Gastro Hep Advances 2023;2:209–218

ORIGINAL RESEARCH—CLINICAL

It Is Time for a Simplified Approach to Hepatitis B Elimination

Douglas Dieterich,[1] Camilla Graham,[2] Su Wang,[3] Paul Kwo,[4] Young-Suk Lim,[5] Chun-Jen Liu,[6] Kosh Agarwal,[7] and Mark Sulkowski[8]

[1]Division of Liver Disease, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [3]Center for Asian Health, Saint Barnabas Medical Center, RWJ Barnabas Health, Florham Park, New Jersey; [4]Department of Gastroenterology and Hepatology, Stanford Medical Center, Pleasanton, California; [5]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [6]Department of Internal Medicine and Hepatitis Research Center at the National Taiwan University Hospital, Taipei, Taiwan; [7]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, England; and [8]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

BACKGROUND AND AIMS: Hepatitis B virus (HBV) infection continues to threaten millions of lives across the globe, despite universal vaccination efforts. Current guidelines for screening, vaccination, and treatment are complex and have left too many people undiagnosed or improperly managed. Antiviral therapy has been shown to significantly reduce the incidence of liver-related complications, including liver cancer. However, the complexity of existing guidelines can make it difficult to identify which patients to target for treatment, and recommendations that are difficult to implement in real-world settings pose a barrier to eligible patients to receive therapy and contribute to health disparities in HBV care. The goal of this global expert panel was to gain consensus on a streamlined approach to HBV care to facilitate implementation of HBV intervention and treatment, especially in the primary care setting. **METHODS:** A group of 8 liver and infectious disease specialists attended a meeting in January 2021 with the objective of gaining consensus on a streamlined algorithm for HBV care that would encourage implementation of HBV intervention and treatment. **RESULTS:** We have created a comprehensive perspective highlighting screening optimization, diagnostic workup, treatment, and monitoring. This treatment algorithm is designed to provide a streamlined visual pathway for risk stratification and management of patients with HBV that can be adapted in various care settings. **CONCLUSION:** Simplification of guidelines will be critical to achieving health equity to address this public health threat and achieve HBV elimination.

Keywords: Hepatitis B; Simplified treatment; HBV algorithm

See editorial on page 277.

Introduction

Hepatitis B virus (HBV) infection is the leading cause of hepatocellular carcinoma (HCC) and liver-related deaths worldwide, causing 780,000 HBV-related deaths each year.[1,2] More than 2 billion people have been infected with HBV worldwide, of which 296 million people were living with chronic HBV infection in 2019; by comparison, 58 million people were living with hepatitis C virus (HCV) infection in 2019 and 38 million were living with human immunodeficiency virus (HIV) in 2019.[3,4] HBV is an ongoing viral pandemic with an estimated 1.5 million new HBV infections each year despite the existence of highly effective vaccines.[4]

The World Health Organization (WHO) aims to achieve elimination of HBV as a public health threat and has set goals to increase the diagnosis of people infected to 90% and to reduce the number of people dying from HBV infection by 65% by 2030.[4] Yet not a single country is on track to achieve the WHO HBV mortality goal by 2030.[5] Decentralized care and primary care health providers are the key to the expansion of testing, vaccination, and treatment in order to reach hepatitis elimination global targets. Shifts of decentralizing have already begun with hepatitis C globally and have led to increases in screening and linkage to care and treatment.[6] Such task shifting toward primary care and frontline workers is also much needed for HBV, or its elimination as a public health threat will not be achieved.

The current HBV guidelines and recommendations are directed toward specialists (whether gastroenterologists, hepatologists, or infectious disease specialists), and data show that significant gaps in care persist.[7–9] Many people living with HBV are not receiving regular monitoring for their HBV treatment or liver cancer screening. Key challenges include complex and difficult to implement, risk-based recommendations for screening and vaccination. Current treatment guidelines leave many patients uncategorized, who

Abbreviations used in this paper: HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; APRI, AST-to-platelet ratio index; HDV, delta virus; ETV, entecavir; FIB-4, Fibrosis-4; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; NAs, nucleos(t)ide analogues; WHO, World Health Organization.

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2022.10.004

often require experience and judgment for management.[10,11] Recommendations that are difficult to implement or ambiguous recommendations are barriers for treatment. These challenges lead to the exacerbation and perpetuation of health care disparities in populations who often already experience societal inequalities. The simplification of guidelines is critical to health equity, and a few working groups have simplified algorithms for primary care providers.[12,13] However, our expert panel recognizes the need for further simplification and set forth to gain consensus on a streamlined approach for HBV care encompassing screening, vaccination, diagnostic workup, treatment, monitoring, and particularly, driving patient awareness.

Screening for HBV: An Integral Part of Liver Cancer Prevention

Screening is a crucial tool in the global elimination of HBV. The asymptomatic nature of HBV disease drives the need to implement a proactive screening approach with the goal of identifying those who require vaccination, disease progression monitoring, and HCC surveillance, and of treating those at risk for complications.[14–16] Most guidelines recommend general population screening in countries with intermediate to high seroprevalence ($\geq$ 2%) and risk-based screening for all other countries.[14–19] However, this screening approach has failed to achieve significant progress in increasing the diagnosis of HBV. Only 10% of those with chronic HBV across the globe were diagnosed in 2019, a minor progress toward achieving the 2030 WHO goals.[4,20,21]

Several studies have demonstrated that fewer than half of primary care providers are screening at-risk patients.[22–25] Risk-based screening failed to identify sufficient numbers of patients with HCV or HIV infection, and thus the guidelines for these infections have shifted to a universal, one-time test for all adults. A recent cost-effectiveness study demonstrated that universal HBV and related screenings of adults in the United States could save an additional $263,000 for every 100,000 adults screened as compared with current screening practices.[26] Two additional cost-effectiveness studies have demonstrated that general population screening of HBV in adults remained economically feasible even in populations with low seroprevalence (as low as 0.3%–1.5%).[27,28]

Our expert panel recommends universal, one-time testing for HBV for all adults and for all pregnant women with each pregnancy (see Figure). All adults over age 18 should be screened at least once in their lifetime, which will also ensure that those who did not mount an antibody response with infant vaccination or who were never vaccinated are identified and vaccinated.

