# Hepatitis B

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**Hepatitis B virus (HBV) infection is a major public health problem, with an estimated 296 million people chronically infected and 820 000 deaths worldwide in 2019. Diagnosis of HBV infection requires serological testing for HBsAg and for acute infection additional testing for IgM hepatitis B core antibody (IgM anti-HBc, for the window period when neither HBsAg nor anti-HBs is detected). Assessment of HBV replication status to guide treatment decisions involves testing for HBV DNA, whereas assessment of liver disease activity and staging is mainly based on aminotransferases, platelet count, and elastography. Universal infant immunisation, including birth dose vaccination is the most effective means to prevent chronic HBV infection. Two vaccines with improved immunogenicity have recently been approved for adults in the USA and EU, with availability expected to expand. Current therapies, pegylated interferon, and nucleos(t)ide analogues can prevent development of cirrhosis and hepatocellular carcinoma, but do not eradicate the virus and rarely clear HBsAg. Treatment is recommended for patients with cirrhosis or with high HBV DNA levels and active or advanced liver disease. New antiviral and immunomodulatory therapies aiming to achieve functional cure (ie, clearance of HBsAg) are in clinical development. Improved vaccination coverage, increased screening, diagnosis and linkage to care, development of curative therapies, and removal of stigma are important in achieving WHO's goal of eliminating HBV infection by 2030.**

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## Introduction

Hepatitis B virus (HBV) infection can be prevented by vaccination, and sequelae of chronic hepatitis B (CHB) infection—cirrhosis, liver failure, and hepatocellular carcinoma (HCC)—can be prevented by antiviral therapy. In 2016, WHO set the goals to reduce the incidence of viral hepatitis by 90%, and its associated mortality by 65%, by 2030.[1] In 2019, WHO estimated there were 1·5 million new cases of CHB and 820 000 deaths related to HBV, putting many metrics used to gauge success toward viral hepatitis elimination at risk.[2] This Seminar provides an update on epidemiology, natural history, and HBV treatment, and discusses strategies to meet the WHO goals of viral hepatitis elimination.

## Epidemiology

In 2019, 296 million people were positive for hepatitis B surface antigen (HBsAg) worldwide, and the global prevalence of CHB infection was approximately 3·5%.[2] The prevalence of HBsAg or CHB infection varies widely in different parts of the world (figure 1).[3] In all countries, both incidence of acute and prevalence of chronic HBV infection have declined, especially among children and young adults, mainly due to universal infant vaccination.[4] However, outbreaks still occur even in high-income countries, such as the USA, where the epidemic of opioid use coupled with low vaccination rates among adults have been associated with an increase in incidence of acute HBV infection.[5] In addition, prevalence of CHB infection in low-endemic countries might not be decreasing due to new immigrants from intermediate-endemic or high-endemic countries.[6,7] The ageing of people with CHB infection with increased prevalence of comorbidities increases the risks of both liver and non-liver complications.[8,9]

HBV is transmitted through percutaneous or mucosal exposure of non-immune individuals to infectious biological material such as blood, semen, and saliva. HBV survives in the environment for 7 days or more and is more infectious than HIV.[10,11] HBV can be detected in breastmilk, but there are no reports of transmission to breastfeeding infants of mothers who are HBsAg positive.[12] The most common modes of transmission include sexual contacts, perinatal or vertical transmission from mothers who are HBsAg positive to newborns, horizontal intrafamilial spread (especially in children) through inapparent parenteral exposure (presumably by open cuts and sores), and transmission through contaminated syringes or needles among people who inject drugs. The risk of progression from acute to chronic infection is inversely proportional to the age at infection, approximately 90% when infection occurs in newborns, 20% in children, and less than 5% in immunocompetent adults.[10,11,13] High-risk groups for HBV infection are people born in regions of intermediate or high endemicity, people who inject drugs, men who have sex with men, people with HIV infection, and sexual partners, needle-sharing contacts, and household contacts of people who are HBsAg positive [10,11]

### Search strategy and selection criteria

We focused on advances in the management of hepatitis B in the past 5 years. We searched PubMed using the terms "hepatitis B", "hepatitis B virus", "HBV", and "chronic hepatitis B" for articles published in English or with English abstract in print or online between Jan 1, 2017, and Dec 31, 2021. We also searched the WHO and the US Centers for Disease Prevention and Control websites for the most current epidemiological data and reference lists of articles identified by this search strategy and included any papers we deemed relevant. Landmark articles published before 2016 were also included. We did not include studies with low quality or few patients.

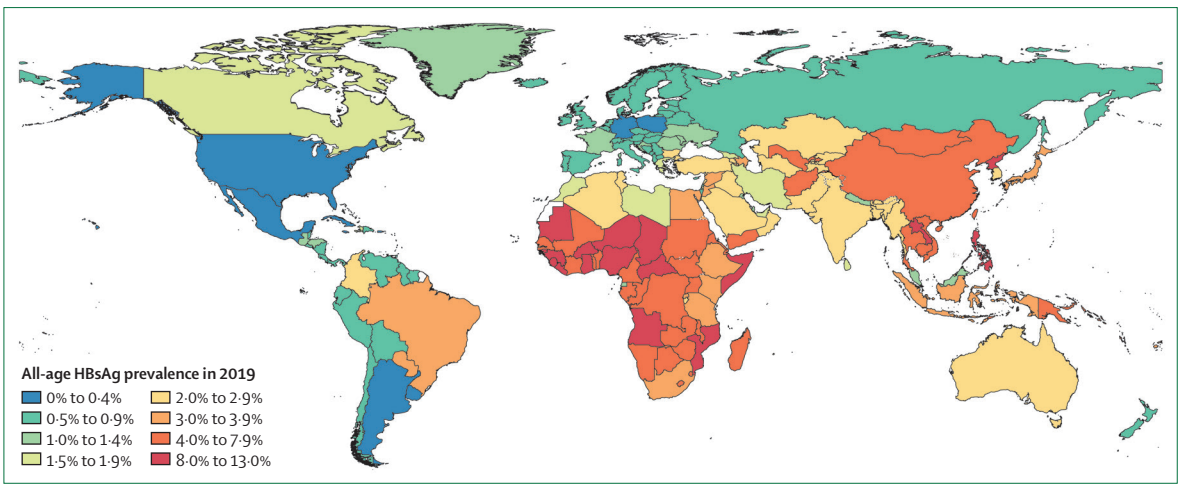



***Figure 1:*** **Global prevalence of HBsAg or chronic hepatitis B virus infection**
Reproduced from GBD 2019 Hepatitis B Collaborators. HBsAg=hepatitis B surface antigen.

