 2020 estimated prevalence among HBsAg carriers as 4.5%, with a global HDV prevalence of 0.16%, equaling approximately 12 million people,[85] but exact global HDV infection prevalence is unknown due to lack of universal testing and reporting and limited laboratory test access, making epidemiological data scant or not available for many countries.

Chronic viral infection with HDV has been suspected to cause primary Sjögren syndrome. In a viral microarray analysis of salivary glands of patients with and without Sjögren syndrome, HDV was found 50% more often in those with primary Sjögren syndrome compared to healthy controls. However, these patients were negative for HBsAg, anti-HBc antibodies, and HDV antigens in the serum.[87] Additionally, patients with chronic HDV tend to have higher frequency of autoantibodies compared to those with HBV alone. These autoantibodies are antiliver kidney microsomes, antibasal cell layer antibodies, and antithymic antibodies (stellate epithelial cell antibodies, thymic reticular cell antibodies, and perithymocytic cell antibodies).[88] Therefore, the "test all and treat all who are HBV-DNA positive" approach may reduce the risk of contaminant HDV infections and associated systemic manifestations.

Quality of Life

Clinicians should be aware of the reduced quality of life for patients with HBV, which is due to the stigmatization, chronicity of HBV infection, and the extrahepatic manifestations of HBV. Current evidence suggests that there is a gap between the clinician's and the patient's perspective on the impact of the disease on patients' daily lives.[20,22] This can be bridged with patient-reported outcomes (PROs) questionnaires. PROs come directly from the patient without any interpretation by a health-care professional.[22] Recently, Younossi et al developed and validated a new PROs instrument known as the HBV-specific version of Chronic Liver Disease Questionnaire (CLDQ-HBV).[21] This questionnaire can be used to monitor disease progression and identify factors that can strengthen patients' adherence to treatment.[22,23] Younossi et al found that patients with depression, type 2 diabetes, and obesity had more impaired health-related quality of life.[21] In a recent cohort study,

depression was independently and positively correlated with liver-related mortality and liver cancer mortality.[24] Therefore, we should treat all who are HBV-DNA positive.

Stigma

In the United States, HBV is highly prevalent in Asian immigrants.[89,90] Unfortunately, many of these immigrants neither have access to nor seek testing, vaccination, or care for HBV, increasing the risk of transmission and disease progression.[89] A study performed on Vietnamese Americans in Chicago showed that up to 55% of the population is unaware that HBV can be spread by sexual intercourse, instead believing that it can be transmitted by sharing utensils.[90] In the same study, more than 60% believed that HBV carriers put others at risk and should avoid close contact with others.[89] This social stigma is compounded by self-stigma, in which people living with CHB blame themselves for their infection. The resulting shame, denial, self-isolation, self-rejection, self-hatred, and depression result in a withdrawal from public activities, family, and friends, which can increase risk of depression and suicidal ideation, increasing the mortality risk for these patients. These misconceptions and stigma affect all aspects of the HBV pandemic from primary prevention to prevention of progression and spread. At-risk populations are less likely to get vaccinated, tested, or seek treatment and are more likely to conceal their infection, further increasing the risk of spread.[19,89] Therefore, by adopting the "test all and treat all who are HBV-DNA positive" approach, these authors emphasize the ability to reduce spread and the stigma associated with HBV infection.

Current Therapies

The treatment goals of managing HBV are directed toward managing stigma, preventing transmission, and preventing liver cirrhosis, decompensated cirrhosis, HCC, liver transplantation, and death. This can be achieved through normalizing liver enzyme levels and halting necroinflammatory activity by stopping HBV replication. There are currently 9 approved drugs for CHB, though only 3 are in active use globally. There are 2 interferon (INF) formulations: conventional and pegylated interferon (pegINF). There are 7 nucleos(t)ide analogs: lamivudine, telbivudine, adefovir, ETV, TDF, tenofovir alafenamide fumarate (TAF), and clevudine and besifovir dipivoxil (only in Korea) (Table 3).