Trio of HBV Serologic Markers. The following tests are recommended when screening for HBV infection[12–18,29]:

- HBV surface antigen (HBsAg), if reactive or positive, indicates the presence (acute or chronic) of HBV infection (detectable as early as 1–2 weeks after infection)
- Antibodies to HBsAg (anti-HBs), if reactive or positive, indicates immunity against HBV either from vaccination or seroconversion from prior HBV infection
- Antibody to the core antigen of HBV (total anti-HBc), if reactive or positive, indicates exposure to HBV with previous or current infection (detectable around 3 months after infection)

The panel recommends universal vaccination against HBV in all patients who have negative serologies, given that it is impossible to determine potential future risks for exposure to HBV. Recently, the Center for Disease Control's Advisory Committee on Immunization Practices recommended HBV vaccination for all adults aged 19 through 59 years and those aged 60 or older with risk factors.[30] Given the high rate of risk factors, such as diabetes and fatty liver disease in older patients, universal vaccination will be a more simplified approach for implementation. We strongly recommend testing adults prior to vaccination to avoid the risk of false reassurance for patients who already have chronic HBV infection. In patients with previously known anti-HBs reactivity, but current negative anti-HBs test results, revaccination (a single booster) is only recommended for health care workers, sexual partners of persons with HBV, people who use drugs, chronic hemodialysis patients, and immunocompromised people (eg, those with HIV). Point-of-care hepatitis B testing is available and could be a valuable option in expanding accessibility, especially in low-resource settings, and help reduce costs of widespread testing.[31]

Reactive Antibody to the Core Antigen of HBV (Total Anti-HBc)

Patients with reactive anti-HBc antibody have most likely been exposed to HBV and have HBV genetic material within their hepatocytes. When these patients receive immunosuppressive medications, such as certain cancer chemotherapies, high-dose steroids, or biologics for autoimmune diseases, they are at risk for reactivation of HBV and can develop serious complications, such as liver failure.[32,33] Recommendations for the management of these patients are beyond the scope of this perspective, but they may benefit from expert consultation, especially if they will potentially receive chemotherapy or biologic agents. If there is any concern that a repeated, isolated anti-HBc Ab could be a false positive result, it is not harmful to provide HBV vaccination, but these patients should still be considered at risk for reactivation.[34]

Screening Recommendations

- Perform one-time testing of HBV in all adults who were not vaccinated at birth (born before 1991 for the United States), with each pregnancy, and in those at high risk for HBV infection regardless of age
- Use HBsAg, anti-HBs, and total anti-HBc as serologic markers for screening