People with HBV infection can be co-infected with other viruses that share common modes of transmission. Hepatitis D virus (HDV), a defective virus, can only infect people who are HBsAg positive and is estimated to affect 5% of people with CHB worldwide.[14,15] Co-infection with hepatitis C virus (HCV) can be present in 1–15%[16] and with HIV in 1–2% of people with CHB.[15,17]

## Virology

HBV is a DNA virus belonging to the Hepadnaviridae family. HBV enters hepatocytes through a receptor sodium taurocholate cotransporting polypeptide (figure 2).[18] The relaxed circular DNA in the virion is converted to covalently closed circular DNA (cccDNA), which is transcribed into the pregenomic RNA (a template for reverse transcription into HBV DNA) and mRNAs for translation into HBV proteins.[19] Persistence of cccDNA in the liver is the main reason for the difficulty in eradicating HBV and for reactivation of HBV replication in recovered people when immunosuppressed.[20] HBV DNA can be integrated into the host genome and can be a source of HBsAg, as well as a contributor to hepatocarcinogenesis.[21,22]

There are at least ten HBV genotypes (A–J). The prevalence of HBV genotypes varies geographically, with genotype A found mainly in northern Europe, North America, India, and Africa; genotypes B and C in east Asia; genotype D in southern Europe, the Middle East, India, and Africa; genotype E in west Africa; and genotypes F and H in central and South America.[23] Data on other genotypes are scarce. The increasing migration in recent years has affected the distribution of HBV genotypes[6]—eg, genotypes B and C, which are most common in Asia, are now dominant in the USA because more than 70% of Americans who are HBsAg-positive migrated from Asian countries.[24] The clinical significance of HBV genotypes remains unclear, although studies in Asia suggest that genotype C is associated with higher HCC risk than genotype B,[25] and many studies have found genotype A to be associated with higher chance of HBsAg clearance after pegylated-interferon-alfa therapy.[26,27]

The precore and core promoter variants, which block and decrease HBeAg production, respectively, are more commonly found in HBeAg-negative patients.[28,29] These variants have predilection for specific HBV genotypes, accounting for regional differences,[28–30] and core promoter variants have been shown to be associated with increased HCC risk.[31]

## Pathophysiology

HBV has been considered to be non-cytopathic and liver injury is mostly immune mediated.[32] Whereas vigorous T-cell responses are detected after recovery from acute HBV infection, people with CHB have impaired innate and adaptive immune responses to HBV.[32,33] Impairment in HBV-specific T-cell response in CHB is mostly due to immune exhaustion rather than deletion of T cells, as restoration of T-cell response has been observed in patients with spontaneous or treatment-related HBeAg or HBsAg clearance.[34] B-cell immune response is important in recovery from acute infection, and high levels of hepatitis B surface antibody can be detected many decades after recovery. The high risk of HBV reactivation in patients with CHB receiving B-cell-depleting therapies suggests that B cells also play an important role in the control of chronic infection.[32,35]

## Prevention

Vaccination is the most effective way to prevent HBV infection. Recombinant HBV vaccines are safe, highly effective, and available as single vaccines or combination vaccines with other antigens used in infancy immunisation programmes, or with hepatitis A virus vaccine for use in all age groups (appendix).[36,37] Age and immunocompetency are key factors influencing immunogenic response to

See Online for appendix

vaccination.[36,38] After a primary series of three (or four, for many infants) doses, protective anti-HBs levels (≥10 mIU/mL) develop in more than 95% of infants, children, and young adults, but in only 60–75% of people older than 60 years. Factors that decrease vaccination efficacy include obesity, smoking, genetic factors, and comorbidities such as chronic renal failure, chronic liver disease, and diabetes.[38]

Given the high risk of chronicity after HBV infection during infancy, universal infant immunisation (including birth dose) is the most effective means of preventing chronic HBV infection. As of 2020, 98% of countries worldwide have adopted universal infant HBV vaccination with 83% coverage of the three to four-dose series,[39] but timely coverage of birth dose remains less than 50%.[2] HBV prevalence among children younger than 5 years has decreased from 4·7% before 2000 to less than 1% after 2016.[2] In countries such as Taiwan, where universal HBV vaccination was initiated in 1984, decrease in HBV prevalence as well as incidence of HCC has been observed not only in children, but also among young adults.[40]

Since many adults remain susceptible, adult vaccination is required in high-risk populations (people who have high-risk sexual behaviours [multiple sex partners, men who have sex with men] and people who inject drugs) to reduce HBV infection.[36,38] In 2022, the recommendations for adult HBV vaccination in the USA were broadened to include all people younger than 60 years and those aged 60 years or older who seek protection.[41] Safe sex practices, global implementation of blood safety strategies, and reduction of unsafe injections are also important in preventing transmission.

Although anti-HBs decrease over time, protection appears to last for 30 years or more after vaccination due to immune memory. Thus, a booster dose is not recommended in healthy, fully vaccinated children or immunocompetent adults, but only in dialysis patients in whom annual testing shows anti-HBs levels less than 10 mIU/mL.[36–38,42]

Testing for HBV markers before vaccination is not routinely recommended and should not be a deterrent to vaccination.[36–38] Prevaccination testing in high-risk groups and those living in endemic areas can identify infected people so they can receive appropriate care. Postvaccination anti-HBs testing 1–2 months after completion of the vaccine series is recommended only in people with decreased probability of response or high risk of exposure (eg, patients on dialysis, infants of HBsAg-positive mothers, and sexual partners of HBsAg-positive people).[36,42] Non-responders can receive a second course of the same vaccine at the usual or double dose or one of the new vaccines described later in this Seminar.

