JAMA | Review

Hepatitis B
A Review

Wen-Juei Jeng, MD, PhD; Terry Cheuk-Fung Yip, PhD; Anna S. Lok, MD

IMPORTANCE Hepatitis B virus (HBV) infection affects an estimated 254 million people worldwide and causes approximately 1.1 million deaths annually. In 2022, there were approximately 1.2 million new HBV infections worldwide and 14 000 in the US.

OBSERVATIONS HBV is a DNA virus transmitted through percutaneous or mucosal exposure to infected blood, semen, or body fluids. Mother-to-child transmission, which is the principal cause of chronic HBV infection globally, occurs in 70% to 90% of infants born to mothers who are hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) positive and in 5% to 20% of those born to HBsAg-positive/HBeAg-negative mothers. However, HBV vaccination and administration of hepatitis B immune globulin within 12 to 24 hours of birth prevent approximately 94% of perinatal infections, and adding antiviral therapy in pregnant women with high HBV DNA reduces transmission to less than 1%. Although universal birth-dose HBV vaccination is the most effective strategy for eliminating HBV infection, global birth-dose HBV vaccine coverage was only 45% in 2024. The risk of developing chronic infection (HBsAg positive for more than 6 months) is 90% if HBV infection occurs during infancy, 30% in children aged 1 to 5 years, and less than or equal to 5% in immunocompetent adolescents and adults. HBV infection is diagnosed by serologic testing: HBsAg indicates ongoing infection, antibody to HBsAg indicates immunity, and antibody to hepatitis B core antigen indicates ongoing or past infection. Serum HBV DNA levels quantify virus-replication activity. Assessment of liver inflammation and fibrosis with alanine aminotransferase (ALT) and noninvasive tests such as Fibrosis-4 index and liver elastography guide treatment decisions. Chronic HBV infection may progress to cirrhosis and hepatocellular carcinoma (HCC); the 5-year cumulative risk of cirrhosis is 8% to 15% in untreated chronic HBV infection, and annual HCC incidence is 3% to 5% among patients with cirrhosis. Antiviral therapies—pegylated interferon alfa and nucleos(t)ide analogues (entecavir or tenofovir)—suppress HBV DNA replication and reduce the risk of HCC by approximately 50%. Antiviral treatment is recommended for all patients with chronic HBV and cirrhosis and for those without cirrhosis who have high HBV DNA with elevated ALT or significant inflammation/fibrosis. Patients at high risk of HCC should undergo surveillance with ultrasonography and alpha-fetoprotein testing every 6 months.

CONCLUSIONS AND RELEVANCE HBV infection causes approximately 1.1 million deaths annually worldwide. Universal HBV vaccination, particularly birth-dose administration, is the most effective strategy to prevent HBV infection. Among patients with HBV infection, antiviral therapy decreases progression to cirrhosis and liver failure and reduces the risk of HCC.

JAMA. doi:10.1001/jama.2026.6070
Published online May 4, 2026.

Multimedia

Supplemental content

CME at jamacmelookup.com

Author Affiliations: Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Main Branch, Taoyuan, Taiwan (Jeng); College of Medicine, Chang Gung University, Taiwan (Jeng); Medical Data Analytics Centre, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong (Yip); Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong (Yip); Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor (Lok).

Corresponding Author: Anna S. Lok, MD, Division of Gastroenterology and Hepatology, University of Michigan, 1500 E Medical Center Dr, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109 (aslok@med.umich.edu).

Hepatitis B virus (HBV) is a DNA virus that can cause acute or chronic liver injury. Acute HBV infection may resolve or progress to chronic infection, defined as persistence of hepatitis B surface antigen (HBsAg) for more than 6 months. The risk of chronic infection is approximately 90% when infection occurs during infancy and decreases to 30% in children who acquire HBV infection between age 1 and 5 years and to 5% or less in immunocompetent adolescents and adults.[1] Chronic HBV infection may progress to cirrhosis and hepatocellular carcinoma (HCC). Currently available antiviral therapies—pegylated interferon alfa and nucleos(t)ide analogues—suppress HBV DNA replication and reduce the risk of progression to cirrhosis and HCC. This review summarizes current evidence on the epidemiology, virology, pathogenesis, clinical presentation, diagnosis, treatment, and prevention of HBV infection, with a focus on evidence applicable to clinical practice (**Box**).

Methods

A comprehensive literature search was conducted using 3 strategies. First, current clinical practice guidelines were obtained from the official websites of the World Health Organization (WHO), the American Association for the Study of Liver Diseases, the Asian Pacific Association for the Study of the Liver, and the European Association for the Study of the Liver. Second, peer-reviewed research articles, systematic reviews, and meta-analyses published in English between January 1, 2019, and January 31, 2026, were retrieved from PubMed (search strategy detailed in the Supplement). Third, landmark articles published before 2019 were identified through manual review of reference lists from selected articles and guidelines. A total of 558 articles were retrieved, of which 112 articles were included: 11 clinical trials, 41 observational studies, 16 narrative reviews, 18 systematic reviews or meta-analyses, 17 guidelines or consensus statements, 1 basic/translational study, and 8 data reports from WHO/Centers for Disease Control and Prevention (CDC) sources.

Discussion

Transmission

HBV is transmitted through percutaneous or mucosal exposure to infected blood or body fluids (such as semen). Routes of transmission include perinatal, sexual, sharing of needles or drug paraphernalia among people who inject drugs, unsafe medical injections in health care settings, unscreened transfusions, and sharing of personal items such as razors or toothbrushes.[2] HBV can survive on environmental surfaces and remain infectious for at least 7 days.[3]

Mother-to-child transmission is the primary cause of chronic HBV infection globally, because infection at birth carries 90% risk of chronic infection. Perinatal transmission predominates in Asian countries, sexual exposure and injection drug use predominate in Western countries, and horizontal transmission in childhood predominates in Africa. In the US, based on the CDC's 2023 Viral Hepatitis Surveillance Report, approximately 47% of acute HBV cases were attributed to sexual transmission and 19% were attributed to injection drug use.[4]

Box. Frequently Asked Questions About Chronic Hepatitis B Virus (HBV)

How can mother-to-child transmission of HBV infection be prevented?

Administration of hepatitis B vaccine and hepatitis B immune globulin within 12 to 24 hours of birth for infants born to hepatitis B surface antigen (HBsAg)–positive mothers prevents approximately 94% of perinatal infections. Maternal antiviral therapy (tenofovir) initiated at 28 to 32 weeks of gestation in pregnant women with high HBV DNA levels (>200 000 IU/mL) further reduces transmission risk to less than 1%.

What patients with chronic HBV should receive antiviral therapy?

Antiviral therapy is indicated for all patients with cirrhosis and detectable HBV DNA. Among patients without cirrhosis, treatment is recommended when alanine aminotransferase (ALT) is persistently elevated (eg, >2 times the upper limit of normal), and HBV DNA levels exceed 20 000 IU/mL in hepatitis B e antigen (HBeAg)–positive or 2000 IU/mL in HBeAg-negative individuals. Treatment is also indicated in patients with significant necroinflammation or fibrosis (≥METAVIR stage F2; range, F0-F4) regardless of HBV DNA and ALT levels.

What patients with chronic HBV should undergo HCC surveillance?

Patients at increased risk for hepatocellular carcinoma (HCC) should undergo surveillance with abdominal ultrasound and alpha-fetoprotein testing every 6 months. Surveillance is recommended for all patients with cirrhosis and for selected individuals without cirrhosis based on age (>40 years for males and >50 years for females), geographic origin, family history of HCC, and viral coinfection. Surveillance should continue after HBsAg seroclearance unless it occurred at a young age (≤40 years for males and ≤50 years for females) and in the absence of cirrhosis or a family history of HCC.

Epidemiology

WHO estimated that approximately 254 million people worldwide were living with HBV infection in 2022, corresponding to a global prevalence of about 3.2%.[5] The annual incidence of HBV infection was approximately 1.2 million, and there were 1.1 million HBV-related deaths.[5]

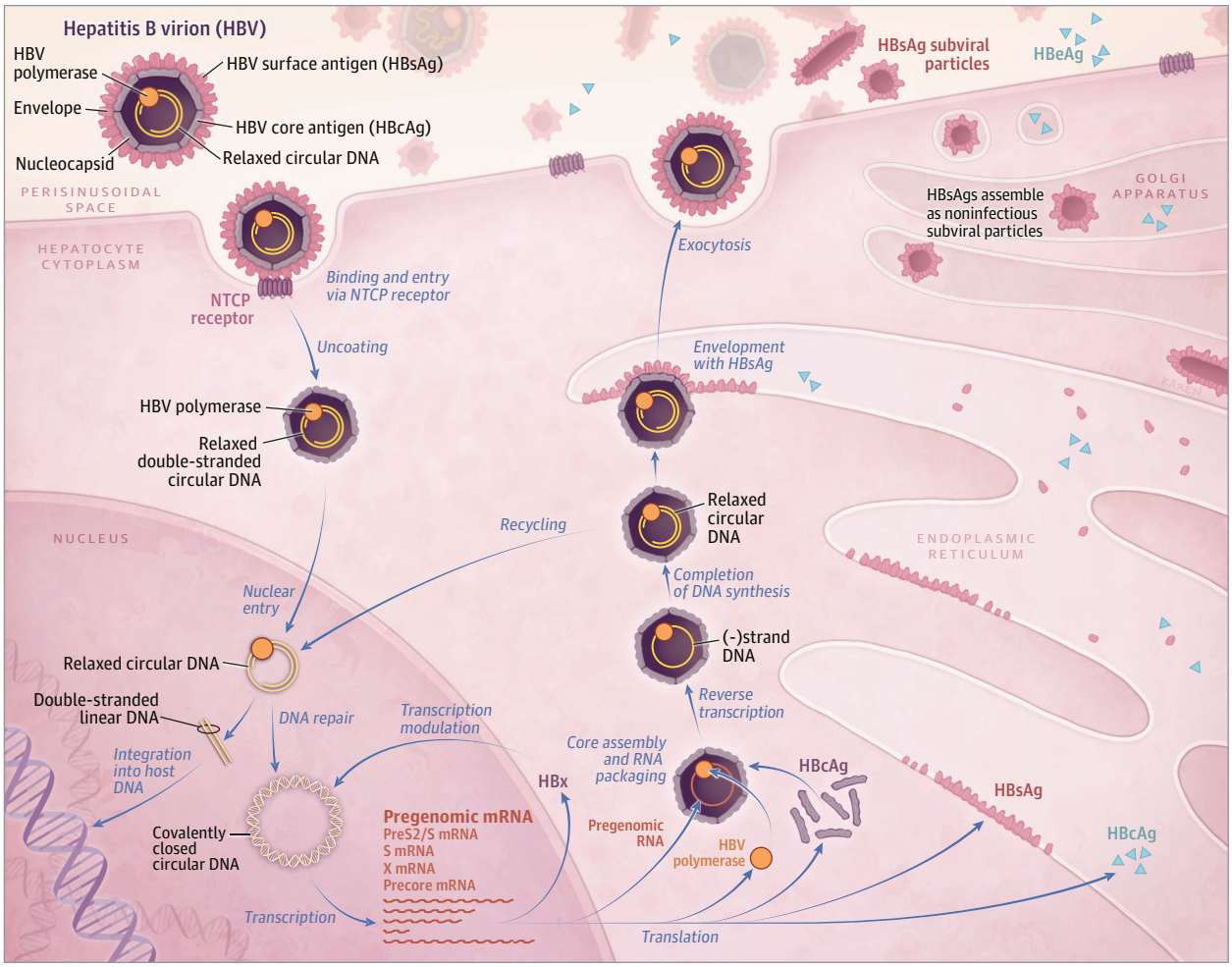
The CDC estimated an annual incidence of HBV infection of 14 000 in 2022 and prevalence of less than 0.3%, affecting 640 000 individuals,[6] but may be up to 2.4 million individuals based on community-based estimates including populations not born in the US.[5]