A virological response with INF treatment is defined as HBV-DNA <2000 IU/mL after 6 months of therapy. For treatment with nucleos(t)ide analogs, virological response is defined as HBV-DNA <10–20 IU/mL. A biochemical response is defined as normalization of ALT.[93] For CHB treatments, cutoff values of 35 U/L for males and 25 U/L for females for ALT are used to help guide treatment decisions.[11] Although our overall goal is to functionally cure and resolve HBV infection (HBsAg loss or detection of HBsAg lower than 0.05 IU/mL), it is extremely rare to achieve (<1% of patients per year).[11,93] Given the high rates

Table 3. Summary of Current HBV Therapies

Types	Notes
Interferon formulations	
Conventional INF pegINF	-Poor efficacy and tolerability -HBsAg loss after 5 y of follow-up occurs in <10% of patients[91] -Should not be used in patient with decompensated liver failure[92]
TDF	
Lamivudine Telbivudine Adefovir ETV TDF TAF Clevudine Besifovir dipivoxil[a]	-TAF is first-line treatment. -TAF is more stable than TDF, thus able to more effectively deliver to hepatocytes. -TAF has less renal and bone toxicity.[11] -TAF is not recommended for CrCl <15 mL/min or those receiving dialysis.[11] -ETV has no bone or renal toxicity risk. -ETV is not recommended for women of childbearing age or for children.[92]

CrCl, creatinine clearance; NA, nucleos(t)ides analog.
[a]Only available in Korea.

of relapse after cessation of nucleos(t)ide analogs, the American Association for the Study of Liver Diseases (AASLD) recommends stopping treatment only after HBsAg loss with or without seroconversion. Emerging data on hepatitis B core-related antigen (HBcrAg), quantitative HBV-RNA (qHBV-RNA), and other biomarkers will help with the viral clearance prediction. Discontinuation is not recommended for those with cirrhosis due to hepatitis flares after virological response and the risk of liver failure and death.[92]

Standard of Care

Five-Line Guidelines for HBV

We agree with the recent Morbidity and Mortality Weekly Report from the Centers for Disease Control and Prevention on HBV testing and vaccinations. They advise testing all adults who are 18 years or older with a triple panel consisting of HBsAg, anti-HBc, and hepatitis B surface antibody (anti-HBs) at least once in their lifetime.[16] If the person is at increased risk for HBV, periodic testing should take place regardless of age, as long as the risk for exposure persists.[16] A recent article by the Infectious Disease Society of America found that screening everyone with HBsAg once is more cost-effective compared to the current practice guided by the current HBV guidelines.[15] The study found that it would prevent an additional 23,000 deaths from liver disease and liver cancer, resulting in an estimated savings of $596,000,000.[15] Universal screening of adults is cost-effective, and it may prevent transmission with the management of CHB, identify those who are at risk of HBV reactivation, and identify those who would benefit from HBV vaccination.[16] A 2022 Morbidity and Mortality Weekly Report recommends HBV vaccination for all, as it proven to be safe, efficacious, and well tolerated.[94] For these reasons, we recommend testing all adults with a

triple panel at least once in their lifetime and vaccinating all triple-panel-negative adults (Figure).

It is generally agreed that the current HBV treatment guidelines by the European Association for the Study of the Liver, AASLD, and Asian Pacific Association for the Study of the Liver are complex and impractical to implement[32,95] (Table 4). Additionally, a recent multicenter longitudinal cohort study in North America found that lower percentages of African American (AA) or black participants met the AASLD treatment criteria compared to Asians and white participants.[96] The treatment initiation rates were highest among Asians and lowest among AA or blacks.[96] This may be due to Africa-born AA or black participants have a lower prevalence of HBeAg and genotype A2 compared to US-born participants.[96] Similarly, AA or blacks had a lower presence of HBeAg and or lower ALT levels compared to Asian participants.[96] The lower prevalence of HBeAg and lower HBV-DNA levels among those who are HBeAg negative lead to lower percentages of AA or blacks meeting the treatment criteria.[96] This emphasizes the presence of racial disparities within the treatment guidelines. Therefore, simplified treatment guidelines are important to reach all races, to reduce morbidity and mortality due to HBV, and to eliminate HBV as a public health threat.