Two new recombinant vaccines, which increase the response rates in people older than 60 years or immunocompromised people, have been recently licensed for use in adults in the USA and EU, and their availability is expected to expand to other countries with a greater burden. HepB-CpG (Heplisav-B) contains a potent adjuvant and is administered in two doses, and might be most appropriate when rapid achievement of immune protection is desired.[43–46] PreHevbrio (VBI vaccines, MA, USA) contains all three surface antigens (large, middle, and small) and is administered in three doses.[47–49] These new vaccines have not been approved for children, and safety and effectiveness in pregnant women and dialysis patients have not been established.[43,44,46,47]

Hepatitis B immune globulin (HBIG) usually in combination with the first vaccine dose, can be administered to non-immune people with exposure to biological materials from HBsAg-positive people, to newborns from HBsAg-positive mothers, or patients who underwent liver transplantation for HBV-related liver disease.[10,11,36]

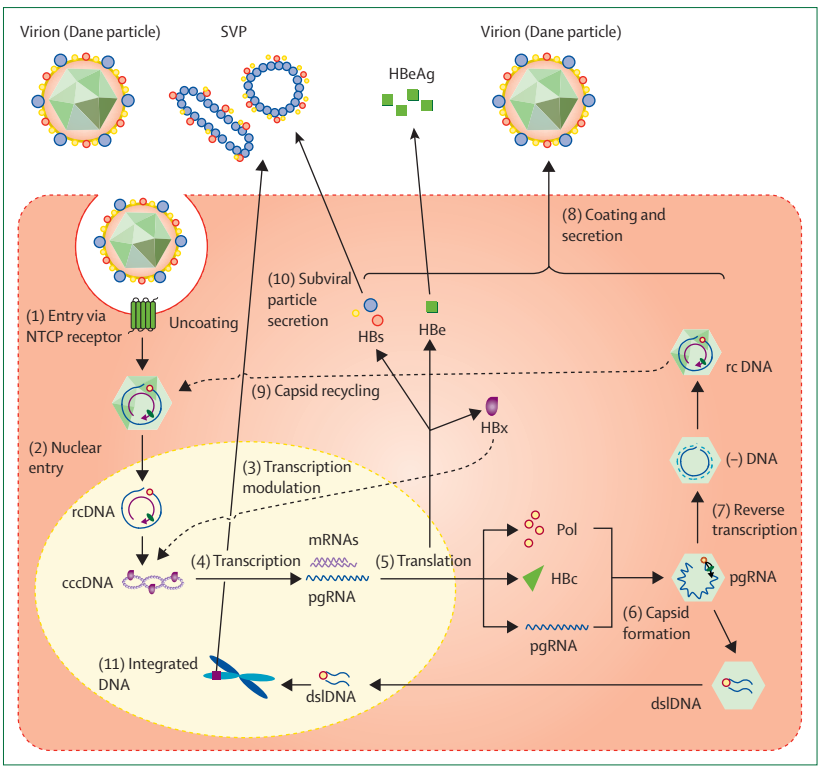



***Figure 2:*** **Lifecycle of HBV and the potential sites of action of antiviral therapies, approved and in clinical development**

(1) HBV enters hepatocytes through attachment to the NTCP receptor. (2) After uncoating, the rcDNA in the viral capsid enters the hepatocyte nucleus where the second strand HBV DNA is completed, forming the cccDNA. (3, 4) cccDNA serves as a template for transcription of pgRNA and mRNAs; this step is modulated by HBx protein. (5) HBV mRNAs are translated into viral proteins (core, polymerase, X, e [processed from precore or core] and S [large, middle, and small]). (6) pgRNA, core, and polymerase proteins are packaged into capsids, inside which (7) pgRNA is reverse transcribed into HBV DNA. (8) Capsids with rcDNA can be enveloped with surface proteins for secretion as virions or (9) recycled back to the nucleus to replenish the cccDNA pool. (10) HBV also secretes an excess of subviral particles that contain HBs proteins but not HBV DNA. (11) A minority of pgRNA is reverse transcribed into dslDNA which can be integrated into host DNA. Integrated HBV DNA is not replication competent but can be translated into S proteins and are secreted as SVP. Sites of action of antiviral therapies in HBV lifecycle: entry inhibitors (1), transcription modulation (3), capsid assembly modulators (6, and possibly 2 and 9), translation inhibitors (5), nucleos(t)ide analogues at reverse transcription (7), secretion inhibitors (8, 10). dslDNA=double-stranded linear DNA. HBc=hepatitis B core. HBs=hepatitis B surface. HBsAg=hepatitis B virus surface antigen. HBx=hepatitis B X. HBV=hepatitis B virus. NTCP=sodium taurocholate cotransporting polypeptide. pgRNA=pregenomic RNA. cccDNA=covalently closed circular DNA. Pol=polymerase. rcDNA=relaxed circular DNA.

For more on **The Antiretroviral Pregnancy Registry** see http://www.apregistry.com

Passive–active immunisation at birth has an overall efficacy of approximately 95% in preventing mother-to-child transmission[50] (MTCT). This involves screening all pregnant women for HBsAg and administering one dose of HBIG and HBV vaccine within 12 h of birth followed by three-dose vaccination series starting at month 1.

Confirmation of immunity is recommended by testing infants for anti-HBs between months 9 and 15. MTCT might occur due to delays or failure in administering HBIG or the birth dose vaccine, failure to complete the vaccine series, or transmission from highly viraemic mothers. Antiviral therapy administered to these mothers during the third trimester can further reduce the risk of MTCT. Thus, the current recommendation is to screen all pregnant women for HBsAg and to test HBV DNA levels in those who are HBsAg positive. Tenofovir disoproxil fumarate (TDF) starting at week 24–32 of pregnancy is recommended in people with a HBV DNA concentration of more than 200 000 IU/mL.[10,11] Treatment can be stopped immediately or continued for an additional 12 weeks after delivery, and with monitoring for serum alanine aminotransferase (ALT) flares every 1–3 months for 6 months afterwards. TDF has established safety in pregnancy even when administered during the first trimester and can be continued in breastfeeding mothers if indicated.[10,11] Implementation of the above measures can completely eliminate MTCT of HBV, but can be challenging in countries where a substantial percentage of births occur at home, access to diagnostic tests in particular HBV DNA assays is low, and HBIG is not available or affordable. There is no evidence that HBV can be transmitted through breastmilk and breastfeeding should not be discouraged if the preventive measures described are followed.