HBV endemicity is classified as high (HBsAg prevalence ≥8%), intermediate (HBsAg prevalence of 2%-7%), and low (HBsAg prevalence <2%).[7] High-endemic regions include sub-Saharan Africa and parts of East and Southeast Asia; parts of Eastern Europe and the Middle East are considered intermediate-endemic regions; and North America, Western Europe, and Australia are low-endemic regions. Although HBV vaccination has markedly reduced incidence in many Western countries, the prevalence of chronic HBV infection is influenced by immigration from endemic countries.

Virology and Pathogenesis

HBV is a small, enveloped DNA virus of the *Hepadnaviridae* family with a 3.2-kb partially double-stranded circular genome (**Figure 1**).[8,9] There are at least 10 HBV genotypes (A-J), whose distribution vary geographically.[10] Although HBV genotype does not alter treatment indications or antiviral selection, genotype A (and to a lesser

Figure 1. Hepatitis B Virus Life Cycle



HBV comprises an envelope with hepatitis B surface antigen (HBsAg) and a nucleocapsid with hepatitis B core antigen (HBcAG) on its surface and HBV DNA and polymerase protein inside. HBV enters hepatocytes via the sodium taurocholate cotransporting polypeptide (NTCP; a bile acid transporter) receptor. Following entry and uncoating, relaxed circular DNA (rcDNA) is transported to the nucleus and converted into covalently closed circular DNA (cccDNA), which serves as the transcriptional template for all viral RNAs including pregenomic RNA (pgRNA) and mRNAs that encode viral proteins. Newly transcribed pgRNA is packaged together with HBV polymerase into nucleocapsids assembled from HBcAG, where reverse transcription generates partially double-stranded DNA (rcDNA or dslDNA). The mature nucleocapsids are either enveloped and secreted as infectious mature virions (Dane particles) or recycled to replenish the nucleus cccDNA pool. In addition, HBV produces large quantities of noninfectious subviral particles (SVPs) composed of surface proteins. Hepatitis B e antigen (HBeAg) is a secretory protein derived from precore/core protein. HBsAg indicates hepatitis B surface antigen; HBx, hepatitis B virus X protein; and dslDNA, double-stranded linear DNA.

extent genotype B) is associated with higher rates of HBsAg seroclearance after pegylated interferon alfa therapy,[11] whereas genotypes C and F are associated with a higher HCC risk.[12,13]

HBV enters hepatocytes through a bile acid transporter. HBV DNA replication proceeds through reverse transcription of an RNA intermediate, the pregenomic RNA (Figure 1).

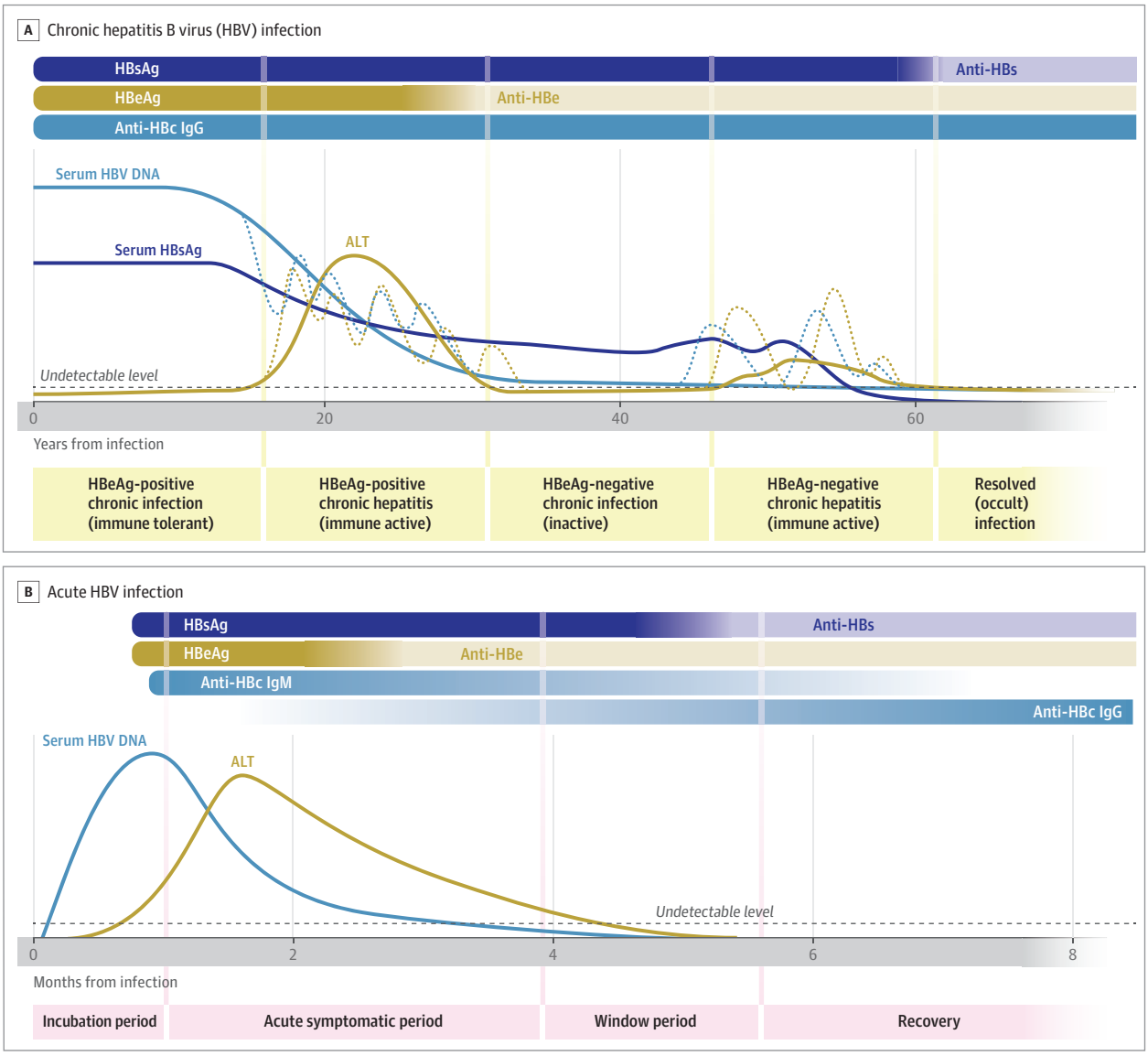
HBV is not a cytopathic virus.[14] Liver injury is largely immune mediated. Approximately 95% of immunocompetent adults with acute HBV infection mount effective immune responses resulting in spontaneous serological recovery.[14,15] Patients with chronic HBV infection have impaired immune responses to HBV.[16] Cycles of immune-mediated liver injury, inflammation, and regeneration lead to fibrosis and cirrhosis and, together with viral integration into the host genome, contribute to hepatocarcinogenesis.[14,17,18]

Natural History of Chronic Hepatitis B

Chronic HBV infection may progress through 5 phases (**Figure 2**A),[8,19] although not all patients progress through each phase, and reversion to an earlier phase can occur. Some patients stay in an indeterminate phase for years.[20] The duration of each phase varies from less than 5 years to more than 50 years.

The first phase (hepatitis B e antigen [HBeAg]–positive chronic infection or immune-tolerant phase) is characterized by the presence of HBeAg and high serum HBV DNA (>7 $\log_{10}$ IU/mL) but normal alanine aminotransferase (ALT) levels. This phase is most common in children and young adults who were infected perinatally. During the second phase (HBeAg-positive chronic hepatitis or immune-active phase), serum HBV DNA levels remain high with elevated or fluctuating ALT levels reflecting immune clearance of infected hepatocytes.

Figure 2. Serological and Virological Markers in Acute and Chronic Hepatitis B Virus (HBV) Infection



A, Chronic HBV infection is defined by the persistence of hepatitis B surface antigen (HBsAg) for more than 6 months. IgG antibody to hepatitis B core antigen (IgG anti-HBc) is also present. Disease evolution for patients with perinatally acquired HBV infection that progress to chronic infection is illustrated across 5 clinical phases, each characterized by distinct patterns of hepatitis B e antigen (HBeAg)/antibody to HBeAg (anti-HBe) status, HBV DNA, alanine aminotransferase (ALT), and HBsAg levels. Phase 1: HBeAg-positive chronic infection (immune tolerant)—very high HBV DNA, normal ALT, and high HBsAg level, minimal hepatic inflammation, and no or minimal fibrosis. Phase 2: HBeAg-positive chronic hepatitis (immune-active phase)—elevated or fluctuating ALT, high but declining HBV DNA and HBsAg levels. Phase 3: HBeAg-negative chronic infection (inactive phase)—low HBV DNA and HBsAg levels, and normal ALT. Phase 4: HBeAg-negative chronic hepatitis—intermittent or persistent ALT elevation with variable increases in HBV DNA, low to moderate HBsAg levels. Phase 5: resolved (occult) infection—HBsAg negative, antibody to HBsAg (anti-HBs) detected after varying interval, and HBV DNA usually not detected in serum but persists in the liver. Dash curves represent episodic fluctuations in HBV DNA and ALT levels characteristic of immune-active phases. B, In acute HBV infection, HBV DNA, HBsAg, and HBeAg appear early, often before ALT elevation or symptom onset. Anti-HBc IgM indicates recent infection and may be the only detectable marker during the window period after HBsAg seroclearance and before the appearance of anti-HBs.