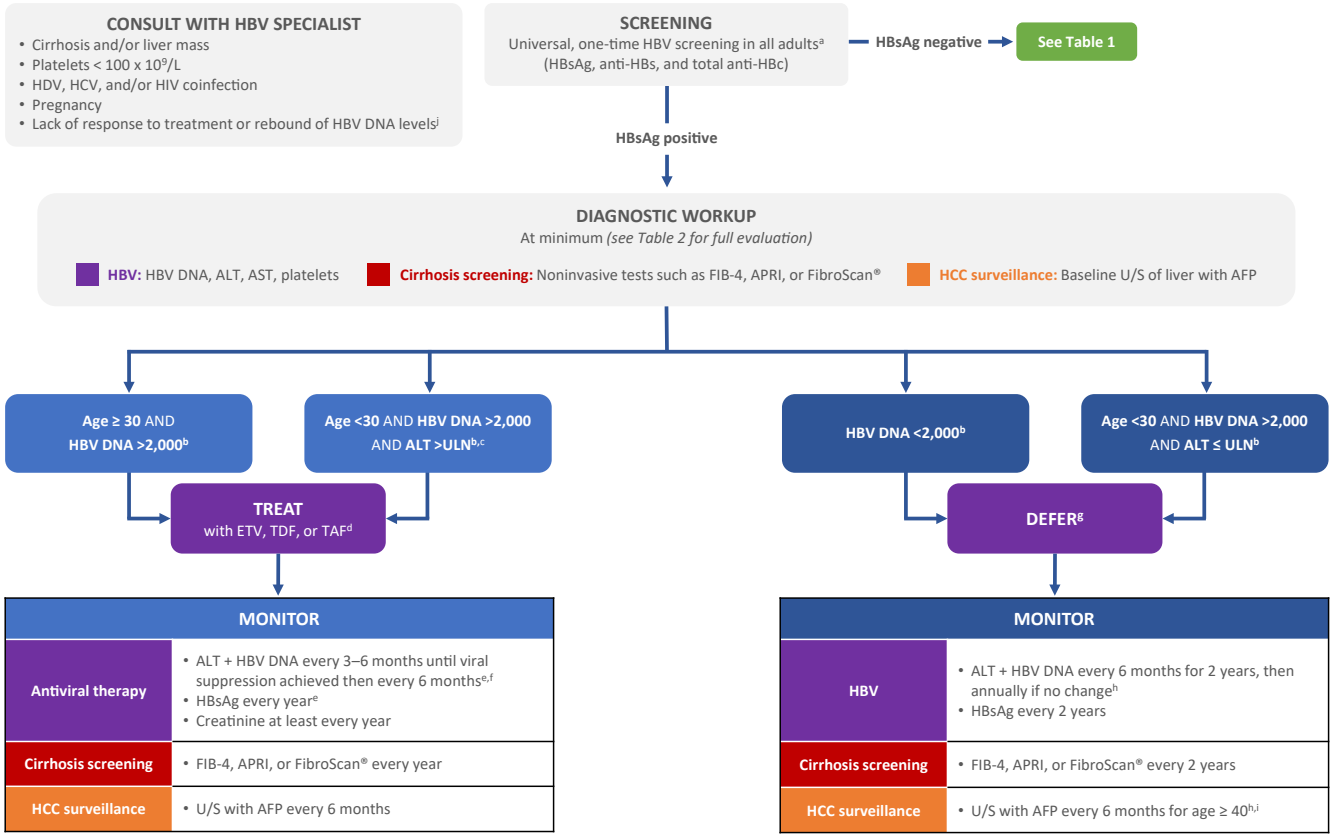

Figure. Simplified treatment algorithm for HBV care. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; APRI, aspartate aminotransferase [AST]-to-platelet ratio index; AST, aspartate aminotransferase; ETV, entecavir, FIB-4, Fibrosis-4; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; U/S, ultrasound; ULN, upper limit of normal. a. In particular, those who did not receive birth HBV vaccination (or unknown status) and all pregnant women with each pregnancy. b. In settings in which HBV DNA testing is not routinely accessible, the WHO guidelines provide guidance for antiviral therapy based on consideration of the patient's age and serum ALT level.[10] c. The upper limit of normal for ALT in healthy adults is 30 U/L for men and 19 U/L for females.[11] d. See Table 3 for more information about dosing and administration. e. Patients often require long-term antiviral treatment; treatment can be stopped if patients meet all criteria: loss of HBsAg, complete $\geq$ 1 additional year of treatment, maintain persistently normal ALT and undetectable HBV DNA, and are willing to undergo monitoring for HBsAg seroreversion for $\geq$ 2 additional years. f. In low-resource settings, monitor ALT every 6 months and HBV DNA annually. g. Use clinical judgment and shared decision-making to determine if patient would benefit from or prefer treatment. h. In low-resource settings, ALT and U/S with AFP can be conducted once a year; if ALT rises above upper limit of normal, initiation of HBV treatment should be strongly considered. i. Age $\geq$ 20 in patients born in Africa. j. Failure of drug to reduce HBV DNA levels by $\geq 1\times \log_{10}$ IU/mL within 3 months of initiating treatment or rebound of $\geq 1\times \log_{10}$ IU/mL in patients with initial response.

- Patients with negative serological markers should be vaccinated
- Patients with anti-HBc positive results should be counseled about the risk of reactivation with immunosuppressive conditions
- Patients with HBsAg should undergo evaluation for treatment

Education for Patients With Chronic HBV Infection

- Inform about HBV tests and how to interpret the results
- Reassure patients that they can live a long and healthy life with ongoing care
- Review ways to minimize risk of transmission and need for further workup to determine if treatment is necessary
- Counsel on protecting the liver through limiting alcohol, avoiding herbals and supplements, and the need for screening/vaccination for hepatitis A
- Connect patients with substance use with harm-reduction services

Diagnostic Workup to Determine Treatment Eligibility

Patients who are found to be HBsAg positive require additional evaluation, education, counseling, and consideration of antiviral therapy (Table 1 and Figure). Patients

Table 1. Interpretation of Serological Testing Results and Recommended Actions

Test results			Action items	Patient education and counseling
+ HBsAg			• Proceed to further work-up (Figure)	• Inform patient they have HBV infection and further evaluation is necessary to determine next steps • Counsel regarding risk of HBV transmission • Household and sexual contacts should be evaluated for HBV and vaccination
− HBsAg	+ Anti-HBs	+ Total anti-HBc	• No further action required[a]	• Inform patient they had previous HBV infection that has resolved • Counsel regarding risk of HBV reactivation
		− Total anti-HBc	• No further action required	• Inform patient they have HBV immunity due to vaccination and no further follow-up is necessary
	− Anti-HBs	+ Total anti-HBc	• No further action required[a]	• Counsel on risk of reactivation
		− Total anti-HBc	• Vaccinate at-risk patients[b]	• Inform patient they are susceptible to HBV infection; initiate HBV vaccination

Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCW, health care worker; HIV, human immunodeficiency virus.
[a]Consult with a specialist if patient is on any immunosuppressive therapy.[35]
[b]Booster vaccine followed by serologic testing 1–2 mo later is only recommended for HCWs, sexual partners or household contacts of persons with HBV, people who use drugs, persons with a history of incarceration, chronic hemodialysis patients, and immunocompromised people (eg, those with HIV). If negative anti-HBs test, repeat the full vaccination series and retest 1–2 mo after the last vaccine dose.[13]

should undergo a physical examination, blood work, and cirrhosis screening to identify whether or not they would benefit from antiviral treatment (Table 2).

A physical examination should be performed to look for stigmata of cirrhosis (eg, jaundice, hepatomegaly, splenomegaly, palmar erythema, ascites, spider hemangiomas, gynecomastia, encephalopathy) and extrahepatic manifestations (eg, vasculitis, glomerulonephritis, fever). Factors that may influence liver health, such as obesity, alcohol consumption, and other comorbid conditions (eg, diabetes, metabolic syndrome, and renal disease) should also be taken into consideration and addressed as part of lifestyle health and well-being maintenance. Laboratory testing should include tests that measure liver function and/or injury, HBV replication and infectivity (ie, quantitative HBV DNA), and the presence and prevention of comorbidities (Table 2). In a setting in which HBV DNA testing is not routinely accessible, the WHO guidelines provide guidance for antiviral therapy based on consideration of the patient's age and serum alanine aminotransferase (ALT) level.[15]

Cirrhosis Screening. Cirrhosis screening is an important step in determining the appropriate HBV management pathway. Liver biopsy remains the gold standard for the assessment of fibrosis stage as well as the diagnosis of liver cirrhosis. However, the panel recommends that all patients undergo liver disease assessment based on readily accessible laboratory tests, such as aspartate aminotransferase (AST), ALT, and platelet count. Specifically, clinicians should calculate the AST-to-platelet ratio index (APRI; https://www.hepatitisc.uw.edu/page/clinical-calculators/apri) and/or the Fibrosis-4 (FIB-4; https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4). For both tests, a higher score indicates a higher likelihood of advanced liver fibrosis. In addition, all patients should also undergo a baseline ultrasound of the liver with alpha-fetoprotein (AFP) to assess for the presence of HCC. While ultrasound of the liver has relatively moderate sensitivity for detecting HCC at an early stage, obtaining an AFP may improve sensitivity of early HCC detection.[1]

Alternatively, other noninvasive modalities, such as vibration controlled elastography, magnetic resonance elastography, and enhanced liver fibrosis testing can be considered, however, these may be costly or not available in most primary care centers.