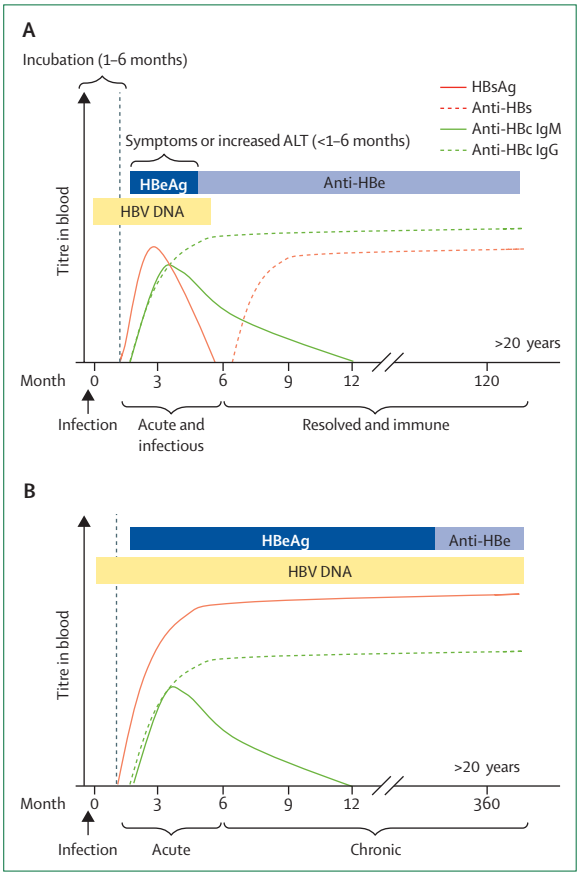



***Figure 3:*** **Serological profile during acute (A) and chronic (B) HBV infection**
During acute infection, there might be a period between the loss of HBsAg and the appearance of anti-HBs of 1–6 months when diagnosis has to rely on IgM anti-HBc. Chronic infection is defined as persistence of HBsAg for more than 6 months. Anti-HBc=hepatitis B core antibody. Anti-HBe=hepatitis B e antibody. ALT=alanine aminotransferase. HBeAG=hepatitis B e-antigen. HBsAg=hepatitis B virus surface antigen. HBV=hepatitis B virus.

## Diagnosis

The incubation period of HBV ranges from 1–6 months. Clinical manifestation of acute infection varies from asymptomatic (approximately 70%), to symptomatic hepatitis presenting with non-specific symptoms, such as fatigue, anorexia, nausea, right upper quadrant discomfort, and jaundice (approximately 30%); and fulminant hepatitis (encephalopathy and coagulopathy) in 0·1–1% of immunocompetent adults. Serological testing for HBsAg and IgM anti-HBc is essential in diagnosing acute HBV infection, because clinical symptoms and elevations in liver enzymes cannot differentiate hepatitis B from other types of acute hepatitis. During the early phase, patients have positive HBsAg, IgM anti-HBc and HBeAg, and high HBV DNA levels. During recovery, HBsAg becomes undetectable, and patients seroconvert to anti-HBs, but there can be a period of 1–6 months when neither HBsAg nor anti-HBs is detected, and diagnosis relies on IgM anti-HBc. After recovery, patients remain anti-HBs and IgG anti-HBc positive, HBV DNA is undetectable in circulation but can persist in the liver (figure 3A).

Chronic HBV infection is defined by persistent detection of HBsAg for more than 6 months, along with positive IgG anti-HBc. During the early phase, HBeAg and high HBV DNA levels are detected, although anti-HBe and variable HBV DNA levels are present in later phases (figure 3B).

Concomitant detection of anti-HBs has been reported in less than 10% of HBsAg-positive patients,[51] who should be managed similarly to other HBsAg-positive patients. Some people have isolated IgG anti-HBc; most had chronic HBV infection with spontaneous HBsAg loss (occult HBV) or recovered acute HBV infection with spontaneous anti-HBs loss, particularly in endemic areas and high-risk populations (eg, those with HIV or HCV co-infection). A minority could have false-positive anti-HBc or be in the phase of acute HBV infection when IgM anti-HBc would be positive.

Quantification of serum HBV DNA is the cornerstone in assessing HBV replication status to guide treatment decisions and to assess response. It can also predict risk of cirrhosis and HCC.[52,53] However, HBV DNA levels vary

markedly (<10 IU/mL to >10⁹ IU/mL) during chronic HBV infection and serial assessment is crucial in management and prognostication.

Historically, liver biopsy was used to assess liver disease, but it has been largely replaced by non-invasive tests, such as panels of blood markers and elastography. Low platelet count is an early indicator of cirrhosis. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels indicate hepatic inflammation, with an AST:ALT ratio of more than 1 being a marker of advanced fibrosis or cirrhosis. Among the blood markers, APRI (AST:platelet ratio index) and FIB-4 index (age, AST, ALT, platelets), are widely used.[54] Low APRI and low FIB-4 have excellent performance in ruling out cirrhosis, but high scores have only modest performance in diagnosing cirrhosis. Elastography measures liver stiffness, a fibrosis indicator, and can be accomplished using vibration controlled transient elastography (VCTE), ultrasound shear wave, or MRI plus low-frequency vibration. Both blood markers and elastography are more accurate in dichotomising advanced fibrosis or cirrhosis from no or moderate fibrosis than in differentiating fibrosis stages, might yield falsely high readings in patients with ALT flares, and cannot reliably assess fibrosis regression during therapy.[55–57] The sensitivity of VCTE varies from 64% to 93%, and specificity varies from 38% to 92%, for predicting at least moderate fibrosis (stage ≥2) depending on patient selection. Sensitivity increases to 70–100% and specificity to 82–92% for predicting cirrhosis (stage 4).[58] In general, elastography is more accurate than blood-based markers, and a two-tier approach using blood tests to rule out advanced fibrosis or cirrhosis, followed by elastography in the remainder who do not have low scores to identify those with advanced fibrosis or cirrhosis, has been proposed to decrease the percentage of patients who have scores between low cutoff and high cutoff with indeterminate fibrosis stage.[59]