Seroconversion from HBeAg to HBe antibody with a decline of serum HBV DNA to low (usually <2000 IU/mL) or undetectable levels and normalization of ALT levels indicates transition to the third HBeAg-negative chronic infection or inactive phase. During the fourth HBeAg-negative chronic hepatitis or immune-active phase, patients are HBeAg negative with HBV DNA levels typically greater than 2000 IU/mL (usually 3-5 $\log_{10}$ IU/mL or higher) and elevated or fluctuating ALT levels.

The fifth phase (resolved or occult HBV infection) occurs after HBsAg seroclearance, which occurs at a rate of approximately 1% per year, with a higher annual rate of 1.7% after age 50 to 60 years.[21]

Clinical Presentation

Acute Infection

After exposure to HBV, the mean incubation period is about 90 days, and 50% to 70% of acute infections are asymptomatic.[22] Among patients who are symptomatic, common symptoms include fatigue, fever, and anorexia. Approximately 95% of immunocompetent adults with acute HBV infection recover spontaneously, but 0.1% to 0.5% develop acute liver failure with encephalopathy, jaundice, and coagulopathy within days to weeks of initial infection (Figure 2B).[23] Risk factors for acute liver failure include older age, underlying liver disease, and coinfection with other hepatitis viruses such as hepatitis D and hepatitis C.

Chronic HBV Infection

Many patients with chronic HBV infection remain asymptomatic for decades and have normal physical examination findings. Others may experience fatigue and right upper-abdominal discomfort and have physical examination findings of chronic liver disease (eg, spider angiomata) or signs of portal hypertension (eg, ascites, splenomegaly). Among patients with chronic HBV infection, the only biochemical abnormality may be mild to moderately elevated ALT levels until cirrhosis is advanced, at which point patients may develop impaired hepatic synthetic function (eg, hypoalbuminemia, hyperbilirubinemia, prolonged prothrombin time).

Exacerbations of HBV Infection

Exacerbations of HBV infection with a sudden increase in HBV DNA replication may occur spontaneously or be precipitated by immunosuppressive therapy, hepatotoxic drugs, coinfection with other hepatitis viruses, or discontinuation of antiviral therapy with anti-HBV activity.[24,25] During severe exacerbations, ALT levels can exceed 1000 U/L and may be misdiagnosed as acute hepatitis.[26] Severe acute exacerbations may occur in patients with or without cirrhosis and can precipitate hepatic decompensation. Liver function may improve if the HBV exacerbation resolves promptly.[27]

Extrahepatic Manifestations

Approximately 1% to 3% of patients with chronic HBV infection develop immune complex–mediated extrahepatic manifestations (eg, membranous glomerulonephritis). These complications may improve after effective antiviral therapy.[28]

Screening

Early diagnosis of HBV infection is important because most individuals with chronic HBV infection are asymptomatic until the development of advanced liver disease. The CDC recommends universal screening for HBV infection and immunity with HBsAg, antibody to HBsAg, and antibody to hepatitis B core antigen (HBcAg) (total) for all adults 18 years or older at least once in their lifetime and during each pregnancy and periodic screening of persons with ongoing risks for exposure (eg, people who inject drugs or have unprotected sex with multiple partners).[22]

Diagnosis

Diagnosis of HBV infection depends on serological and virological markers (**Figure 3**). HBsAg is the serological hallmark of infection; persistence of HBsAg for more than 6 months defines chronic infection and HBsAg seroclearance followed by antibody to HBsAg seroconversion indicates recovery and immunity.

In acute infection, HBV DNA, HBsAg, and HBeAg appear early, often preceding ALT elevation or symptoms (Figure 2B). IgM antibody to HBcAg indicates recent infection and may be the sole marker during the window period when HBsAg has disappeared but antibody to HBsAg is not yet present.[29] IgM antibody to HBcAg may occasionally be detected during severe flares of chronic HBV infection, although typically at lower titers than in acute infection.

In chronic infection, HBsAg persists with IgG antibody to HBcAg (Figure 2A). HBeAg is present along with high levels of HBV DNA during the early phase of chronic infection, which may last from a few months to several decades. After HBeAg to antibody to HBeAg seroconversion, HBV DNA levels decrease but remain detectable.[30]

Isolated antibody to HBcAg positivity (HBsAg negative, antibody to HBsAg negative, antibody to HBcAg positive) may represent recovery from past infection with waning antibody to HBsAg, occult HBV infection (past infection with HBsAg seroclearance but not antibody to HBsAg seroconversion), or a false-positive test result. Individuals with isolated antibody to HBcAg positivity may require additional testing, eg, HBV DNA or a trial of HBV vaccination to assess for an immune memory (anamnestic) response.

Management

Patients with chronic HBV infection should be counseled on measures to prevent transmission and advised to limit or avoid alcohol consumption, maintain a healthy diet, and exercise regularly. Clinicians should recommend HBV vaccination for susceptible household and sexual contacts.

Initial evaluation of chronic HBV infection should assess HBV replication (HBV DNA) and activity and stage of liver disease to guide antiviral therapy and determine the need for HCC surveillance (**Figure 4**). Patients should be tested for coinfections including HIV and hepatitis C virus (HCV) and hepatitis D virus (HDV). Immunity to hepatitis A virus (HAV) should also be assessed (anti-HAV IgG or total anti-HAV) and nonimmune individuals should receive hepatitis A vaccination.

All patients with chronic HBV infection should be monitored. For those not receiving antiviral therapy, ALT and HBV DNA should be evaluated every 3 to 6 months during the first year and every 6 to 12 months thereafter.

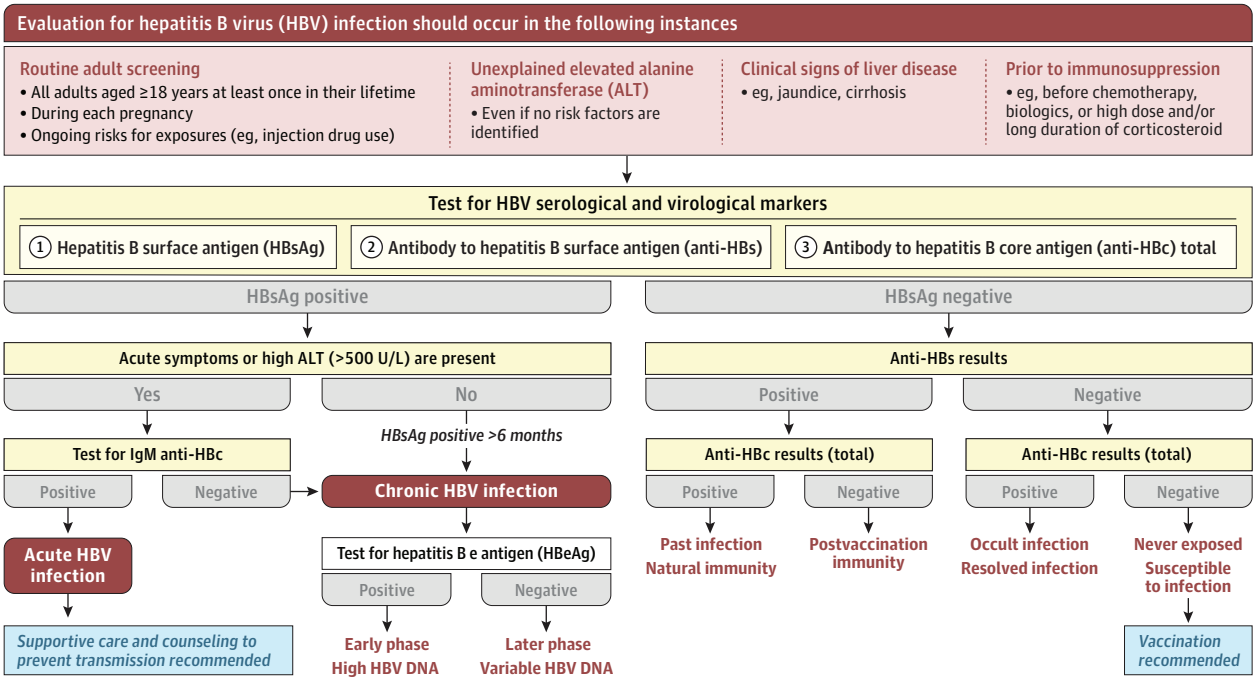
Fibrosis Assessment

All patients with chronic HBV infection should undergo fibrosis assessment during the initial evaluation because fibrosis stage affects treatment decisions and HCC risk stratification. Noninvasive blood tests such as aspartate aminotransferase (AST) to platelet ratio index (APRI) and Fibrosis-4 index (FIB-4: age, AST, ALT, and platelet count) are commonly used for initial assessment of fibrosis risk. Image-based methods (vibration-controlled transient elastography, ultrasonography shear wave elastography, or magnetic resonance elastography) provide more precise fibrosis staging.[31-34] Noninvasive tests are more commonly used than liver biopsy and can distinguish minimal from significant fibrosis or cirrhosis, with reported sensitivity and specificity of approximately 79% and 78%, respectively, for detection of significant fibrosis (≥F2; range, F0 to F4) compared with liver biopsy.[35]

Surveillance for HCC

Surveillance for HCC with abdominal ultrasonography and alpha-fetoprotein testing every 6 months is recommended for patients with HBV infection who are considered at increased risk of developing

Figure 3. Chronic Hepatitis B Management



Interpretation of hepatitis B virus serological and virological markers. Patients with elevated liver enzymes and those with symptoms or signs of liver diseases should be tested for HBV infection. Screening for HBV infection is recommended for all patients prior to the start of immunosuppressive therapies. The US Centers for Disease Control and Prevention recommends screening for HBV for all adults regardless of risk factors. Screening of HBV infection and immunity involves testing for HBsAg, anti-HBs, and total anti-HBc. Acute HBV infection is indicated by presence of HBsAg and IgM anti-HBc. Chronic HBV infection is indicated by presence of HBsAg for more than 6 months and concomitant presence of total anti-HBc. During the early phase of chronic HBV infection, HBeAg is also present, and HBV DNA level is high. During the later phase of chronic HBV infection, HBeAg is absent and HBV DNA level variable (low or moderate). Anti-HBs indicates immunity from past infection when anti-HBc is also present and from past vaccination when anti-HBc is absent. Isolated presence of anti-HBc without HBsAg or anti-HBs is most commonly seen in occult HBV infection. Absence of HBsAg, anti-HBs, and anti-HBc indicates no prior exposure to HBV and vaccination is recommended.