Recently, a simplified treatment plan was recommended by Dieterich et al. They recommended antiviral treatment for those without cirrhosis who have HBV-DNA $\geq$2000 IU/mL and are 30 years of age or older or younger than 30 years with an ALT greater than the upper limit of normal (> 30U/L for males, > 19 U/L for females).[95] They recommend cessation of treatment when all the following criteria are met: HBsAg loss, completion of at least 1 year of treatment, maintaining persistently normal ALT levels, undetectable HBV-DNA levels, and available for HBsAg monitoring for at least 2 years.[95]

Although this is a step in the right direction, we argue for a more simplified approach of treating all those who are HBV-DNA positive until there is HBsAg loss for at least 12 months (Figure). This is due to several factors. First, antiviral therapy has been shown to reduce inflammation and fibrosis; therefore, it will be beneficial even for those with normal liver enzymes.[32] Second, there is still an increased

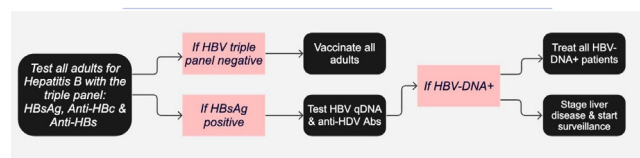| 5-Line Guidelines for HBV	•Test all adults with HBV triple panel: HBsAg, Anti-HBc, Anti-HBs.
	Vaccinate all adults who are triple-panel negative.
	•If HBsAg+, follow up with qDNA and anti-HDV.
	•Treat all HBV-DNA+ patients including cirrhosis (Treat until HBsAg loss +12 months consolidation)
	Stage each patients liver fibrosis status and determine strategy for surveillance of HCC and concomitant liver disease.

Figure. The 5-line guidelines for HBV in adults.

Table 4. Chronic HBV Infection Characteristics, Monitoring Guidelines, and Current Treatment Recommendations

	HBeAg positive	HBeAg negative
Chronic HBV infection[8,10,11]	High HBsAg levels High HBV-DNA levels (typically > 20,000 IU/mL) Normal ALT levels Monitoring guidelines 　-HBeAg checked every 6–12 mo. 　-ALT checked every 3–6 mo. 　-ALT and HBV-DNA checked every 1–3 mo if ALT elevation is noted. 　-Consider liver biopsy if HBV-DNA > 2000 IU/mL and ALT < 2x ULN who are >40 year old with HBV diagnosed at a younger age. 　-Evaluated for HBsAg annually. 　-Sustained HBsAg loss; ALT and HBV-DNA monitoring no longer required. HCC should be monitored if cirrhosis, first-degree family with HCC, or long duration of infection (>40 y for males, >50 y for females). AASLD treatment recommendations 　-HBV-DNA > 20,000 IU/mL and ALT > 2x ULN 　-Biopsy findings: Moderate-severe inflammation (A3 or higher) or fibrosis (F2 or higher) EASL treatment recommendations 　-HBV-DNA > 20,000 IU/ml and ALT > 2x ULN 　-HBV-DNA > 2000 IU/ml, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis 　-Everyone with cirrhosis APASL treatment recommendations 　-Decompensated cirrhosis 　-Compensated cirrhosis with HBV-DNA ≥ 2000 IU/ml and elevated ALT 　-Noncirrhotic with HBV-DNA ≥ 20,000 IU/ml and ALT > 2x ULN 　-Noncirrhotic with HBV-DNA < 20,000 IU/ml and or ALT < 2x ULN if signs of severe inflammation or significant fibrosis.	Anti-HBe antibodies positive Low HBsAg levels HBV-DNA levels 2000–20,000 IU/mL Normal ALT levels Monitoring guidelines 　-ALT checked every 3 mo during the first year, and then every 6–12 mo thereafter. 　-ALT checked every 3–6 mo with HBV-DNA if ALT elevation is noted. 　-HBV-DNA and HBsAg if ALT is persistently elevated. 　-Consider liver biopsy if HBV-DNA > 2000 IU/mL and ALT < 2x ULN who are >40 year old with HBV diagnosed at a younger age. 　-Evaluated for HBsAg annually. 　-Sustained HBsAg loss; ALT and HBV-DNA monitoring no longer required. HCC should be monitored if cirrhosis, first-degree family with HCC, or long duration of infection (>40 y for males, >50 y for females). AASLD treatment recommendations 　-Biopsy findings: Moderate-severe inflammation (A3 or higher) or fibrosis (F2 or higher) EASL treatment recommendations 　-HBV-DNA > 20,000 IU/ml and ALT > 2x ULN 　-HBV-DNA > 2000 IU/ml, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis 　-Everyone with cirrhosis APASL treatment recommendations 　-Decompensated cirrhosis 　-Compensated cirrhosis with HBV-DNA ≥ 2000 IU/ml and elevated ALT 　-Noncirrhotic with HBV-DNA ≥ 2000 IU/ml and ALT > 2x ULN 　-Noncirrhotic with HBV-DNA < 2000 IU/ml and or ALT < 2x ULN if signs of severe inflammation or significant fibrosis.