Recently, three additional HBV tests have emerged; namely, quantification of HBsAg, HBV RNA, and HBcrAg.[7] These tests are not necessary for diagnosis but might help in differentiating CHB phases and predicting clinical outcomes and treatment response. HBsAg levels are higher in HBeAg-positive patients, generally more than 1000 IU/mL, and might vary between 10 IU/mL and more than 1000 IU/mL in HBeAg-negative patients. The main use of HBsAg level in untreated patients is to identify HBeAg-negative inactive carriers with a HBV DNA concentration of less than 2000 IU/mL who have low likelihood of HCC and of transitioning to HBeAg-negative CHB.[61] HBV RNA and HBcrAg are more reliable serum markers of cccDNA transcription than HBV DNA or HBsAg concentrations (which can be derived from both cccDNA and integrated HBV DNA) and might play a role in assessing response to new antiviral therapies,[60] although tests for HBV RNA and serum hepatitis B core-related antigen (HBcrAg) are still being standardised and not yet commercially available.

## Natural history of chronic HBV infection

The natural course of CHB infection is dynamic, reflecting the balance between host immune control and virus replication. The clinical course can be categorised into five phases on the basis of HBsAg and HBeAg status, HBV DNA and ALT levels; however, not all patients go through all phases, and some revert from a later to an earlier phase (figure 4[10,11,62]). Recent studies showed that HBsAg, HBcrAg, and HBV RNA concentrations also differ across these phases, but they provide minimal incremental value in differentiating these phases.[63]

The first phase, immune-tolerant or HBeAg-positive chronic infection, is defined by HBeAg-positive, very high HBV DNA (usually >7 $\log_{10}$ IU/mL) and HBsAg levels (>3 $\log_{10}$ IU/mL), and persistently normal ALT. Most patients are young Asians infected perinatally via vertical transmission.[24] The term immune-tolerant was based on the combination of normal ALT and high HBV DNA concentrations, suggesting absence of immune-mediated liver injury. Recent studies showed that although HBV-specific immune response in immune-tolerant patients is weak, it is not substantially different from that in immune-active patients.[64,65] Despite high HBV DNA levels, prognosis of immune-tolerant patients is favourable, with cumulative 10-year HCC incidence similar to that in inactive carriers.[66,67] One study found that the HCC risk was higher in untreated immune tolerant, than treated, HBeAg-positive patients with CHB, but the median age of immune-tolerant patients was 38 years, and many would have met treatment indications.[68]

Among people with perinatally acquired infection, the transition from the immune-tolerant to immune-active or HBeAg-positive CHB phase usually occurs between the ages of 20 years and 40 years. Patients with immune active, HBeAg-positive CHB have high HBV DNA (5–7 $\log_{10}$ IU/mL) and HBsAg (>3 $\log_{10}$ IU/mL) levels and elevated ALT. Patients in this phase can clear HBeAg with seroconversion to anti-HBe. The estimated annual spontaneous HBeAg seroconversion rate ranges from 2% to 15% with lower rates in people who are male, Asian, younger than 30 years, acquired the infection through vertical transmission, have normal ALT, and an absence of core promoter or precore mutations.[69–72] High ALT is thought to reflect immune-mediated clearance of infected hepatocytes, although not all patients who clear HBeAg have ALT flares. Most ALT flares are asymptomatic, but some can be accompanied by jaundice, and approximately 2–3% by hepatic decompensation (ascites, variceal bleeding, or hepatic encephalopathy).[73] Protracted immune active phase, with or without recurrent flares, increases the risk of cirrhosis and HCC.[74] Patients with late (after age 40 years) compared with people with early (before age 30 years) HBeAg seroconversion have 5·2-fold higher HCC risk.[75]

After HBeAg seroconversion, most patients enter the inactive-carrier or HBeAg-negative chronic infection phase, when they are HBeAg negative, anti-HBe positive,