Diagnostic Workup Recommendations

- Perform physical exam for stigmata of cirrhosis and extrahepatic manifestations

Table 2. Simplified Approach for Hepatitis B Evaluation

Severity of liver disease	Level of viral replication	Presence and prevention of comorbidities
• Stigmata of cirrhosis[a]	• HBV DNA quantitative	• Diabetes, metabolic syndrome, renal disease, other liver diseases
• Extrahepatic manifestations[b]		• Renal function creatinine and eGFR
• CBC with platelets, INR		• Identify coinfections anti-HCV, anti-HIV, anti-HDV
• Liver biochemistries ALT, AST, ALP, total bilirubin, albumin, and creatinine		• Pregnancy test for all women of childbearing age
• Calculate APRI and/or FIB-4		• Current medications (including as needed drugs, over the counter drugs, vitamins, herbals, and supplements)
• Ultrasound of the liver with AFP		• Screen for STDs
• Other noninvasive methods such as elastography, if available		• Risk factors for progressive liver disease (ie, alcohol consumption, obesity)

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase [AST]-to-platelet ratio index; AST, aspartate aminotransferase; CBC, complete blood count; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; INR, international normalized ratio; FIB-4, Fibrosis 4; STDs, sexually transmitted diseases.
[a]Stigmata of cirrhosis include jaundice, hepatomegaly, splenomegaly, palmar erythema, ascites, edema, spider hemangiomas, gynecomastia, asterixis, and encephalopathy.
[b]Extrahepatic manifestations include vasculitis, erythematous skin rash, fever, glomerulonephritis, polyarthritis, and cryoglobulinemia.[36]

- Obtain HBV DNA level, liver tests (ie, complete blood count, AST, ALT, and coinfection status)
- Calculate APRI or FIB-4 to detect advanced fibrosis or cirrhosis
- Screen for HIV, delta virus (HDV), and HCV coinfections
- Screen for HCC by ultrasound and AFP

Education for Patients With HBV

- Reiterate ways to minimize risk of transmission
- Discuss risks of cirrhosis and HCC as related to HBV
- Provide patient education materials and support

Treatment for an Oncogenic Virus

HBV infection is considered oncogenic due to direct and indirect mechanisms that cause an increase in the risk of HCC.[37] Persons with chronic HBV infection (HBsAg positive) are at a 25- to 37-fold increased risk of HCC compared to noninfected people. The approach to treating HBV should be focused on reducing the carcinogenicity of HBV infection through antiviral treatment. Currently there is no cure for HBV, but goals of antiviral therapy are to suppress viral replication and to reduce the risk of mortality, HCC, progression of liver disease, and transmission to others, particularly mother-to-child transmission in pregnancy.[12,14–18,29,38] Despite the strong association of chronic HBV infection with HCC, many patients at risk for HCC go untreated for HBV infection.[8,39] In 2016, only 1.7% of all persons with chronic HBV received treatment worldwide.[39] Data collected from Center for Disease Control's US Chronic Hepatitis Cohort Study (CHeCS) show unacceptably low treatment of HBV patients with cirrhosis (only 56% with cirrhosis were on HBV antiviral therapy).[40] A follow-up of this study showed that treating HBV was associated with a 61% lower HCC risk.[41]

Treatment Eligibility. The panel recognized that existing guidelines are confusing, ambiguous, and leave many patients with HBV infection in a "grey" area where there is no clear guidance on how to manage them. The panel reviewed how these patients are actually being treated in their respective practices and reviewed the literature on clinical outcomes for patients who do not fit into treatment categories specified in other guidelines. The goal was to have clear management strategies for all patients with HBV infection. The shared approach was to assume that all patients with chronic HBV infection need to be treated, and then to exclude those who do not "qualify" for treatment, rather than the currently prevailing, reverse perspective, to reduce the number of patients who are not receiving appropriate treatment. Therefore, we recommend utilizing 3 objective factors: severity of liver disease, age, and HBV DNA level. With this approach, hepatitis B e antigen (HBeAg) or hepatitis B e antibody (anti-HBe) is not required in treatment decision-making, as it does not add further discriminating information, but instead may contribute to confusion around selecting appropriate treatment candidates.

All persons who have stigmata of cirrhosis and/or a fibrosis assessment that suggests cirrhosis (ie, APRI score >

2.0; FIB-4 > 3.25) with any detectable HBV DNA should initiate antiviral treatment with oral nucleos(t)ide analogues (NAs), regardless of age or HBV DNA level. Patients with cirrhosis, compensated or decompensated, or with a mass on ultrasound or other liver imaging, should be referred immediately to a specialist, regardless of HBV DNA level, due to additional complex management of cirrhosis and cancer (see Figure for other instances needing consultation). In addition, patients with HIV, HCV, and/or HDV coinfection should also be referred to an HBV specialist.