JSH, Japan Society of Hepatology; ULN, upper limit of normal.

risk for HCC- or liver-related death even for those with normal serum ALT levels and low HBV-DNA levels.[97] Antiviral therapies have been shown to reduce integration of HBV-DNA, thereby reducing direct carcinogenesis.[97] Additionally, early HBV treatment has been shown to reduce disease progression, improve inflammation, and even reverse cirrhosis, even in those with normal ALT levels.[97] Furthermore, transmission can still occur with as little as 16 viral copies, which is equivalent to 3 IU.[32] As mentioned above, there is a risk of transmission with blood exposures, MTCT, and sexual transmission, even with low HBV-DNA levels.

Several studies have estimated that the cost of expanding CHB therapy may be offset by the reduction in medical costs resulting from the disease progression of CHB. China has the largest CHB burden in the world. A recent study conducted in China investigated the effect of expanding CHB therapy to those with elevated ALT levels vs HBsAg-positive individuals.[98] The study found that treating HBsAg positive, regardless of ALT levels, with 80% coverage not only allowed them to achieve WHO's 2030 goal of a 65% reduction in HBV-related mortality but was also the most cost-effective in the long run by 2050.[98] The study also found that this approach had the highest reduction in HBV-related complications and death, with the highest quality-adjusted life years compared to ALT level-based treatments.[98]

As mentioned above, there are additional poor outcomes associated with CHB. Those with CHB are at risk for extrahepatic manifestations (Table 1), coinfection with HDV with associated complications, reduced quality of life, and stigma. For these reasons, we urge the treatment of all who are HBV-DNA positive with an antiviral therapy until they are HBsAg negative for at least 12 months (Figure). Although expanding treatment guidelines may be difficult logistically, we urge government officials and the medical community to support this approach, as it will decrease morbidity and mortality due to HBV, improve the quality of life of patients with CHB, help achieve WHO's goal of eliminating HBV as a health threat by 2030, and be cost-effective in the end.

Acute HBV Infection

Most adult patients who acquire HBV acutely do not require therapy as >95% of immunocompetent adult patients will recover spontaneously. It may be reasonable to treat in the context of severe liver injury or acute liver failure. Severe liver injury is defined by total bilirubin >3 mg/dL (or direct bilirubin >1.5 mg/dL), international normalized ratio >1.5, encephalopathy, or ascites. The preferred antiviral treatments are ETV, TAF, or TDF. INF-alpha is avoided due to the risk of decompensation. The treatment should be continued until HBsAg is no longer detectable, or indefinitely if the patient is to undergo liver transplantation.[11]

Resolved HBV Infection

Resolved HBV infection (ie, functional cure) is defined as HBsAg negative, anti-HBc total positive, HBeAg negative,

and undetectable HBV-DNA. Spontaneous resolution of CHB with HBsAg loss is possible but only occurs in about 1% of patients per year. The progression of liver damage to cirrhosis or in patients with cirrhosis is halted with the loss of HBsAg unless the HBsAg loss occurs in individuals who are older than 50 years of age, already have cirrhosis, or have coinfection with HCV or HDV. Luckily, even in these patients, the disease progression is often halted. Once the patient achieves sustained HBsAg seroclearance, routine ALT and HBV-DNA surveillance is no longer needed. However, surveillance for HCC should continue if the patient has cirrhosis, has a first-degree relative with HCC, or has a long duration of infection (>40 years for males, >50 years for females).[11,53]