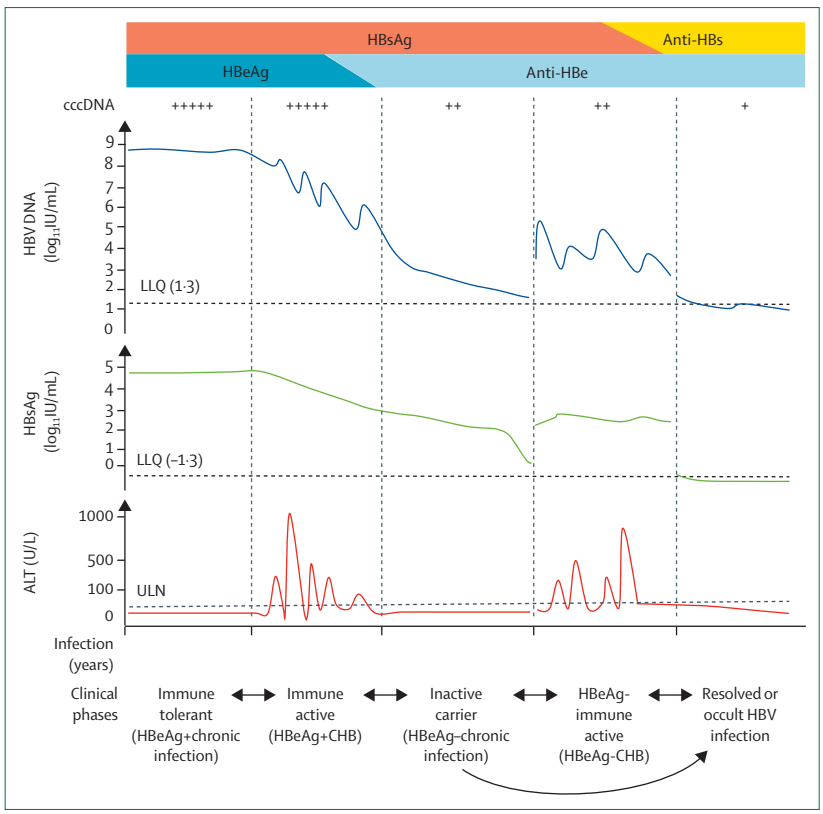



***Figure 4:*** **Phases of chronic hepatitis B virus infection**
During the early phases, patients are HBeAg positive, whereas during later phases patients are HBeAg negative, anti-HBe positive. Some patients eventually become HBsAg negative. Not all patients go through all phases and although most transitions progress from early to late phases, occasionally some patients can revert to early phases. Dotted lines depict LLQ or ULN. ALT=alanine aminotransferase. Anti-HBe=hepatitis B e antibody. Anti-HBs= hepatitis B surface antibody. CHB=chronic hepatitis B. HBeAG=hepatitis B e-antigen. HBsAG=hepatitis B virus surface antigen. cccDNA=covalently closed circular DNA. LLQ=lower limit of quantification. ULN=upper limit of normal.

with persistently normal ALT and usually low HBV DNA (<2000 IU/mL) and HBsAg (<1000 IU/mL) levels. Roughly 5% might revert to HBeAg-positive phase and 10–25% might progress directly or later to HBeAg-negative CHB.[72,76] The prognosis of patients who remain in the inactive carrier phase is favourable, particularly if liver injury before HBeAg clearance was mild. The risk for disease progression is very low (annual incidence less than 0·2% for cirrhosis and less than 0·1% for HCC),[77] and one study showed that HCC incidence, liver-related mortality and all-cause mortality were similar to age-matched and gender-matched controls.[78]

HBeAg-negative, immune-active phase or HBeAg-negative CHB is characterised by absence of HBeAg and, usually, presence of anti-HBe, and fluctuating HBV DNA (usually >2000 IU/mL) and ALT (usually elevated) levels.

Some HBeAg-negative patients have indeterminate characteristics, perhaps transitioning from one phase to another, or having concomitant causes of liver injury, often steatosis, especially those with low HBV DNA and elevated ALT.[79] Most of these patients transition to the inactive carrier phase during follow-up, some remain in the indeterminate zone, and others transition to HBeAg-negative CHB.[80]

Patients who clear HBsAg enter the last phase of CHB (resolved or occult HBV infection), being HBsAg negative and IgG anti-HBc positive, with or without anti-HBs. HBV DNA is usually not detected in blood, but persists in the liver and can reactivate on immune suppression.[20] HBsAg clearance occurs at an average annual rate of 1%, but its incidence is not linear, occurring rarely during the early years and accelerating after age 50 years.[81] Older age than 50 years, male gender, HBeAg negativity, and low HBsAg levels are predictors for spontaneous HBsAg clearance.[82] HBsAg clearance is associated with improved clinical outcomes compared with patients remaining HBsAg-positive and undetectable HBV DNA.[83,84] However, HCC can still develop in patients who clear HBsAg after cirrhosis development or older than 50 years.[85]

Studies in untreated patients estimated that about 25% of men and 8% of women with CHB acquired perinatally will die from HBV-related cirrhosis or HCC.[86] Several host (male gender, older age or longer duration of infection, diabetes, and family history of HCC), virus (persistently HBeAg positive; persistently high HBV DNA; HBV genotype; or HIV, HCV, and HDV co-infection), liver (persistent ALT elevation and concomitant liver diseases), and environmental factors (smoking and alcohol) increase the risks of cirrhosis and HCC.[87–89] The incidence of HCC has been estimated to be 0·02 per 100 person-years in inactive carriers, 0·3 per 100 person-years in patients with CHB without cirrhosis, and 2·2 per 100 person-years in people with compensated cirrhosis.[90] Patients with CHB and concomitant metabolic fatty liver have increased risk of HCC and non-HCC cancer, and all-cause mortality.[91]

## Management

### Acute HBV infection

Most (>95%) immunocompetent adults with acute HBV infection recover spontaneously and do not require specific treatment.[9,10,61] Management of acute HBV infection is focused on supportive care and prevention of HBV transmission to household and sexual contacts.

Antiviral therapy can be considered in people with protracted or severe hepatitis. Although robust data supporting a benefit is lacking, nucleos(t)ide analogue therapy is safe and can decrease the risk of re-infection should liver transplantation be necessary. Differentiation between severe acute hepatitis B and severe exacerbation of previously undiagnosed CHB can be difficult, unless there is a history of recent exposure or evidence of cirrhosis, because IgM anti-HBc can be positive in the latter setting. Nucleos(t)ide analogue therapy should be initiated when in doubt.

### Chronic HBV infection

Evaluation of patients with CHB should include an assessment of HBV replication (HBeAg status and HBV

DNA level); activity (ALT) and stage of liver disease; screening for HIV, HCV, and HDV coinfection; and evaluation for hepatitis A immunity. The course of CHB is characterised by fluctuations in HBV replication and liver inflammatory activity; thus, long-term monitoring is required even in patients with low-level HBV replication, normal ALT, and no cirrhosis (figure 5).