When cirrhosis is not present, we recommend using the patient's age and HBV DNA level to determine treatment necessity and monitoring decisions. There is clinical evidence demonstrating that HBV DNA levels of >2000 IU/mL are associated with an increased risk of HCC or progression to cirrhosis, regardless of HBeAg status or ALT level.[42–48] Based on recent clinical data and real-world experience, the expert panel recommends antiviral treatment of all patients > 30 years of age with HBV DNA levels > 2000 IU/mL, regardless of ALT level or HBeAg status, and of all patients < 30 years of age with HBV DNA levels > 2000 IU/mL along with ALT above the upper limit of normal on repeat testing (Figure). Similarly, the WHO guidelines utilize the > 30 years of age, when no cirrhosis is present, as a threshold for treatment.[15]

With expanding treatment to more patients, concern arises for the cost-effectiveness of such interventions. The cost of generic HBV treatments is relatively low.[39] Several studies have demonstrated that treating all patients diagnosed with chronic HBV is cost-effective.[49–53] Lepers et al analyzed different treatment models to determine the most cost-effective strategy in France and found that broadening treatment eligibility to include the treatment of all patients soon after being diagnosed with chronic HBV infection was the most cost-effective strategy.[49] Lim et al demonstrated that using HBV DNA level of >2000 IU/mL alone for noncirrhotic patients and removing ALT and HBeAg treatment eligibility parameters would avoid 43,300 cases of HCC, save 37,000 lives in Korea, and be considered highly cost-effective.[53]

Treatment Options. Entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) are second-generation NAs that inhibit HBV DNA replication and are recommended as first-line, monotherapy agents due to their lower risk of drug resistance, as compared to other NAs.[15,16,29] The surrogate marker of treatment response is sustained HBV DNA suppression at undetectable levels, while the primary endpoint at which therapy could potentially be discontinued is HBsAg loss.[16,29] While HBsAg loss is not considered a "virological" or "sterilizing" cure, since covalently closed circular DNA typically persists within the hepatocytes of persons with resolved HBV infection, this is recognized as a "functional" cure. Interferon therapy is not recommended as a first-line therapy due to the low rate of serological responses, delivery mode (ie, injection), poor tolerability, and the need for close monitoring, despite being a finite treatment with statistically greater potential for HBsAg loss, as compared to NAs.[15,54] The WHO recommends switching to TDF or TAF in patients with suspected antiviral resistance to lamivudine, ETV, adefovir, or telbivudine (defined as failure of drug to reduce HBV DNA levels by $\geq 1\times \log_{10}$ IU/mL within 3 months of initiating treatment or rebound of $\geq 1\times \log_{10}$ IU/mL in patients with initial response).[15] Lack of response or rebound of HBV DNA level in patients with initial response warrants referral to an HBV specialist.

Table 3 provides information on the dosing and key considerations of ETV, TDF, and TAF. TAF is not recommended in patients with decompensated cirrhosis (Child-Turcotte-Pugh CTP [CTP] B or C), although recent data presented at the European Association for the Study of the Liver (EASL) 2020 conference demonstrated high rates of viral suppression and stable safety outcomes in chronic HBV patients with hepatic impairment (CTP $\geq$ 7 and $\leq$ 12) who switched from TDF to TAF.[55,58] Resistance to ETV has been reported in patients with pre-exposure to lamivudine, especially in those who were treatment resistant; as such, ETV is not recommended for persons with prior exposure to lamivudine, and TDF or TAF is recommended for these patients.[59–62] All first-line treatments are generally well tolerated, including among patients with cirrhosis.[14,16]

Treatment Recommendations

- Treat all patients with cirrhosis (with detectable HBV DNA)
- Treat all patients > 30 years of age and HBV DNA > 2000 IU/mL if they have no evidence of cirrhosis
- Refer to specialist if decompensated cirrhosis is suspected or if HIV coinfection exists
- Use ETV, TDF, or TAF as first-line agents for treatment of HBV

Education for Patients With HBV

- Address access to therapy in addition to cost
- All appropriate family members should be screened for HBV
- Be optimistic about future research and treatments for HBV
- Engage patients in treatment decision process to enhance adherence
- Discuss potential side effects, including bone mineral density and renal function with TDF therapy

Optimizing Long-Term Outcomes With Monitoring

In patients on antiviral therapy, ongoing monitoring is necessary to detect HCC and liver disease progression, as well as treatment response, toxicity, and adherence. HBV DNA suppression, the strongest predictor of disease progression and long-term outcomes, is achieved by 24–48

Table 3. First-Line Treatments for Hepatitis B Infection[55–57]

Key considerations	Entecavir (ETV)	Tenofovir disoproxil fumarate (TDF)	Tenofovir alafenamide fumarate (TAF)
Dosage and administration			
No cirrhosis or compensated cirrhosis	0.5 mg tablet once daily	300 mg QD	25 mg QD
Decompensated cirrhosis	1 mg QD	300 mg QD	25 mg QD[58]
Prior treatment failure with lamivudine or telbivudine	Not recommended	300 mg QD	25 mg QD
Use in renal impairment	Dosage adjustment in eGFR < 50 mL/min	Dosage adjustment in eGFR < 50 mL/min	Not recommended in eGFR < 15 mL/min not on hemodialysis
Most common side effects	Headache, fatigue, dizziness, and nausea[a]	Nausea[b]	Headache[c]
Key drug-drug interactions[d]	Drugs that reduce renal function or compete for active tubular secretion N/A	Adefovir, didanosine, protease inhibitors, HCV antivirals	Drugs that strongly affect P-gp and BCRP activity, carbamazepine, phenytoin, rifampin, St. John's wort

BCRP, breast cancer resistance protein; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; QD, every day; mg, milligram; mL, milliliter; min, minute; P-gp, P-glycoprotein.
[a]Most common adverse reactions of any severity in ≥3% of subjects with at least a possible relation to study drug.
[b]Most common adverse reactions in HBV-treated subjects with compensated liver disease.
[c]Most common adverse reactions of any severity in ≥ 10% of subjects.
[d]Health care providers should consult prescribing information, their local pharmacist, and/or online tools (eg, HEP Drug Interactions, http://www.hepdruginteractions.org) to confirm interaction or lack of interaction for specific drugs within a class, as exceptions may exist.