HBV in Pregnancy, Postpartum, and Newborn

All pregnant patients should be screened for HBV with HBsAg, core total antibody, and surface antibody testing. However, if the pregnant person has a history of appropriately timed triple-panel screening without subsequent exposure risk, only HBsAg screening is needed.[16] If necessary, HBV vaccination is recommended and is safe and efficacious during pregnancy. Although CHB infection typically does not confer teratogenicity, the mother should receive antiviral therapy in the third trimester if serum HBV-DNA is greater than 200,000 IU/mL. TDF is the preferred choice due to its antiviral potency and concerns about resistance with other antiviral agents.[11] There was no difference in rates of prematurity, congenital malformations, or Apgar scores between babies birthed to TDF-treated and untreated women.[99–101] Clinical studies have shown safety in breastfeeding when receiving antiviral treatments.[102,103] Additionally, a newborn from a mother with HBV infection should receive HBIG and HBV vaccine within 12 hours after delivery.[104,105]

Coinfection With HDV

These authors agree with the European Association for the Study of the Liver guidelines and the Hepatitis B Foundation's stance that all patients who are HBsAg positive should be tested for HDV with antibody tests. We disagree with the AASLD guidance that recommends testing only if patients are considered at risk. Risk-based testing has failed for HIV, HCV, and HDV, as well as HBV. The risk factors that would stimulate repeat testing include patients with HIV and or HCV, IVDU, MSM, those with multiple sexually transmitted infections, patients born in high HDV-endemic areas, and those with ongoing risk behaviors.

The initial screening test for HDV is anti-hepatitis Delta virus total antibody; if positive, HDV-RNA quantification should be checked. If there is a diagnosis of HDV infection with polymerase chain reaction testing, treatment should be considered promptly. The preferred treatment for chronic HDV infection is pegINF-alpha for 12–18 months with no difference in efficacy between pegINF-alpha-2a and -2b[11,92]

in patients with no evidence of hepatic decompensation. The treatment should be continued for up to 6 months after HDV-RNA becomes undetectable, which is seen in almost 25% of patients. After 12–18 months, treatment for chronic HDV can be stopped with ALT normalization and decline of HDV-RNA.[92] In some cases, HBV-DNA levels can increase during the treatment. If the HBV-DNA levels increase after stopping INF, we recommend health-care providers continue or start nucleos(t)ide analogs (ETV, TDF, or TAF)[11] in all HBV-DNA-positive patients.

There are many novel treatments being developed for HBV-HDV infection, such as small interfering RNAs (siRNAs), nucleic acid polymers, and the entry-blocking antiviral bulevirtide (BLV). BLV inhibits the binding of HBsAg to sodium taurocholate cotransporting polypeptide. This blocks the entry of both HBV and HDV.[106,107] BLV was conditionally approved for the treatment of HDV by the European Medicines Agency in 2020[108] as a chronic suppressive therapy. Given its novelty, we do not have clear clinical guidance on the drug, optimal dose, duration, the need for combination therapy, accepted virological efficacy marker, or criteria for stopping therapy.[109]

Coinfection With HCV

Every patient with positive HBsAg should be tested for HCV. HBV-associated HCV coinfections in many countries are in the 0.9%–5% range and are often seen in patients with a history of IVDU, HIV, end-stage renal disease receiving hemodialysis, and frequent blood transfusions. Those with coinfection are at increased risk for progression to cirrhosis, HCC, and liver-related deaths. The coinfection may occur simultaneously or as a superinfection (infection of HCV after HBV infection).[110] HCV treatment should be started when HCV-RNA levels are detectable. The disease progression can be monitored by measuring HBV-DNA and HCV-RNA levels.[111] Due to the risk of HBV flares during HCV treatment, HBV-DNA should be monitored every 4–8 weeks during and for 3 months after treatment of HCV.[112] Providers can consider prophylactic therapy with nucleos(t)ide analogs. If liver enzymes, especially ALT, fail to normalize or increase despite declining HCV-RNA, it is recommended to test for HBsAg and HBV-DNA to check for HBV reactivation in anti-HBc-positive patients. If laboratory findings suggest HBV reactivation, HBV antiviral therapy should be initiated.[11] If the patient is found to meet the criteria for both HBV and HCV therapies, HBV antiviral therapy should be started, along with direct antiviral therapy for HCV. There are no known drug-to-drug interactions between HBV and HCV antiviral therapy.[11]

Emerging Therapies

New therapies are being studied that would permit discontinuation of nucleos(t)ide analogs and possible cure. There are several new drugs that are currently under development that target HBV replication cycle or enhance human immune response (Table 5).