As a consequence of CHB, HBV-related HCC is often diagnosed late and has high mortality. Many models have been developed to predict HCC risk to guide treatment decisions and assess need for surveillance. Most models in untreated Asian patients comprise age, cirrhosis, and HBV DNA level with good to excellent accuracies for HCC prediction over 5–10 years.[92] HCC surveillance with ultrasonography and optional alpha-fetoprotein every 6 months should be conducted in patients with increased HCC risk, including people with cirrhosis, family history of HCC, Asian men younger than 40 years, Asian women older than 50 years, and African men younger than 40 years.[10,11,62] Race-based recommendations for HCC surveillance stem from data showing higher incidence and earlier age at occurrence of HCC in Asian and African patients, which is likely related to earlier age at infection, although other factors, such as HBV genotypes or environmental carcinogens, could also contribute.[93,94] Since alcohol and smoking are associated with increased risk of HCC and concomitant metabolic fatty liver has been shown to accelerate progression to cirrhosis,[95,96] patients should be counselled to limit alcohol intake, avoid smoking, and to maintain healthy diet and exercise regularly.

## Treatment

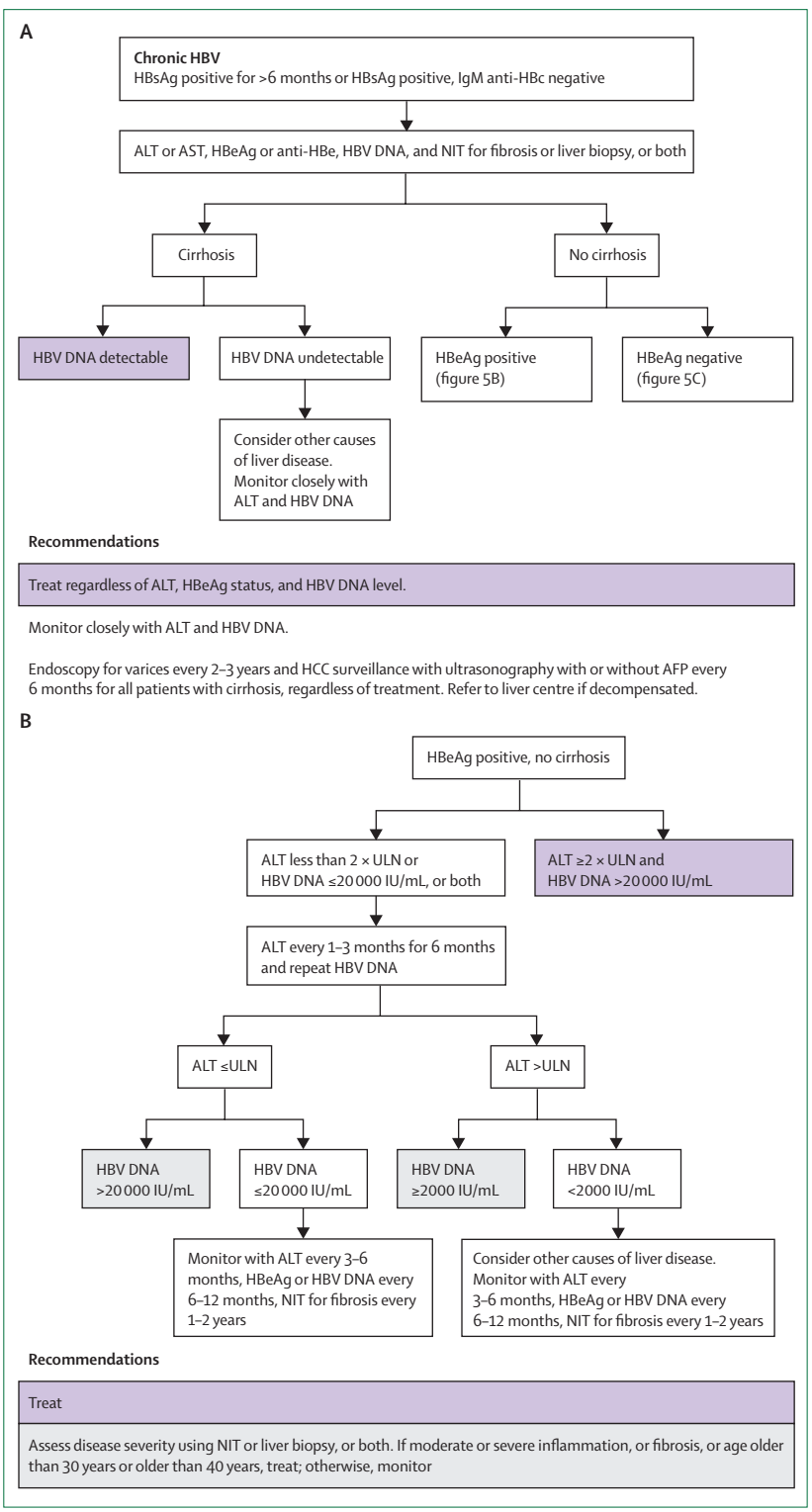
### Goals of treatment

The goal of treatment is to prevent progression to cirrhosis, liver failure, and HCC. Response to treatment is assessed using surrogate measures: biochemical (ALT normalisation), virological (undetectable HBV DNA), and serological (HBeAg to anti-HBe seroconversion in HBeAg-positive patients, and HBsAg to anti-HBs seroconversion). Sustained virological response has been shown to decrease liver inflammation, decrease risk of cirrhosis and HCC, and reverse fibrosis even in patients with established cirrhosis.[10,11,62]

### Indications for treatment

Indications for antiviral treatment are the same for children and adults, and include all patients with cirrhosis and detectable HBV DNA regardless of HBeAg status or ALT level, acute liver failure, or severe exacerbations of CHB (figure 5A). Among patients without cirrhosis, treatment is recommended for those with HBeAg-positive or HBeAg-negative CHB—the second and fourth immune-active phases of CHB (figure 5B and figure 5C).[10,11,62] Patients with a family history of HCC have increased risk of HCC[97] and could be considered for treatment even if HBV DNA or ALT levels are low or normal.[10,11,62]

Treatment is not recommended for patients in the immune tolerant (HBeAg-positive chronic infection) phase, except for those older than 30 or 40 years