weeks of treatment with TDF, TAF, or ETV in at least half of patients with HBV monoinfection.[15,29] It is also an excellent marker to use for adherence. In patients starting treatment, we recommend scheduling an in-person office visit, or a telemedicine telephone or video consultation, around 3 months after starting therapy to check in with the patient regarding treatment adherence and any side effects, as well as to provide an opportunity for additional patient counseling. The results of a recent nationwide, population-based cohort study demonstrated a more than 30% reduction in risk of death and/or transplantation in patients who were fully adherent (≥ 90%), which was more than 60% of the patients in this study, compared with those with partial adherence (< 90%).[63] While single, daily dosing of antivirals coupled with minimal side effects can positively influence adherence, barriers similar to other long-term treatments for chronic diseases such as asymptomatic disease, forgetfulness, competing priorities, and patient-related factors continue to be an issue. Therefore, the importance of long-term treatment adherence should be regularly discussed with patients and novel approaches to improving adherence are still warranted.

Our expert panel recommends monitoring ALT and HBV DNA every 3–6 months until viral suppression is achieved, and then every 6 months; HBsAg testing should be conducted annually (see Figure). Genotypic resistance is low with first line ETV, TDF, and TAF and, therefore, testing is not recommended unless patients fail to respond to treatment or resistance is suspected. In low-resource settings, however, ALT can be performed every 6 months, and HBV DNA annually. In addition, cirrhosis screening should be conducted at least annually, and ultrasound with AFP for HCC surveillance should be performed every 6 months (see Figure). Renal function should be monitored at least annually in those patients receiving TDF therapy; monitoring may be increased for individuals with underlying kidney disease. Studies of up to 96 weeks have demonstrated TAF had significantly less progression of chronic kidney disease and bone mineral loss, as compared to TDF.[64,65]

Newly diagnosed patients without cirrhosis who do not meet criteria for treatment initiation (see Figure) should have HBV DNA monitored every 6 months for approximately 2 years to ensure patients are truly in a low replicative state (HBV DNA levels consistently remain <2000 IU/mL), and annually thereafter. Obtaining ultrasound with AFP is recommended every 6 months in patients ≥ 40 years of age. Patients born in Africa have a higher risk of early onset of HCC; therefore, we recommend HCC surveillance should begin at age 20 in these individuals.[66] HBsAg and cirrhosis screening should be monitored every 2 years. In low-resource settings without access to HBV DNA testing, ALT and ultrasound with AFP can be conducted once a year;

if ALT rises above ULN, initiation of HBV treatment should be strongly considered.

Stopping Treatment. All patients with cirrhosis require lifelong treatment with NAs as severe liver injury can occur with HBV reactivation.[15] In patients without cirrhosis, treatment should continue until therapeutic response has been achieved, defined as meeting all the following criteria: loss of HBsAg plus completing at least one additional year of treatment, maintaining persistently normal ALTs and undetectable HBV DNA, and willingness to undergo monitoring for HBsAg seroreversion for at least 2 additional years.[15,29] Only a small percentage of patients per year will achieve HBsAg loss; therefore, long-term, continuous treatment is required for most patients until novel drugs become available that can induce functional HBV cure.[67]

Monitoring Recommendations

- Obtain ALT and HBV DNA every 3 months for the first year, then every 6 months thereafter
- Perform ultrasound with AFP every 6 months
- Obtain HBsAg and assess fibrosis (testing consistent with cirrhosis) annually

Education for Patients With HBV

- Connect patient to support services (eg, patient assistance programs, copay cards, peer support)
- Discuss any side effects, challenges with adherence, etc.
- Promote maintenance of health and well-being; counsel patient on healthy lifestyle and assess for metabolic-associated fatty liver disease risk factors

Conclusion

Universal screening and the simplification of HBV care pathways for primary care providers and front-line workers are critical steps to finding the missing millions living with hepatitis B and to ensuring equitable access to life saving care for them. Adapting recommendations so they are realistic and implementable within diverse settings is important. We must also take into account resource limitations and the cost burden to patients in our complicated health care system and create guidelines that are not so rigid as to become a barrier to care. Creating dashboards, registries, and electronic medical record tools are also valuable to support HBV monitoring. Educating patients and soliciting their treatment preferences are also part of ensuring that care has a meaningful impact on their lives. Increasing overall community awareness about hepatitis B, its link to liver cancer, and the interventions we have for testing, vaccination, and cure are importance messages, especially in affected communities. We must apply our scientific advances and medical recommendations with a lens of equity and population health if we are to achieve hepatitis B elimination.

References

1. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. J Hepatol 2020;72:250–261.
2. Jefferies M, Rauff B, Rashid H, et al. Update on global epidemiology of viral hepatitis and preventive strategies. World J Clin Cases 2018;6:589–599.
3. Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of hepatitis B virus infection and impact of vaccination on disease. Clin Liver Dis 2016;20:607–628.
4. World Health Organization. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Web Annex 2. Accountability for the global sector strategies, 2016–2021. www.who.int/hiv/strategy2016-2021/progress-report-2019/en/. Accessed March 29, 2021.
5. CDA Foundation. POLARIS Observatory. cdafound.org/dashboard/polaris/dashboard.html. Accessed March 29, 2021.
6. Oru E, Trickey A, Shirali R, et al. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. Lancet Glob Health 2021;9(4):e431–e445.
7. Sarkar M, Shvachko VA, Ready JB, et al. Characteristics and management of patients with chronic hepatitis B in an integrated care setting. Dig Dis Sci 2014;59(9):2100–2108.
8. Ogawa E, Yeo YH, Dang N, et al. Diagnosis rates of chronic hepatitis B in privately insured patients in the United States. JAMA Netw Open 2020;3:e201844.
9. Harris AM, Osinubi A, Nelson NP, et al. The hepatitis B care cascade using administrative claims data, 2016. Am J Manag Care 2020;26(8):331–338.
10. Evans AA, London WT, Gish RG, et al. Chronic HBV infection outside treatment guidelines: is treatment needed? Antivir Ther 2013;18(2):229–235.
11. Nguyen VH, Le AK, Trinh HN, et al. Poor adherence to guidelines for treatment of chronic hepatitis B virus infection at primary care and referral practices. Clin Gastroenterol Hepatol 2019;17(5):957–967.e7.
12. Han SH, Tran TT. Management of chronic hepatitis B: an overview of practice guidelines for primary care providers. J Am Board Fam Med 2015;28:822–837.
13. Tang AS, Thornton K, HBV Primary Care Workgroup. Hepatitis B management: guidance for the primary care provider. www.hepatitisB.uw.edu/hbv-pcw/guidance. Accessed March 31, 2021.
14. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
15. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization, 2015.
16. Terrault NA, Bzowej NH, Chang KM, et al. American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283.
17. Centers for Disease Control and Prevention. Recommendations for routine testing and follow-up for chronic hepatitis b virus (HBV) infection. www.cdc.gov/hepatitis/hbv/HBV-RoutineTesting-Followup.htm. Accessed March 29, 2021.