HBV Life Cycle

There are many modes by which an antiviral can disrupt the HBV life cycle: blocking HBV entry, blocking HBV protein synthesis, blocking core synthesis, inactivating closed covalent circular DNA (cccDNA), and blocking the release and formation of virions.

a. Blocking entry: BLV is an entry-blocking antiviral that competitively and irreversibly binds to the large HBsAg envelope protein, preventing entry of the HBV into healthy cells.[92,113,114] It has been approved by the European Union for HDV-RNA-positive chronic HDV hepatitis. It has shown to improve HDV-RNA clearance when used synergistically with other antivirals.[115]

b. Blocking HBV protein synthesis (siRNA, locked nucleic acid, antisense oligonucleotide [ASO]): There are many antivirals that are being developed that target HBV synthesis: siRNA, locked nucleic acid, and ASO target specific gene products and cause degradation of mRNA. siRNA limitations include the lack of reduction in cccDNA, unmediated effects on other organs (ie, kidney), and problems with the mode of delivery.[92,93] siRNA is administered parenterally as it is degraded in the gastrointestinal system. A new form in subcutaneous injection is also on the market with fewer side effects. The subcutaneous form targets the liver and requires less frequent dosing, reducing its negative effects on off-target sites and

Table 5. HBV Therapy Targets and Associated Drugs

HBV therapy targets	Associated drugs
HBV life cycle	
Blocking entry	BLV
Blocking protein synthesis (siRNA, LNA, ASO)	ARC520
	RG6004, RO7062931
	GSK3389404
	Bepirovirsen
Inactivating cccDNA (CRISPR-Cas9)	
Blocking core synthesis (CpAMs)	NVR3-778
	JNJ-6379
	Vebicorvir (ABI-H0731)
Blocking release and formation of virions (HBsAg)	REP-2139
Directly inhibit HBsAg with monoclonal antibody	Lenvervimab
	VIR-3434
Vaccines	
Mediate T-cell response	GS-4774
Stimulate innate immune response	
TLR7 agonist	Vestaolimod (GS-9620)
TLR8 agonist	GS-9688
RIG-1 agonist	SB-9200
PD-1 and PD-1 inhibitors	

LNA, locked nucleic acid.

inducing host immune response. Pairing siRNA with N-acetylgalactosamine enhances liver cell uptake via the asialoglycoprotein receptor.[116,117]

An siRNA ARC520 can silence transcription of HBsAg by targeting cccDNA-derived pregenomic RNA (pgRNA) in HBeAg-positive patients.[92,118] In a randomized multicenter study, high doses of ARC520 (2 mg/kg) showed significant reduction of HBsAg levels compared to placebo. HBsAg reduction persisted longer (>85 days) after the last dose in HBeAg-positive patients when compared to HBeAg-negative patients (85 days). This is likely due to the origin of the siRNA derivation. Overall, ARC520 was well tolerated.[92,118]

There are several ASO-based drugs that are approved for treatment of HBV infection. Previous N-acetylgalactosamine ASOs (RG6004, RO7062931 and GSK3389404) have shown to have variable HBsAg decline.[119,120] Bepirovirsen is an unconjugated variant of GSK3389404 and is delivered mainly to liver cells, liver sinusoidal endothelial cells, and Kupffer cells, unlike GSK3389404, which is delivered primarily to hepatocytes. It has shown significant reduction of HBsAg and HBV-DNA in treatment-naive patients with CHB[121] with direct effects on mRNA as well as immune stimulation. There was a dose-dependent HBsAg reduction regardless of baseline HBsAg, with 9% of participants maintaining HBsAg and HBV-DNA loss 24 weeks after the end of treatment.[119]