HCC (eg, all patients with cirrhosis and select individuals without cirrhosis based on age, geographic origin, family history of HCC, viral coinfection, and validated risk scores depending on treatment status) (Figure 4). Risk prediction models such as the PAGE-B score (platelet count, age, and sex) can be used to estimate 5-year HCC risk in patients receiving antiviral therapy.[36-39]

Treatment

Acute HBV Infection

Because 95% of immunocompetent adults recover spontaneously,[40] acute HBV infection is typically managed with supportive care and counseling to prevent transmission.

Chronic HBV Infection

Goals of antiviral treatment for chronic HBV infection are to prevent cirrhosis, hepatic decompensation, and HCC. Currently approved therapies include pegylated interferon alfa and nucleos(t)ide analogues (entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide) (**Table 1**). New treatments aimed at functional cure, defined as undetectable HBsAg and serum HBV DNA at least 24 weeks after a finite course of treatment, are in clinical trials.[46] They include antivirals targeting different steps in the HBV lifecycle (eg, entry inhibitors, capsid assembly modulators, small interfering RNAs and antisense oligonucleotides) and immunomodulatory therapies (eg, therapeutic vaccines, antibody to HBsAg monoclonal antibodies, immune checkpoint inhibitors, and toll-like receptor agonists). Of these new therapies, only 1, an antisense oligonucleotide, has a completed phase 3 trial.

Indications

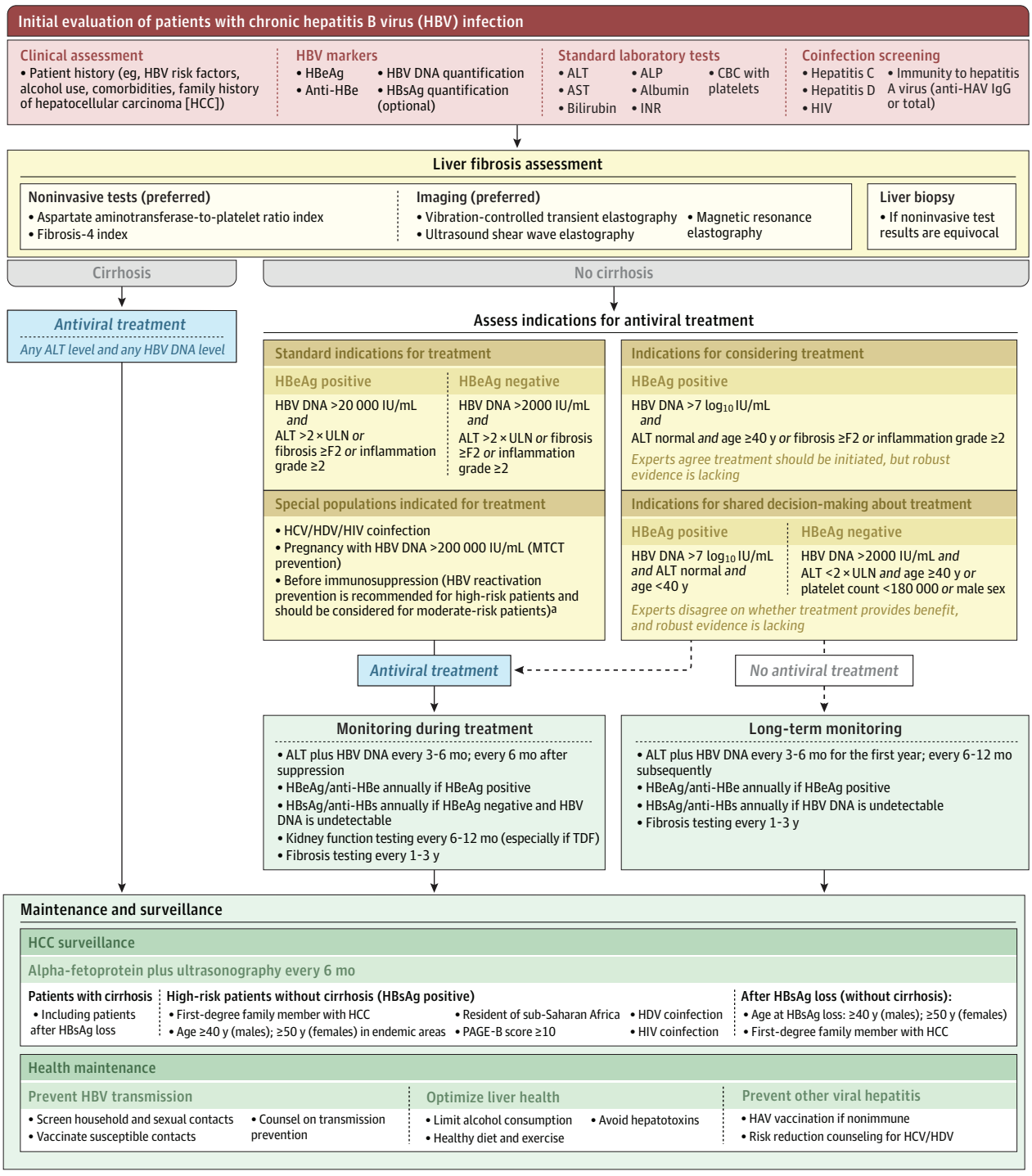
All guidelines recommend that patients (adults and children) with cirrhosis and detectable HBV DNA should receive antiviral treatment regardless of ALT level or HBV DNA levels.[41,42,44,45] For patients without cirrhosis, guidelines recommend antiviral treatment for those with elevated levels of HBV DNA and ALT or F2 or higher fibrosis (Table 1 and Figure 4).

Treatment may be considered for patients in the immune-tolerant phase (HBeAg-positive with high HBV DNA level but normal ALT level) who are 40 years or older or who have evidence of significant liver inflammation or fibrosis. Other factors that influence treatment decisions include male sex and family history of HCC. Some guidelines such as WHO and the Chinese Medical Association propose broader indications for treatment of HBV infection[42-45,47] (Table 1 shows a summary of treatment indications).

Nucleos(t)ide Analogues

Nucleos(t)ide analogues inhibit HBV DNA replication and have potent antiviral activity. Currently used nucleos(t)ide analogues—entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)—are administered orally daily. There has been no

Figure 4. Evaluation and Management of Chronic Hepatitis B Infection



Clinical decision algorithm for the evaluation and management of chronic hepatitis B virus (HBV) infection, including initial evaluation, fibrosis assessment, treatment indications, long-term monitoring, hepatocellular carcinoma surveillance, and health maintenance. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood cell count; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; INR, international normalized ratio; MTCT, mother-to-child transmission; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

[a]Refer to eTable 1 in Supplement 1 for immunosuppressive therapies associated with high, moderate, or low risk of HBV reactivation.

confirmed resistance to tenofovir after 10 years of monotherapy.[48,49] In patients with HBeAg-positive chronic hepatitis, a 1-year course of entecavir, TDF, or TAF achieved undetectable HBV DNA in 64% to 76% of patients, normalization of ALT in 68% to 72%, and histological

Table 1. Treatment Indications for Chronic Hepatitis B Based on International Guidelines[a]

	APASL 2016[41]	AASLD 2018[42]	AASLD 2025[43,b]	EASL 2025[44]	WHO 2024[45]
Cirrhosis	Recommend treatment of patients with cirrhosis and detectable HBV DNA regardless of ALT level	Recommend treatment of patients with cirrhosis and detectable HBV DNA regardless of ALT level	Recommend treatment of patients with cirrhosis and detectable HBV DNA regardless of ALT level	Recommend treatment of patients with cirrhosis and detectable HBV DNA regardless of ALT level	Recommend treatment of patients with cirrhosis and detectable HBV DNA regardless of ALT level
No cirrhosis and HBeAg-positive	HBV DNA >20 000 IU/mL and ALT >2 × ULN or fibrosis ≥F2 or inflammation ≥A2 regardless of ALT; ULN: 40 U/L (sex-neutral)	HBV DNA >20 000 IU/mL and ALT >2 × ULN or significant fibrosis (≥F2) or inflammation (≥A2) regardless of ALT ULN: male, 35 U/L; female, 25 U/L	Conditional recommendations for select scenarios: do not replace 2018 core criteria; immune-tolerant phase (HBeAg-positive, HBV DNA >7 $\log_{10}$ IU/mL, and normal ALT): consider treatment if age ≥40 y, fibrosis ≥F2, or inflammation ≥ grade 2	HBV DNA >2000 IU/mL (regardless of HBeAg status) and ALT >ULN or fibrosis ≥F2 regardless of ALT; ULN: 40 U/L (sex-neutral)	Significant fibrosis (≥F2: APRI >0.5 or TE >7 kPa), regardless of ALT or HBV DNA or HBV DNA ≥2000 IU/mL and ALT >ULN on ≥2 occasions within 6-12 mo or HBV DNA unavailable and ALT persistently >ULN or fibrosis ≥F2; ULN: male, 30 U/L; female, 19 U/L
No cirrhosis and HBeAg-negative	HBV DNA >2000 IU/mL and ALT >2 × ULN or fibrosis ≥F2 or inflammation ≥A2 regardless of ALT; ULN: 40 U/L (sex-neutral)	HBV DNA >2000 IU/mL and ALT >2 × ULN or significant fibrosis (≥F2) or inflammation (≥A2) regardless of ALT; ULN: male, 35 U/L; female, 25 U/L	Conditional recommendations for select scenarios: do not replace 2018 core criteria HBeAg-negative indeterminate phase (HBeAg-negative, HBV DNA >2000 IU/mL, and ALT 1-2 × ULN); consider treatment if age >40 y, male sex, low platelets (<180 × 10^3/μL), or fibrosis ≥F3	HBV DNA >2000 IU/mL (regardless of HBeAg status) and ALT >ULN or fibrosis ≥F2 regardless of ALT; ULN: 40 U/L (sex-neutral)	Significant fibrosis (≥F2: APRI >0.5, or TE >7 kPa), regardless of ALT or HBV DNA or HBV DNA ≥2000 IU/mL and ALT >ULN on ≥2 occasions within 6-12 mo or HBV DNA unavailable and ALT persistently >ULN or fibrosis ≥F2; ULN: male, 30 U/L; female, 19 U/L
Comments	Similar to AASLD 2018	Standard guideline, based on strong evidence	Based on very low-certainty evidence; shared decision-making recommended	Single HBV DNA threshold regardless of HBeAg status simplifies criteria; lower ALT threshold	Designed for resource-limited settings where HBV DNA testing may not be routinely available; more liberal criteria, regardless of HBeAg status, permit treatment initiation when HBV DNA testing is unavailable

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; APRI, aspartate aminotransferase-to-platelet ratio index; EASL, European Association for the Study of the Liver; F, METAVIR fibrosis stage (0-4); HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TE, transient elastography; ULN, upper limit of normal; WHO, World Health Organization.