18. Public Health Agency of Canada. Primary care management of hepatitis B–quick reference. www.liver.ca/wp-content/uploads/2017/09/HBV-QR-EN-_FINAL_Web.pdf. Accessed March 29, 2021.
19. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, et al. Screening for hepatitis B virus infection in adolescents and adults: US Preventive Services Task Force recommendation statement. JAMA 2020;324:2415–2422.
20. World Health Organization. New hepatitis data highlight need for urgent global response. www.afro.who.int/news/new-hepatitis-data-highlight-need-urgent-global-response. Accessed March 29, 2021.
21. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2019;4:135–184.
22. Mukhtar NA, Kathpalia P, Hilton JF, et al. Provider, patient, and practice factors shape hepatitis B prevention and management by primary care providers. J Clin Gastroenterol 2017;51:626–631.
23. Chu D, Yang JD, Lok AS, et al. Hepatitis B screening and vaccination practices in Asian American primary care. Gut Liver 2013;7:450–457.
24. Loo NM, Kim WR, Larson JJ, et al. Hepatitis B screening in a US academic primary care practice. Arch. Intern Med 2012;172:1517–1519.
25. Hwang JP, Fisch MJ, Zhang H, et al. Low rates of hepatitis B virus screening at the onset of chemotherapy. J Oncol Pract 2012;8:e32–e39.
26. Toy M, Hutton D, Harris AM, et al. Cost-effectiveness of one-time universal screening for chronic hepatitis B infection in adults in the United States. Clin Infect Dis 2022;74:210–217.
27. Eckman MH, Kaiser TE, Sherman KE. The cost-effectiveness of screening for chronic hepatitis B infection in the United States. Clin Infect Dis 2011;52:1294–1306.
28. Nayagam S, Conteh L, Sicuri E, et al. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in the Gambia: an economic modelling analysis. Lancet Glob Health 2016;4:e568–e578.
29. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
30. Melville NA. New hepatitis B vaccination recommendations praised amid low awareness. Medscape. 2021. https://www.medscape.com/viewarticle/965023_print. Accessed February 10, 2022.
31. Xiao Y, Thompson AJ, Howell J. Point-of-care tests for hepatitis B: an overview. Cells 2020;9:2233.
32. Myint A, Tong MJ, Beaven SW. Reactivation of hepatitis B virus: a review of clinical guidelines. Clin Liver Dis (Hoboken) 2020;15(4):162–167.
33. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017;152(6):1297–1309.
34. Hyun CS, Lee S, Ventura WR. The prevalence and significance of isolated hepatitis B core antibody (anti-HBc) in endemic population. BMC Res Notes 2019;12(1):251.
35. Su J, Lim JK. Hepatitis B virus reactivation in the setting of immunosuppressive drug therapy. Gastroenterol Hepatol (N Y) 2019;15(11):585–592.
36. Kappus MR, Sterling RK. Extrahepatic manifestations of acute hepatitis B virus infection. Gastroenterol Hepatol (N Y) 2013;9:123–126.
37. Lupberger J, Hildt E. Hepatitis B virus-induced oncogenesis. World J Gastroenterol 2007;13:74–81.
38. Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology. JSH guidelines for the management of hepatitis B virus infection. Hepatol Res 2014;44(Suppl S1):1–58.
39. Hutin Y, Nasrullah M, Easterbrook P, et al. Access to treatment for hepatitis B virus infection - worldwide, 2016. MMWR Morb Mortal Wkly Rep 2018;67:773–777.
40. Spradling PR, Xing J, Rupp LB, et al. Infrequent clinical assessment of chronic hepatitis B patients in United States general healthcare settings. Clin Infect Dis 2016;63(9):1205–1208.
41. Gordon SC, Lamerato LE, Rupp LB, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. Clin Gastroenterol Hepatol 2014;12(5):885–893.
42. Iloeje UH, Yang HI, Su J, et al. Risk evaluation of viral load elevation and associated liver disease/cancer-in HBV (the REVEAL-HBV) study group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678–686.
43. Kim GA, Han S, Choi GH, et al. Moderate levels of serum hepatitis B virus DNA are associated with the highest risk of hepatocellular carcinoma in chronic hepatitis B patients. Aliment Pharmacol Ther 2020;51:1169–1179.
44. Chan HL, Tse CH, Mo F, et al. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26(2):177–182.
45. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
46. Choi GH, Kim GA, Choi J, et al. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther 2019;50:215–226.
47. Lee HW, Kim SU, Park JY, et al. Prognosis of untreated minimally active chronic hepatitis B patients in comparison with virological responders by antivirals. Clin Transl Gastroenterol 2019;10:e00036.
48. Choi WM, Kim GA, Choi J, et al. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. J Clin Invest 2022;132(10):e154833.
49. Lepers C, Fontaine H, Carrat F, et al. Cost-effectiveness of scaling-up treatment with nucleoside analogue (NA) for chronic HBV infection: towards a simplification of recommendations? (ANRS study). J Hepatol 2020;73:S797–S798.
50. Sanai FM, Alghamdi M, Dugan E, et al. A tool to measure the economic impact of hepatitis B elimination: a case study in Saudi Arabia. J Infect Public Health 2020;13:1715–1723.