c. Inactivating cccDNA (CRISPR-Cas9): The only way to decrease the risk of reactivation is to deactivate or eliminate cccDNA. cccDNA clearance is also needed for complete and sterilizing cure of HBV. Within bacteria, short DNA sequences from the virus are inserted into the CRISPR within the bacterial genome. This serves as a memory function to remember previous infections. The mechanism of viral clearance is through triggers of CRISPR-associated nuclease to cause double-stranded breaks at the viral DNA sequence, causing deactivation of the targeted genes. In humans, CRISPR/Cas9 has been studied for hereditary gene editing. In vitro CRISPR/Cas9 experiments have shown rapid reduction of cccDNA and HBV proteins. Combining siRNA with CRISPR/Cas9 has shown improved reduction and even disappearance of cccDNA.[122,123]

There are a few challenges to using CRISPR-Cas9 for patients with CHB. There is a risk of cross-reactivity with human genetic material and a need for a delivery system specific to hepatocytes. Currently, there are no standardized assays for cccDNA, which limits the measurement of end points (changes in the level of cccDNA and their proteins). If even 1 residual cccDNA survives, it could result in persistent HBV infection.[123]

d. Blocking core synthesis (capsid assembly modulators [CpAMs]): The CpAMs target capsid assembly or cause disassembly, creating aberrant capsids or empty capsids.[124] This process inhibits formation and release of new viruses, reduces spread of the virus to uninfected cells, and prevents relaxed-circular DNA transformation to cccDNA.[92,125] Unfortunately, several CpAMs have been discontinued due to liver toxicity (AB-506, AB-836, and ABI-H2173).[126] Currently, there are several core protein allosteric modulators being studied.

NVR3-778 is a class I CpAM that is being studied alone or in combination with pegINF or ETV. Combination therapy with pegINF was found to reduce HBV-DNA levels more so than with CpAM alone but did not reduce HBsAg levels, and viral rebound was observed after treatment cessation.[92,127]

JNJ-6379 is a class II CpAM that is currently being studied in a phase 2 trial[93,128] as a combination therapy. This drug has so far shown dose-dependent antiviral activity, with decreases in HBV-DNA and HBV-RNA. However, this drug is limited in its efficacy since it does not target HBsAg, and subviral particles (SVPs) of HBsAg can still be released into the blood.

One promising class II CpAM was vebicorvir (ABI-H0731); however, development of this drug was recently discontinued in March 2021 as the phase 2b trial did not achieve the desired antiviral effect in patients with CHB infection.[129] Although recent data showed 100% of HBeAg-negative patients with CHB achieved virological suppression of HBV-DNA plus pgRNA <20 IU/mL after 48 weeks of treatment when vebicorvir was combined with ETV, TDF, or TAF, the study did not demonstrate improvements in viral antigen levels.[93,129]

e. Blocking release and formation of virions (HBsAg): Most of the HBsAg that is circulating in the blood is assembled into noninfectious HBV SVPs.[130–132] HBsAg can be targeted by preventing its release from infected hepatocytes. REP-2139 is a nucleic acid polymer that targets the assembly and or secretion of SVPs, reducing circulating HBsAg levels.[133] A phase 2 trial showed that REP-2139 in combination with TDF or pegINF in HBeAg-negative patients resulted in significantly reduced HBsAg levels in 60% of patients and functional cure in 35% of patients at follow-up after 48 weeks without treatment.[133]

f. HBsAg inhibition with monoclonal antibody: HBsAg can also be targeted directly with a recombinant human monoclonal antibody. Lenvervimab can bind to HBsAg directly and neutralize the antigen by forming ICs, thereby preventing entry into hepatocytes. In a prospective trial, there was a correlation between baseline HBsAg and sustained HBsAg loss.[134]

When a monoclonal antibody targeting HBsAg (VIR-3434) and siRNA was combined, a significant reduction in HBsAg levels in all participants and HBsAg <10 IU/mL in most participants were observed. The HBsAg levels were reduced more in combination therapy than either alone, affirming the complimentary effects.[135]

Therapeutic vaccines

The patient's own immune response to HBV infection, if robust enough, can clear HBV infection. The goal of therapeutic vaccines is to stimulate host immune system to restore HBV-specific immune control and suppress HBV activity while ultimately inducing HBsAg loss.