[a] Guidelines are listed in order from most restrictive to broadest treatment indications, reflecting the spectrum from traditional evidence-based criteria (APASL, AASLD) to simplified or expanded approaches designed for broader implementation (EASL, WHO).

[b] AASLD 2025 includes conditional recommendations for selected clinical scenarios and does not replace the core 2018 treatment-initiation criteria.

improvement in 49% to 74%, but HBeAg seroconversion in only 10% to 21% and HBsAg seroclearance in 1% to 3% (**Table 2**).[50-52] After 7 to 10 years of treatment with nucleos(t)ide analogues, cumulative HBeAg seroconversion increased to 27% to 38%, whereas HBsAg loss remained at 3% to 5%.[8,49,53,54] For patients with HBeAg-negative chronic hepatitis, 1 year of entecavir, TDF, or TAF yielded undetectable HBV DNA in 90% to 94% of patients, normalization of ALT in 76% to 83%, and histological improvement in 60% to 72%, but HBsAg seroclearance in less than 1%.[51,55,56] Extending treatment to 7 to 10 years maintained HBV DNA suppression in 80% to 100%, yet cumulative HBsAg seroclearance remained 1% to 4%.[49,53,54]

Discontinuation of Nucleos(t)ide Analogue Treatment

If nucleos(t)ide analogues are stopped prior to HBsAg seroclearance, viral relapses are universal. In some patients, HBV DNA levels increase rapidly, accompanied by elevated ALT and hepatic decompensation.[57,58] Society guidelines recommend lifelong antiviral therapy for patients with cirrhosis to avoid the risk of hepatitis flares.[41,42,44]

For HBeAg-positive patients without cirrhosis, nucleos(t)ide analogue treatment may be discontinued in those who have HBeAg seroconversion and have completed consolidation therapy (continuation of nucleos[t]ide analogue for ≥12 months after HBeAg seroconversion to antibody to HBeAg).[41,42,44] After stopping therapy, close monitoring is required, especially during the first year. Repeat treatment should be considered in patients with virologic relapse or HBeAg reappearance, especially when accompanied by ALT elevation, and should be initiated promptly in those with severe flares or hepatic decompensation during monitoring.

For HBeAg-negative patients without cirrhosis, the Asian Pacific Association for the Study of the Liver and European Association for the Study of the Liver guidelines suggest nucleos(t)ide analogue may be discontinued after at least 2 to 3 years of undetectable serum HBV DNA in patients who agree to close monitoring after stopping therapy.[41,44] Stopping nucleos(t)ide analogue prior to HBsAg loss is associated with virological relapse (HBV DNA >2000 IU/mL) in 65% to 80% of patients, hepatitis flares in 15% to 30%, and hepatic decompensation in less than 1% to 1.8% (predominantly in patients with cirrhosis). HBsAg seroclearance rate has been reported in 4% to 39% of patients at 4 to 5 years after nucleos(t)ide analogue withdrawal, which is substantially higher compared with continued nucleos(t)ide analogue therapy (<1% per year).[59-62] Low HBsAg level (<100 IU/mL) at the time of nucleos(t)ide analogue discontinuation is the strongest predictor of HBsAg seroclearance post–nucleos(t)ide analogue withdrawal.[63] White patients have 8.3-fold higher odds of HBsAg seroclearance than Asian patients, even after stratifying for HBsAg level at the time of nucleos(t)ide analogue discontinuation, likely reflecting differences in age at infection and immune restoration.[63,64]

The 2025 American Association for the Study of Liver Diseases guidelines recommend not stopping treatment prior to HBsAg seroclearance and shared decision-making for patients who contemplate doing so.[43]

Table 2. Dosing, Key Efficacy Outcomes, and Adverse Effects of Approved Antiviral Therapies for Chronic Hepatitis B

Drug information	Entecavir	Tenofovir disoproxil fumarate	Tenofovir alafenamide	Peginterferon alfa-2a
First-line therapy	Yes	Yes	Yes	Select patients only[a]
Key considerations	Preferred when cost is a barrier; caution in patients with prior lamivudine treatment or inadequately treated HIV coinfection (risk of resistance) and in pregnancy	Preferred with pregnancy, HIV coinfection, but cost is a barrier; caution in patients with or at risk of impaired kidney function, reduced bone mineral density, or high fracture risk	Preferred with pregnancy, HIV coinfection, tenofovir needed in patients with or at risk of impaired kidney function, reduced bone mineral density or high fracture risk; caution: limited data in decompensated cirrhosis and higher cost	Preferred when age <40 y, high ALT, low HBV DNA, genotype A or B, and preference for finite therapy; avoid if patient has decompensated cirrhosis, pregnancy, autoimmune disease, or significant psychiatric illness
Dose and treatment duration				
Standard dose	0.5 mg Orally daily[b]	300 mg Orally daily	25 mg Orally daily	180 µg Subcutaneously weekly
Treatment duration	Long-term in most patients; finite therapy possible in select patients with no cirrhosis under close monitoring[c]	Long-term in most patients; finite therapy possible in select patients with no cirrhosis under close monitoring[c]	Long-term in most patients; finite therapy possible in select patients with no cirrhosis under close monitoring[c]	48 Weeks (finite)
Dose adjustment for kidney impairment	Required if CrCl <50 mL/min[d]	Required if CrCl <50 mL/min[e]	No adjustment needed if CrCl >15 mL/min[e]	135 µg Subcutaneously weekly if receiving hemodialysis
Efficacy at week 48, %[f]				
HBeAg-positive patients				
HBV DNA suppression[g]	67	76	64	25
HBeAg seroconversion	21	21	10	27
HBsAg seroclearance	2	3	1	3
HBeAg-negative patients				
HBV DNA suppression[g]	90	93	94	63
HBsAg seroclearance	<1	0	0	4
Long-term outcomes				
HBsAg loss, %	4-5 (10 y Receiving treatment)	3-5 (10 y Receiving treatment)	3% (8 y Receiving treatment)	8%-11% (3 y Not receiving treatment)
HBV DNA suppression, %[g]	97 (10 y Receiving treatment)	98 (10 y Receiving treatment)	95 (8 y Receiving treatment)	25% (3 y Not receiving treatment)[h]
Adverse effects	Rare lactic acidosis (primarily in decompensated cirrhosis)	Kidney impairment and tubular dysfunction, reduced bone mineral density; monitor serum creatinine, phosphate, and bone density in at-risk patients	Significantly less kidney and bone toxicity than TDF	Common: flu-like symptoms, fatigue, injection-site reactions; notable: cytopenia (thrombocytopenia, neutropenia), depression, thyroid dysfunction (hyper- and hypothyroidism)

Abbreviations: ALT, alanine aminotransferase; CrCl, creatinine clearance; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a] Consider peginterferon only in motivated patients without contraindications who prefer finite therapy.

[b] Use 1.0 mg daily for lamivudine-resistant HBV; TDF or TAF preferred.

[c] Stopping rules apply to select patients with no cirrhosis. HBeAg-positive patients: after HBeAg to antibody to HBeAg seroconversion plus ≥1 year of undetectable HBV DNA and HBeAg. HBeAg-negative patients: after ≥3 years of undetectable HBV DNA (per some guidelines). Patients with cirrhosis: indefinite therapy unless HBsAg seroclearance.

[d] Dose adjustment required; consult prescribing information.

[e] TAF does not require dose adjustment if CrCl >15 mL/min; consult prescribing information.

[f] Week-48 efficacy data reflect registration phase 3 trial end points. For peginterferon, efficacy is assessed at the end of a finite 48-week course; for nucleos(t)ide analogues, week-48 data represent efficacy while receiving treatment, and therapy is typically continued long term or indefinitely.

[g] Defined as HBV DNA less than 20 to 60 IU/mL, depending on assay.

[h] Percentage maintaining viral suppression: not receiving peginterferon and receiving continuous therapy for entecavir, TDF, and TAF.

Pegylated Interferon Alfa

Pegylated interferon alfa is administered as a weekly subcutaneous injection for 48 weeks. It has antiviral and immunomodulatory effects. A 48-week course of pegylated interferon alfa achieved HBeAg seroconversion in approximately 30% of patients with HBeAg-positive chronic hepatitis, HBsAg seroclearance in 8% to 14%,[65,66] and HBV DNA suppression (to <2000 IU/mL) in 20% to 25% of patients with HBeAg-negative chronic hepatitis at 3 years after completion of treatment (Table 2).[67,68] Predictors of response in HBeAg-positive patients include high ALT, low HBV DNA, and HBV genotype A or B; lack of HBsAg decline by week 12 of treatment predicts nonresponse in patients who are HBeAg positive and HBeAg negative.[69,70] Pegylated interferon alfa is associated with many adverse effects including fatigue, headache, myelosuppression, thyroid dysfunction, and depression, and is contraindicated in patients with decompensated cirrhosis, pregnancy, or autoimmune diseases.[71]

Long-Term Benefits

Both pegylated interferon alfa and nucleos(t)ide analogue therapy reduce cirrhosis progression, decompensation, HCC, and mortality.[72,73] Maintained HBV DNA suppression during long-term nucleos(t)ide analogue therapy has been shown to decrease fibrosis and to reverse cirrhosis.[74,75] In a systematic review and meta-analysis including 59 studies (15 randomized clinical trials and 44

observational studies) that included clinical outcomes, long-term nucleos(t)ide analogue therapy was associated with a significantly lower incidence of HCC compared with untreated individuals, with pooled relative risks of 0.57 in patients with cirrhosis and 0.50 in those without cirrhosis.[73] However, HCC risk persists, so HCC surveillance should continue in patients receiving nucleos(t)ide analogue therapy, particularly those with cirrhosis.[72,76] HCC surveillance should also be continued after HBsAg seroclearance unless it occurred at a young age (≤40 years for males and ≤50 years for females) and in the absence of cirrhosis or family history of HCC.[42]

Selection of Antiviral Therapy

Pegylated interferon alfa may be considered for patients seeking a finite course of treatment. Entecavir should be avoided in patients with prior exposure to lamivudine, with HIV coinfection (unless the HIV infection is adequately controlled with antiretroviral therapy), or who are pregnant.[77,78] Entecavir and tenofovir have few adverse effects and can be used by patients with decompensated cirrhosis.[79-81] TDF is associated with a small risk of kidney impairment and decrease in bone mineral density[82] and should be avoided in patients with or at risk of kidney impairment or bone fractures. TAF has similar antiviral activity to TDF but fewer adverse effects on the kidneys and bones.[82] Both TDF and TAF are safe in pregnancy (see Table 2 for a comparison of efficacy and contraindications).[83]

Treatment Response and Monitoring During Therapy

Treatment response is assessed based on suppression of serum HBV DNA to undetectable levels, HBeAg seroconversion (loss of HBeAg with development of antibody to HBeAg), HBsAg seroclearance, normalization of ALT, and decreased hepatic inflammation and fibrosis.[8] Treatment monitoring varies by agent. For pegylated interferon alfa therapy, complete blood count and ALT should be monitored monthly, thyroid function quarterly, and HBV DNA every 3 months. For nucleos(t)ide analogue therapy, HBV DNA and ALT should be monitored every 3 to 6 months initially and every 6 months after HBV DNA suppression (undetectable HBV DNA) is achieved. In HBeAg-positive patients, HBeAg and antibody to HBeAg should be tested annually. In patients who become HBeAg-negative or were HBeAg-negative before treatment and in whom HBV DNA has become undetectable, HBsAg should be monitored annually. Kidney function should be assessed every 6 to 12 months in patients receiving nucleos(t)ide analogues, especially those receiving TDF.[41,42,44]

Special Populations

Patients With HIV Coinfection

HIV/HBV coinfection accelerates progression to cirrhosis, hepatic decompensation, and HCC compared with HBV monoinfection.[45,84,85] All patients with HIV/HBV coinfection should receive antiretroviral therapy directed at both viruses.