51. Kim HL, Kim GA, Park JA, et al. Cost-effectiveness of antiviral treatment in adult patients with immune-tolerant phase chronic hepatitis B. Gut 2020;70:2172–2182.
52. Tordrup D, Hutin Y, Stenberg K, et al. Cost-effectiveness of testing and treatment for hepatitis B virus and hepatitis C virus infections: an analysis by scenarios, regions, and income. Value Health 2020;23:1552–1560.
53. Lim YS, Ahn SH, Shim JJ, et al. Impact of expanding hepatitis B treatment guidelines: a modelling and economic impact analysis. Aliment Pharmacol Ther 2022; 56:519–528.
54. Martin P, Lau DT, Nguyen MH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2015 update. Clin Gastroenterol Hepatol 2015;13:2071–2087.e16.
55. Vemlidy® (tenofovir alafenamide) tablets [prescribing information]. Foster City, CA: Gilead Sciences, Inc, 2021.
56. Viread® (tenofovir disoproxil fumarate) tablets [prescribing information]. Foster City, CA: Gilead Sciences, Inc, 2019.
57. Baraclude® (entecavir) tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb, 2019.
58. Lim YS, Lin CY, Heo J, et al. Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with hepatic impairment: week 48 results from a phase 2 open label study. J Hepatol 2020;73(Suppl 1):S872.
59. Charlton MR, Alam A, Shukla A, et al. An expert review on the use of tenofovir alafenamide for the treatment of chronic hepatitis B virus infection in Asia. J Gastroenterol 2020;55:811–823.
60. Lee JH, Cho Y, Lee DH, et al. Prior exposure to lamivudine increases entecavir resistance risk in chronic hepatitis B Patients without detectable lamivudine resistance. Antimicrob Agents Chemother 2014; 58:1730–1737.
61. Byun KS, Choi J, Kim JH, et al. Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate. Clin Gastroenterol Hepatol 2022;20:427–437.e5.
62. Lim YS, Gwak GY, Choi J, et al. Monotherapy with tenofovir disoproxil fumarate for adefovir-resistant vs. entecavir-resistant chronic hepatitis B: a 5-year clinical trial. J Hepatol 2019;71:35–44.
63. Lee J, Cho S, Kim HJ, et al. High level of medication adherence is required to lower mortality in patients with chronic hepatitis B taking entecavir: a nationwide cohort study. J Viral Hepat 2021;28(2):353–363.
64. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68:672–681.
65. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1:196–206.
66. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1): 182–236.
67. Lee HW, Lee JS, Ahn SH. Hepatitis B virus cure: targets and future therapies. Int J Mol Sci 2020;22(1):213.

Received March 3, 2022. Accepted October 4, 2022.

Correspondence:
Address correspondence to: Douglas Dieterich, MD, Department of Medicine, Division of Liver Disease, Icahn School of Medicine at Mount Sinai, New York, New York. e-mail: Douglas.dieterich@mountsinai.org.

Acknowledgments:
Jamie Kelly, Pharm. D of JK Clinical Solutions provided medical writing support for the manuscript.

Authors' Contributions:
Douglas Dieterich, MD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Camilla Graham, MD, MPH: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Su Wang, MD, MPH: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Paul Kwo, MD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Kosh Agarwal, MD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Chun-Jen Liu, MD, PhD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Mark Sulkowski, MD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission. Young-Suk Lim, MD, PhD: Attended virtual consensus meeting, developed manuscript content and treatment algorithm, and reviewed final manuscript for submission.

Conflicts of Interest:
These authors disclose the following: DD has served in a consulting capacity for Intercept Pharmaceuticals and Gilead. SW has served in an advisory/consulting capacity for Gilead and has received research grants from Gilead Sciences. PK has served in a consulting/advisory capacity to Gilead, Aligos, Abbvie, Mallinckrodt, TwoXR, SUrrozen, HepQuant, Syneos, Durect, and Ambys; he has received institutional grants from Gilead, BMS, Assembly Biosciences and DSMB Janssen. YL has received grants, non-financial support, and other support from Gilead Sciences, apart from the submitted work. KA has served in an advisory/consulting capacity for Aligos, Assembly, Arbutus, Boehringer Ingelheim, Springbank, Roche, Janssen, Immunocore, Gilead, Sobi, Shinoigi, and Sandoz; he has served as a speaker for Gilead and Sobi. CL has served in an advisory capacity for Gilead and has received grants from MSD. MS has served in a consulting/advisory capacity to Antios, Arbutus, Assembly Biosciences, AbbVie, Gilead, Virion, and Viv and has received research grants from AbbVie, Gilead Sciences, Assembly Biosciences, and Janssen Pharmaceuticals. In addition, MS sat on a Data Monitoring Committee for Gilead and AbbVie, as well as an outcome adjudication committee for FH360. The remaining author discloses no conflicts.

Funding:
The meeting and manuscript were funded by Gilead Sciences. Project management and logistical support for the meeting was provided by The Kinetix Group and funded by Gilead Sciences. Writing support was provided by Jamie Kelly, Pharm D of JK Clinical Solutions, LLC and was funded by The Kinetix Group. Gilead Science's role was limited to non-participative attendance of the consensus meeting. Gilead Sciences did not review content of manuscript. Opinions expressed in the manuscript are solely indicative of the providers involved in the consensus meeting.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials will not be made available to other researchers due to the nature of this paper.

Reporting Guidelines:
AGREE.