One vaccine known as GS-4774 has shown to mediate T-cell response in 90% of volunteers with very few of the volunteers developing low-level anti-HBsAg. This vaccine uses a recombinant cerevisiae yeast to express surface, core, and X proteins. Unfortunately, it did not produce significant reduction in HBsAg levels.[136] Another vaccine that is being studied is INO-1800, made from multiple HBV proteins that contain the HBsAg and HBV core antigen encoding.[93]

Stimulation of Innate Immune Response

TLR7. Vestaolimod (GS-9620) is an oral toll-like receptor (TLR) 7 agonist currently being studied. TLR7 influences both innate and adaptive immune response as well as antiviral cytokine responses. In mammals, vestaolimod resulted in a reduction of HBV-DNA levels and a loss of HBsAg. In 2 randomized trials, weekly administration led to viral suppression but had no effect on HBsAg levels in treatment-naive patients with CHB.[92]

TLR8. Myeloid cells (myeloid dendritic cells, monocytes, and Kupffer cells) express toll-like receptor (TLR) 8. Activation of TLR8 causes maturation of professional antigen cells, mostly in the gut lymphoid tissue and the liver. In animals, TLR8 activation induced innate immune response without adverse systemic INF-alpha. Currently, the TLR8 agonist, GS-9688, is being studied.[93]

RIG-1. Retinoic acid-inducible protein (RIG-1) is a cytosolic sensor of RNA that activates interferon regulatory factor 3 and nuclear factor kappa light chain enhancer of activated B cells. RIG-1 has been shown to bind HBV pgRNA and interfere with HBV replication while inducing INF and cytokine production. SB-9200, a RIG-1 activator, is a prodrug, a relative of dinucleotide SB900 that resulted in INF-mediated antiviral immune response in infected cells.[137] The development of this drug was stopped after unexpected liver toxicity.

PD-1 and PD-1 inhibitors. Programmed death-1 (PD-1) receptor is the most expressed in HBV-specific T cells in the liver. A recent clinical trial of anti-PD-1 in patients with chronic HDV showed a significant decrease in HBsAg, and 1 patient achieved complete seroconversion. However, more studies are needed to determine the right dosage to avoid triggering autoimmune conditions and immune-mediated HBV flares.[92,138] Oral liver-targeted PD-1 inhibitors are in development as well.

With these new therapies, we are headed toward HBV treatment with combination therapy. There will likely be 3–4 medications and or antivirals used together to achieve synergistic or additive results. We are hopeful that these will lead to increased functional cure of HBV with a finite course of therapy.

Linkage to Care

Access to HBV testing, diagnosis, and treatment are all limited by access to care. Even for those who are aware of their HBV status, access to clinical services may be limited. Unfortunately, the limited number of specialists available in LMICs and the location of specialists only in major cities in high-income countries[2] make it hard to access testing and treatment in both developing and developed countries. Therefore, there needs to be more public and political efforts to improve HBV awareness and access to care if we are to eliminate HBV as a public threat. One of the best success stories is the San Francisco Hep B Free Campaign: it used wide community and political efforts to destigmatize HBV while increasing awareness and access to care.[139]

Conclusion

In conclusion, HBV is a global health issue that disproportionately affects people from LMICs, with the highest prevalence in Africa, Western Pacific, East Asia, and Southeast Asia regions.[1,4] In the United States, HBV is most frequently seen in Asian immigrants.[89,90] The prevalence of HBV is partly due to the limited access to care, laboratory tests, and understanding of HBV transmission in the community. Although there are treatments for HBV, there still is no definitive cure. This review summarized different presentations of HBV infection (HDV, extrahepatic manifestations, and HCC), social barriers to care, current treatments, and promising future therapies that may lead to the cure of CHB. There is strong effort globally to simplify the guidelines and expand testing and treatment to all patients who are HBV-DNA positive because of the benefit on infectivity, quality of life, stigma, HCC, and cirrhosis risk as well as decreased mortality in all stages of HBV infection. We propose a simplified 5-line guideline for tackling CHB infection worldwide.

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