Patients Receiving Immunosuppressive Therapy

HBV reactivation can occur in patients receiving immunosuppressive therapy (eg, corticosteroids, rituximab, cancer therapies, immune-modulating biologics, or calcineurin inhibitors) (see eTable 1 in the Supplement for a detailed list).[86] HBV reactivation is defined as a substantial increase in HBV DNA levels (typically ≥1-2 $\log_{10}$ IU/mL) or HBeAg seroreversion in HBsAg-positive patients and as reappearance of HBsAg or detectable HBV DNA in HBsAg-negative, anti–HBc-positive patients.[86,87]

All patients initiating immunosuppressive therapy should be tested for HBsAg, antibody to HBsAg, and antibody to HBcAg. HBV DNA should be measured in HBsAg-positive patients and in those with isolated antibody to HBcAg positivity. Prophylactic antiviral therapy (entecavir, TDF, or TAF) is recommended for patients receiving treatment at high risk of HBV reactivation and suggested for those receiving treatment at moderate risk of HBV reactivation. Patients receiving immunosuppressive therapies at low risk of HBV reactivation can be monitored with ALT or HBV DNA testing, with initiation of antiviral therapy at the first sign of HBV reactivation.

Prognosis

Liver-Related Outcomes

Progression from chronic HBV infection to cirrhosis, hepatic decompensation, and HCC depends on host factors (male sex, age >40 years, family history of HCC), viral factors (HBV DNA level, HBV genotypes, and coinfection with HIV, HCV, or HDV), environmental exposures (cigarette smoking and alcohol use), and comorbid conditions (diabetes and metabolic dysfunction–associated steatotic liver disease) associated with higher HCC risk.[38,88] Persistently elevated serum HBV DNA levels are a major risk factor for cirrhosis and HCC, but the association is not strictly linear.[89,90]

Among adults with untreated chronic hepatitis B, the 5-year cumulative risk of cirrhosis is 8% to 15%.[91] For patients with compensated cirrhosis, the 5-year cumulative risk of hepatic decompensation is 20%.[92] The annual HCC incidence rate, defined as the number of new HCC cases per 100 person-years of follow-up, is 0.05% for patients in the HBeAg-negative inactive phase, 0.42% for patients in the immune-active phase,[93] 3% for those with compensated cirrhosis,[93] and 4% to 5% for those with decompensated cirrhosis.[94] HCC risk is reduced by approximately 70% following HBsAg seroclearance,[95] particularly when HBsAg seroclearance occurs before age 50 years and prior to development of cirrhosis.[96] Survival after HCC diagnosis depends primarily on tumor stage and the feasibility of curative therapies.[37,97,98]

Prevention

Vaccination

HBV vaccination is the most effective method for preventing HBV infection. Current alum-adjuvanted HBV vaccines have an excellent safety profile, with more than 1 billion doses administered worldwide, and are approved for use in pregnant women and newborns.[99] HBV vaccines are typically administered in 3 doses at months 0, 1, and 6 and are recommended for all newborns, children, adolescents, and adults without evidence of infection or immunity or who are at high risk of infection.[45,100] In 2022, the CDC expanded HBV vaccine recommendations to all adults aged 19 to 59 years and to adults 60 years or older with risk factors or who desire protection[99] (**Table 3**; eTable 2 in the Supplement).

In 2024, WHO reported global coverage of the 3-dose infant HBV vaccine series of 84% and birth-dose coverage of 45%; in the African region, coverage was 76% and 17%, respectively.[101] Barriers to timely birth-dose vaccination include home deliveries, limited access to skilled birth attendants, and gaps in antenatal screening in

resource-limited settings.[102,103] In the US, missed opportunities for birth-dose vaccination have been attributed to incomplete prenatal screening and system-level barriers in hospital practices.[104]

Combination vaccines that include HBV, diphtheria, tetanus, and pertussis, with or without *Haemophilus influenzae* type b vaccines are available for use in children and a combination of HBV and HAV vaccines for both children and adults.

Hepatitis B vaccine adjuvanted with cytosine phosphoguanosine oligodeoxynucleotide (HepB-CpG), a 2-dose hepatitis B vaccine administered at months 0 and 1, contains a TLR9 agonist adjuvant, is more immunogenic than alum-adjuvanted HBV vaccines, and was approved by the US Food and Drug Administration in 2017.[105-107] HepB-CpG is approved for adults 18 years and older and may be particularly useful for individuals predicted to have poorer response, those requiring rapid protection, or prior nonresponders.

Postvaccination antibody to HBsAg testing is not recommended for the general population, but is indicated for health care workers, patients receiving hemodialysis, people with HIV infection or other immunocompromising conditions, sexual partners of HBsAg-positive persons, and infants born to HBsAg-positive individuals. Seroprotection is defined as an antibody to HBsAg level greater than or equal to 10 mIU/mL measured 1 to 2 months after completion of the vaccine series and is achieved in 95% of immunocompetent vaccinated individuals[108]; protection can persist for 35 years or more.[109] Factors associated with nonresponse include older age (>40 years), obesity, smoking, diabetes, cirrhosis, chronic kidney disease, HIV infection, and immunosuppression.[110] Revaccination or booster dose is not routinely recommended for immunocompetent responders. For nonresponders, a second vaccine series with the alum-adjuvanted vaccine or the more immunogenic HepB-CpG vaccine can be considered.

Table 3. Hepatitis B Vaccination Recommendations[a]

Population	Indication
All newborns	Administer birth-dose HBV vaccine within 24 h of birth (preferably within 12 h)
Children and adolescents	Vaccinate all not previously vaccinated, through age 18 y
Adults 19-59 y	Universal vaccination recommended
Adults ≥60 y	Shared decision-making (vaccinate if risk factors present or if vaccination is desired)
Pregnant persons	Vaccinate if indicated; all approved HBV vaccines may be used during pregnancy
High risk of HBV infection	
• Health care workers with potential blood or body fluid exposure • Men who have sex with men; persons with multiple sexual partners • Persons who inject drugs • Sexual partners, household contacts, and needle-sharing contacts of persons with HBV infection • Persons with HIV infection or history of HCV infection • Persons receiving hemodialysis • Persons born in countries with HBV prevalence ≥2% • US-born persons not vaccinated as infants whose parents were born in regions with HBV prevalence ≥8% • Incarcerated or formerly incarcerated persons; institutionalized persons • Public safety workers; persons with diabetes; persons who received tattoos or body piercings with nonsterile equipment	
High risk of severe liver-related outcomes[b]	
• Persons with chronic liver disease (any etiology) • Persons with unexplained elevated alanine aminotransferase or aspartate aminotransferase levels	
Recommended vaccine dose regimen	
Alum-adjuvanted HBV vaccines (Engerix-B, Recombivax HB)	3-Dose series at months 0, 1, and 6 (standard for all ages)
HepB-CpG vaccine (Heplisav-B)	2-Dose series at months 0 and 1; approved for adults aged ≥18 y
Patients receiving hemodialysis	Higher dose or modified schedules required

Abbreviations: CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; HepB-CpG, hepatitis B vaccine adjuvanted with cytosine phosphoguanosine oligodeoxynucleotide.

[a] 2022 CDC recommendations.[99]

[b] See eTable 2 in the Supplement for details of vaccine dose regimens.

Postexposure Prophylaxis

Postexposure prophylaxis is indicated after recent high-risk exposure (eg, needlestick injury from an HBsAg-positive source, unprotected sexual contact with an HBsAg-positive individual, perinatal exposure). Postexposure prophylaxis consists of hepatitis B immune globulin preferably administered within 24 hours along with initiation of the HBV vaccine series if the exposed person was not previously vaccinated. For known vaccine nonresponders, hepatitis B immune globulin alone (with repeat dosing at 1 month) is recommended.

Mother-to-Child Transmission

Mother-to-child transmission, which is the principal cause of chronic HBV infection globally, occurs in 70% to 90% of infants born to mothers who are HBsAg and HBeAg positive and in 5% to 20% of those born to HBsAg-positive/HBeAg-negative mothers. Prevention of mother-to-child transmission, which is critical for global elimination of HBV infection, includes universal screening of pregnant women for HBsAg, measurement of maternal HBV DNA level if HBsAg is positive, and passive-active immunization. Administering antiviral therapy to pregnant women with a high HBV DNA (>200 000 IU/mL) level in the second or early third trimester can further reduce perinatal transmission.[43,83,111] When maternal antiviral therapy is combined with passive-active immunoprophylaxis (birth-dose vaccination and hepatitis B immune globulin), pooled analyses of randomized clinical trials suggest that the risk of mother-to-child transmission may be reduced from 85% (without intervention) to less than 1%.[83,112] Both TDF and TAF are safe when used in pregnancy.[83]

Limitations

This review has several limitations. First, this was not a systematic review, and the quality of the selected articles was not formally assessed. Second, only articles published in the English language were included. Third, some relevant articles may have been missed. Fourth, detailed discussion of certain topics (pediatric HBV management, decompensated cirrhosis, liver transplant, and coinfection with HIV, HCV, and HDV) was beyond the scope of this article.

Conclusions

HBV infection causes approximately 1.1 million deaths annually worldwide. Universal HBV vaccination, particularly timely birth-dose administration, is the most effective strategy to prevent infection. Among patients with HBV infection, antiviral therapy decreases progression to cirrhosis and liver failure and reduces the risk of HCC.

ARTICLE INFORMATION

Accepted for Publication: April 3, 2026.

Published Online: May 4, 2026. doi:10.1001/jama.2026.6070

Conflict of Interest Disclosures: Dr Jeng reported receiving grants from GSK; serving on advisory boards for Roche, GSK, and Gilead; and receiving speaker fees from Roche, Gilead, and DKSH Healthcare outside the submitted work. Dr Yip reported receiving grants and personal fees from Gilead Sciences and personal fees from Echosens and GSK outside the submitted work. Dr Lok reported receiving grants from TARGET, Ipsen, and KOWA to the university and personal fees from Arbutus, Brii, Chroma, Pfizer, Moderna, Pioneering, Precision, Virion, Zenasbio, and Novo Nordisk outside the submitted work.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis*. 1995;20(4):992-1000. doi:10.1093/clinids/20.4.992

2. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B Virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67(1):1-31. doi:10.15585/mmwr.rr6701a1

3. Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of hepatitis B virus after drying and storage for one week. *Lancet*. 1981;1(8219):550-551. doi:10.1016/S0140-6736(81)92877-4

4. Centers for Disease Control and Prevention. Table 2.3: acute hepatitis B: risk & exposure data. 2023 Viral Hepatitis Surveillance Report. Accessed March 9, 2026. https://www.cdc.gov/hepatitis-surveillance-2023/hepatitis-b/table-2-3.html

5. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. Accessed March 11, 2026. https://iris.who.int/bitstream/handle/10665/376461/9789240091672-eng.pdf

6. Centers for Disease Control and Prevention. Figure 2.1: acute hepatitis B: number of cases & estimated infections. Accessed March 9, 2026. https://www.cdc.gov/hepatitis-surveillance-2023/hepatitis-b/figure-2-1.html

7. MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. *Cold Spring Harb Perspect Med*. 2015;5(5):a021410. doi:10.1101/cshperspect.a021410

8. Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. *Lancet*. 2023;401(10381):1039-1052. doi:10.1016/S0140-6736(22)01468-4

9. Dusheiko G, Agarwal K, Maini MK. New approaches to chronic hepatitis B. *N Engl J Med*. 2023;388(1):55-69. doi:10.1056/NEJMra2211764

10. Liu Z, Zhang Y, Xu M, Li X, Zhang Z. Distribution of hepatitis B virus genotypes and subgenotypes: a meta-analysis. *Medicine (Baltimore)*. 2021;100(50):e27941. doi:10.1097/MD.0000000000027941

11. Jiang S, Guo S, Huang Y, et al. Predictors of HBsAg seroclearance in patients with chronic HBV infection treated with pegylated interferon-α: a systematic review and meta-analysis. *Hepatol Int*. 2024;18(3):892-903. doi:10.1007/s12072-024-10648-8

12. Wong GL, Chan HL, Yiu KK, et al. Meta-analysis: the association of hepatitis B virus genotypes and hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2013;37(5):517-526. doi:10.1111/apt.12207

13. McMahon BJ, Nolen LD, Snowball M, et al. HBV genotype: a significant risk factor in determining which patients with chronic HBV infection should undergo surveillance for HCC: the Hepatitis B Alaska Study. *Hepatology*. 2021;74(6):2965-2973. doi:10.1002/hep.32065

14. Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. *Nat Rev Immunol*. 2022;22(1):19-32. doi:10.1038/s41577-021-00549-4

15. Ferrari C. HBV and the immune response. *Liver Int*. 2015;35(suppl 1):121-128. doi:10.1111/liv.12749

16. Chisari FV, Ferrari C. Hepatitis B virus immunopathogenesis. *Annu Rev Immunol*. 1995;13:29-60. doi:10.1146/annurev.iy.13.040195.000333

17. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64(1)(suppl):S84-S101. doi:10.1016/j.jhep.2016.02.021

18. Mason WS, Jilbert AR, Litwin S. Hepatitis B virus DNA integration and clonal expansion of hepatocytes in the chronically infected liver. *Viruses*. 2021;13(2):210. doi:10.3390/v13020210

19. Liaw YF, Brunetto MR, Hadziyannis S. The natural history of chronic HBV infection and geographical differences. *Antivir Ther*. 2010;15(suppl 3):25-33. doi:10.3851/IMP1621

20. Hui VW, Wong GL, Dai J, et al. Increased risk of HCC in HBeAg-negative indeterminate phase compared with HBeAg-negative chronic infection. *Hepatology*. 2026;83(1):156-168. doi:10.1097/HEP.0000000000001354

21. Yeo YH, Ho HJ, Yang HI, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. *Gastroenterology*. 2019;156(3):635-646.e9. doi:10.1053/j.gastro.2018.10.027

22. Centers for Disease Control and Prevention. Clinical testing and diagnosis for hepatitis B. Accessed March 11, 2026. https://www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/index.html

23. Wai CT, Fontana RJ, Polson J, et al; US Acute Liver Failure Study Group. Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. *J Viral Hepat*. 2005;12(2):192-198. doi:10.1111/j.1365-2893.2005.00581.x

24. Liaw YF, Tai DI, Chu CM, Pao CC, Chen TJ. Acute exacerbation in chronic type B hepatitis: comparison between HBeAg and antibody-positive patients. *Hepatology*. 1987;7(1):20-23. doi:10.1002/hep.1840070106

25. Lok AS, Lai CL. Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection: incidence, predisposing factors and etiology. *J Hepatol*. 1990;10(1):29-34. doi:10.1016/0168-8278(90)90069-4

26. Lall S, Agarwala P, Kumar G, Sharma MK, Gupta E. The dilemma of differentiating between acute hepatitis B and chronic hepatitis B with acute exacerbation: is quantitative serology the answer? *Clin Mol Hepatol*. 2020;26(2):187-195. doi:10.3350/cmh.2019.0060

27. Chang ML, Cheng JS, Chien RN, Liaw YF. Hepatitis flares are associated with better outcomes than no flare in patients with decompensated cirrhosis and chronic hepatitis B virus infection. *Clin Gastroenterol Hepatol*. 2020;18(9):2064-2072.e2. doi:10.1016/j.cgh.2020.01.018

28. Cacoub P, Asselah T. Hepatitis B virus infection and extra-hepatic manifestations: a systemic disease. *Am J Gastroenterol*. 2022;117(2):253-263. doi:10.14309/ajg.0000000000001575

29. Lemon SM, Gates NL, Simms TE, Bancroft WH. IgM antibody to hepatitis B core antigen as a diagnostic parameter of acute infection with hepatitis B virus. *J Infect Dis*. 1981;143(6):803-809. doi:10.1093/infdis/143.6.803

30. Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. *Hepatol Int*. 2009;3(3):425-433. doi:10.1007/s12072-009-9140-3

31. Loomba R, Adams LA. Advances in non-invasive assessment of hepatic fibrosis. *Gut*. 2020;69(7):1343-1352. doi:10.1136/gutjnl-2018-317593

32. Sterling RK, Patel K, Duarte-Rojo A, et al. AASLD Practice Guideline on blood-based noninvasive liver disease assessment of hepatic fibrosis and steatosis. *Hepatology*. 2025;81(1):321-357. doi:10.1097/HEP.0000000000000845

33. Khalifa A, Rockey DC. The utility of liver biopsy in 2020. *Curr Opin Gastroenterol*. 2020;36(3):184-191. doi:10.1097/MOG.0000000000000621

34. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518-526. doi:10.1053/jhep.2003.50346

35. Liguori A, Zoncapè M, Casazza G, Easterbrook P, Tsochatzis EA. Staging liver fibrosis and cirrhosis using non-invasive tests in people with chronic hepatitis B to inform WHO 2024 guidelines: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2025;10(4):332-349. doi:10.1016/S2468-1253(24)00437-0

36. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*. 2017;11(4):317-370. doi:10.1007/s12072-017-9799-9

37. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922-1965. doi:10.1097/HEP.0000000000000466

38. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. *J Hepatol*. 2025;82(2):315-374. doi:10.1016/j.jhep.2024.08.028

39. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. *J Hepatol*. 2016;64(4):800-806. doi:10.1016/j.jhep.2015.11.035

40. Centers for Disease Control and Prevention. Clinical overview of hepatitis B. Accessed January

8, 2026. https://www.cdc.gov/hepatitis-b/hcp/clinical-overview/index.html

41. 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):1-98. doi:10.1007/s12072-015-9675-4

42. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599. doi:10.1002/hep.29800

43. Ghany MG, Pan CQ, Lok AS, et al. AASLD ISDA Practice Guideline on treatment of chronic hepatitis B. *Hepatology*. 2026;83(4):974-997. doi:10.1097/HEP.0000000000001549

44. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2025;83(2):502-583. doi:10.1016/j.jhep.2025.03.018

45. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Accessed June 15, 2025. https://www.who.int/publications/i/item/9789240090903

46. Ghany MG, Buti M, Lampertico P, Lee HM; 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference Faculty. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. *Hepatology*. 2023;78(5):1654-1673. doi:10.1097/HEP.0000000000000431

47. You H, Wang F, Li T, et al; Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the prevention and treatment of chronic hepatitis B (version 2022). *J Clin Transl Hepatol*. 2023;11(6):1425-1442. doi:10.14218/JCTH.2023.00320

48. Lumley SF, Delphin M, Mokaya JF, et al. A systematic review and meta-analysis of the risk of hepatitis B virus (HBV) resistance in people treated with entecavir or tenofovir. *J Clin Virol*. 2024;174:105711. doi:10.1016/j.jcv.2024.105711

49. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int*. 2019;39(10):1868-1875. doi:10.1111/liv.14155

50. Chang TT, Gish RG, de Man R, et al; BEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354(10):1001-1010. doi:10.1056/NEJMoa051285

51. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359(23):2442-2455. doi:10.1056/NEJMoa0802878

52. Chan HL, Fung S, Seto WK, et al; GS-US-320-0110 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-195. doi:10.1016/S2468-1253(16)30024-3

53. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: final results from two randomised phase 3 trials. *Aliment Pharmacol Ther*. 2024;60(11-12):1573-1586. doi:10.1111/apt.18278

54. Suzuki F, Hosaka T, Suzuki Y, et al. Long-term outcome of entecavir treatment of nucleos(t)ide analogue-naïve chronic hepatitis B patients in Japan. *J Gastroenterol*. 2019;54(2):182-193. doi:10.1007/s00535-018-1502-y

55. Lai CL, Shouval D, Lok AS, et al; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2006;354(10):1011-1020. doi:10.1056/NEJMoa051287

56. Buti M, Gane E, Seto WK, et al; GS-US-320-0108 Investigators. 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(3):196-206. doi:10.1016/S2468-1253(16)30107-8

57. Liu YC, Jeng WJ, Peng CW, Chien RN, Liaw YF. The role of off-therapy viral kinetics in the timing and severity of flares in hepatitis B e antigen-negative patients. *Clin Gastroenterol Hepatol*. 2023;21(6):1533-1541.e11. doi:10.1016/j.cgh.2022.08.021

58. Jeng WJ, Sheen IS, Liaw YF. Hepatitis B virus DNA level predicts hepatic decompensation in patients with acute exacerbation of chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2010;8(6):541-545. doi:10.1016/j.cgh.2010.02.023

59. Liaw YF, Papatheodoridis G. Finite nucleos(t)ide analog therapy for functional cure in HBeAg-negative chronic hepatitis B: recent development in the paradigm shift. *Hepatology*. 2026;83(3):679-692. doi:10.1097/HEP.0000000000001107

60. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. *Hepatology*. 2018;68(2):425-434. doi:10.1002/hep.29640

61. Dongelmans EJ, Hirode G, Hansen BE, et al; RETRACT-B study group. Predictors of hepatic flares after nucleos(t)ide analogue cessation: results of a global cohort study (RETRACT-B study). *J Hepatol*. 2025;82(3):446-455. doi:10.1016/j.jhep.2024.08.015

62. Chang ML, Liaw YF, Hadziyannis SJ. Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2015;42(3):243-257. doi:10.1111/apt.13272

63. Lim SG, Teo AE, Chan ES, Phyo WW, Chen DHY, Hargreaves CA. Stopping nucleos(t)ide analogues in chronic hepatitis B using HBsAg thresholds: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol*. 2024;22(12):2403-2412. doi:10.1016/j.cgh.2024.05.040

64. Hirode G, Choi HSJ, Chen CH, et al; RETRACT-B Study Group. Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: an international, multicenter, multiethnic cohort (RETRACT-B Study). *Gastroenterology*. 2022;162(3):757-771.e4. doi:10.1053/j.gastro.2021.11.002

65. Lau GK, Piratvisuth T, Luo KX, et al; Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352(26):2682-2695. doi:10.1056/NEJMoa043470

66. Buster EH, Flink HJ, Cakaloglu Y, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. *Gastroenterology*. 2008;135(2):459-467. doi:10.1053/j.gastro.2008.05.031

67. Marcellin P, Lau GK, Bonino F, et al; Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351(12):1206-1217. doi:10.1056/NEJMoa040431

68. Marcellin P, Bonino F, Lau GK, et al. Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. *Gastroenterology*. 2009;136(7):2169-2179. doi:10.1053/j.gastro.2009.03.006

69. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology*. 2009;137(6):2002-2009. doi:10.1053/j.gastro.2009.08.061

70. Sonneveld MJ, Hansen BE, Piratvisuth T, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. *Hepatology*. 2013;58(3):872-880. doi:10.1002/hep.26436

71. Perrillo R, Tamburro C, Regenstein F, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology*. 1995;109(3):908-916. doi:10.1016/0016-5085(95)90401-8

72. Yip TC, Wong GL, Chan HL, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. *J Hepatol*. 2019;70(3):361-370. doi:10.1016/j.jhep.2018.10.014

73. Lok AS, McMahon BJ, Brown RS Jr, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. *Hepatology*. 2016;63(1):284-306. doi:10.1002/hep.28280

74. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*. 2010;52(3):886-893. doi:10.1002/hep.23785

75. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381(9865):468-475. doi:10.1016/S0140-6736(12)61425-1

76. Papatheodoridis GV, Sypsa V, Dalekos GN, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. *J Hepatol*. 2020;72(6):1088-1096. doi:10.1016/j.jhep.2020.01.007

77. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir: effects on HIV-1 replication and

resistance. *N Engl J Med*. 2007;356(25):2614-2621. doi:10.1056/NEJMoa067710

78. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology*. 2009;49(5):1503-1514. doi:10.1002/hep.22841

79. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol*. 2010;52(2):176-182. doi:10.1016/j.jhep.2009.11.007

80. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology*. 2011;53(1):62-72. doi:10.1002/hep.23952

81. Chen L, Zhang HF, Cai YJ, et al. Comparative effectiveness and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in patients with HBV-associated decompensated cirrhosis: insights from a retrospective analysis. *BMC Infect Dis*. 2025;25(1):1039. doi:10.1186/s12879-025-11473-6

82. Chan HLY, Buti M, Lim YS, et al; GS-US-320-0110 and GS-US-320-0108 investigators. Long-term treatment with tenofovir alafenamide for chronic hepatitis B results in high rates of viral suppression and favorable renal and bone safety. *Am J Gastroenterol*. 2024;119(3):486-496. doi:10.14309/ajg.0000000000002468

83. Pan CQ, Zhu L, Yu AS, Zhao Y, Zhu B, Dai E. Tenofovir alafenamide versus tenofovir disoproxil fumarate for preventing vertical transmission in chronic hepatitis B mothers: a systematic review and meta-analysis. *Clin Infect Dis*. 2024;79(4):953-964. doi:10.1093/cid/ciae288

84. Horberg M, Thompson M, Agwu A, et al. Primary care guidance for providers of care for persons with human immunodeficiency virus: 2024 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2024:ciae479. doi:10.1093/cid/ciae479

85. Thio CL, Seaberg EC, Skolasky R Jr, et al; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the multicenter cohort study (MACS). *Lancet*. 2002;360(9349):1921-1926. doi:10.1016/S0140-6736(02)11913-1

86. Ali FS, Nguyen MH, Hernaez R, et al. AGA clinical practice guideline on the prevention and treatment of hepatitis B virus reactivation in at-risk individuals. *Gastroenterology*. 2025;168(2):267-284. doi:10.1053/j.gastro.2024.11.008

87. Papatheodoridis GV, Lekakis V, Voulgaris T, et al. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: a systematic review, meta-analysis, and expert opinion. *J Hepatol*. 2022;77(6):1670-1689. doi:10.1016/j.jhep.2022.07.003

88. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264-1273.e1. doi:10.1053/j.gastro.2011.12.061

89. Chen CJ, Yang HI, Su J, et al; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295(1):65-73. doi:10.1001/jama.295.1.65

90. Kim GA, Lim YS, Han S, et al. Viral load-based prediction of hepatocellular carcinoma risk in noncirrhotic patients with chronic hepatitis B: a multinational study for the development and external validation of a new prognostic model. *Ann Intern Med*. 2024;177(10):1308-1318. doi:10.7326/M24-0384

91. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology*. 1988;8(3):493-496. doi:10.1002/hep.1840080310

92. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. *J Hepatol*. 2012;57(2):442-450. doi:10.1016/j.jhep.2012.02.033

93. Raffetti E, Fattovich G, Donato F. Incidence of hepatocellular carcinoma in untreated subjects with chronic hepatitis B: a systematic review and meta-analysis. *Liver Int*. 2016;36(9):1239-1251. doi:10.1111/liv.13142

94. Ju YC, Jun DW, Choi J, Saeed WK, Lee HY, Oh HW. Long term outcome of antiviral therapy in patients with hepatitis B associated decompensated cirrhosis. *World J Gastroenterol*. 2018;24(40):4606-4614. doi:10.3748/wjg.v24.i40.4606

95. Anderson RT, Choi HSJ, Lenz O, et al. Association between seroclearance of hepatitis b surface antigen and long-term clinical outcomes of patients with chronic hepatitis B virus infection: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(3):463-472. doi:10.1016/j.cgh.2020.05.041

96. Yip TC, Chan HL, Wong VW, Tse YK, Lam KL, Wong GL. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. *J Hepatol*. 2017;67(5):902-908. doi:10.1016/j.jhep.2017.06.019

97. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. *J Hepatol*. 2022;77(1):128-139. doi:10.1016/j.jhep.2022.01.023

98. Johnson P, Berhane S, Kagebayashi C, et al. Impact of disease stage and aetiology on survival in hepatocellular carcinoma: implications for surveillance. *Br J Cancer*. 2017;116(4):441-447. doi:10.1038/bjc.2016.422

99. Weng MK, Doshani M, Khan MA, et al. Universal hepatitis B vaccination in adults aged 19-59 years: updated recommendations of the Advisory Committee on Immunization Practices: United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(13):477-483. doi:10.15585/mmwr.mm7113a1

100. Centers for Disease Control and Prevention. Hepatitis B vaccine administration. Accessed March 10, 2026. https://www.cdc.gov/hepatitis-b/hcp/vaccine-administration/index.html

101. World Health Organization. Hepatitis B vaccination coverage. Accessed October 27, 2025. https://immunizationdata.who.int/global/wiise-detail-page/hepatitis-b-vaccination-coverage

102. Allison RD, Patel MK, Tohme RA. Hepatitis B vaccine birth dose coverage correlates worldwide with rates of institutional deliveries and skilled attendance at birth. *Vaccine*. 2017;35(33):4094-4098. doi:10.1016/j.vaccine.2017.06.051

103. World Health Organization. Hepatitis B vaccines: WHO position paper: July 2017. *Wkly Epidemiol Rec*. 2017;92(27):369-392.

104. Pham TTH, Maria N, Cheng V, et al. Gaps in prenatal hepatitis B screening and management of HBsAg positive pregnant persons in the US, 2015-2020. *Am J Prev Med*. 2023;65(1):52-59. doi:10.1016/j.amepre.2023.01.041

105. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018;67(15):455-458. doi:10.15585/mmwr.mm6715a5

106. Marks KM, Kang M, Umbleja T, et al; ACTG 5379 (BEe-HIVe) Study Team. HepB-CpG vs HepB-alum vaccine in people with HIV and prior vaccine nonresponse: the BEe-HIVe randomized clinical trial. *JAMA*. 2025;333(4):295-306. doi:10.1001/jama.2024.24490

107. Schillie S, Murphy TV, Sawyer M, et al; Centers for Disease Control and Prevention (CDC). CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. *MMWR Recomm Rep*. 2013;62(RR-10):1-19.

108. Schillie SF, Murphy TV. Seroprotection after recombinant hepatitis B vaccination among newborn infants: a review. *Vaccine*. 2013;31(21):2506-2516. doi:10.1016/j.vaccine.2012.12.012

109. Bruce MG, Bruden D, Hurlburt D, et al. Protection and antibody levels 35 years after primary series with hepatitis B vaccine and response to a booster dose. *Hepatology*. 2022;76(4):1180-1189. doi:10.1002/hep.32474

110. Tahir A, Shinkafi SH, Alshrari AS, et al. A comprehensive review of hepatitis B vaccine nonresponse and associated risk factors. *Vaccines (Basel)*. 2024;12(7):710. doi:10.3390/vaccines12070710

111. Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. *Lancet Infect Dis*. 2021;21(1):70-84. doi:10.1016/S1473-3099(20)30586-7

112. Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol*. 1977;105(2):94-98. doi:10.1093/oxfordjournals.aje.a112370