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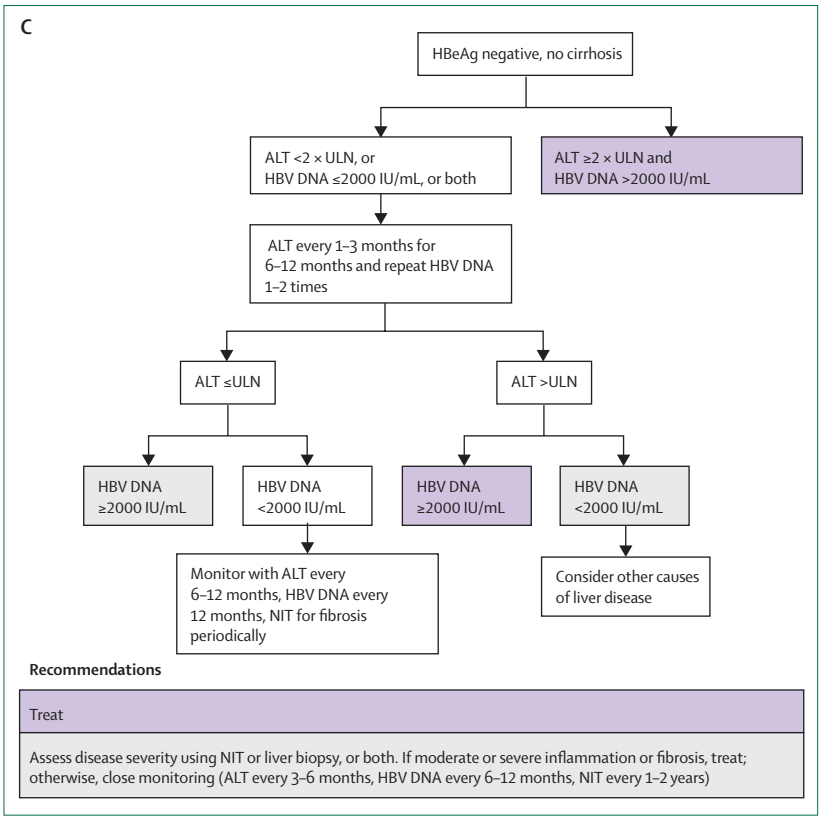


***Figure 5:*** **Monitoring and decisions on treatment for patients with chronic HBV infection in relation to presence of cirrhosis and HBeAg status**

(A) For patients with cirrhosis, most guidelines,[10,11] recommend treatment for patients with decompensated or compensated cirrhosis if HBV DNA is detectable regardless of HBeAg status and ALT levels. (B) For HBeAg-positive patients without cirrhosis, all guidelines[10,11,62] recommend treatment for patients with ALT ≥2 x ULN and HBV DNA >20 000 IU/mL; ALT >ULN and HBV DNA ≥2000 IU/mL with at least moderate inflammation (Metavir activity grade 2–3, range 0–3) or fibrosis (Metavir fibrosis stage ≥2, range 0–4), or both; and ALT ≤ULN and HBV DNA >20 000 IU/mL who are older than 30 years[11] or 40 years.[10] (C) For HBeAg-negative patients without cirrhosis, all guidelines[10,11,62] recommend treatment for patients with ALT ≥2 x ULN and HBV DNA >2000 IU/mL; and HBV DNA ≥2000 IU/mL and at least moderate inflammation or fibrosis, or both, regardless of ALT. For patients with HBV DNA <2000 IU/mL, treatment is recommended only if ALT is persistently >ULN or there is at least moderate inflammation or fibrosis, or both, and other causes of liver disease have been excluded. Patients who do not meet treatment indications should be regularly tested for ALT, HBV DNA, and liver fibrosis. Frequency of monitoring, particularly testing for HBV DNA and liver fibrosis, might vary depending on availability of resources. NIT can be used in place of liver histology to assess stage of liver fibrosis. Patients with cirrhosis and those with increased risk for HCC should undergo surveillance with ultrasonography with or without AFP every 6 months. AFP=alphafetoprotein. ALT=alanine aminotransferase. HCC=hepatocellular carcinoma. HBV=hepatitis B virus. HBeAg=hepatitis B e-antigen. HBsAg=hepatitis B surface antigen. NIT=noninvasive tests. ULN=upper limit of normal. Adapted from Terrault and colleagues,[10] by permission of Wiley.

(figure 4).[10,11,98] Treatment is also not recommended for patients in the inactive carrier phase (HBeAg-negative chronic infection; figure 4). However, treatment can be warranted for patients with significant liver fibrosis (stage ≥2) and close monitoring is recommended in patients with HBsAg of more than 1000 IU/mL. Patients who do not meet treatment criteria must be monitored, such that treatment can be initiated when HBV replication or liver inflammation becomes active (figure 5).

## Current treatments

Currently available treatments include pegylated interferon alfa and nucleos(t)ide analogues (table).[99–102] Pegylated interferon alfa has modest antiviral activity, but can enhance degradation of cccDNA and immune response against HBV. Nucleos(t)ide analogues inhibit reverse transcription of pregenomic RNA to HBV DNA, but have no direct effect on cccDNA, and viral relapse is almost universal when treatment is stopped. Current treatments are effective in suppressing HBV replication, decreasing liver inflammation and fibrosis and risk of cirrhosis and HCC but HBsAg loss rarely occurs and HCC risk remains albeit at lower rates.[10]

### *Pegylated interferon alfa*

Pegylated interferon alfa is administered as 180 µ once a week (pegylated interferon alfa 2a subcutaneous injections) for 48 weeks in both HBeAg-positive and HBeAg-negative patients with CHB. Although only about 30% of patients achieve HBeAg clearance and 3·7% HBsAg clearance within 6 months after treatment, increasing rates might be observed during long-term follow-up (table).[103–105] Pegylated interferon alfa is associated with many side-effects including influenza-like symptoms that are universal during the first 1–2 weeks, neutropenia, thrombocytopenia, and depression, and less commonly exacerbation or unmasking of autoimmune illnesses. Moreover, it can induce hepatitis flares, which can be severe and result in hepatic decompensation.[106] Pegylated interferon alfa is contraindicated in patients with pregnancy, decompensated cirrhosis, autoimmune illnesses, or depression, and should be used with caution in patients with compensated cirrhosis. Given its side-effects, pegylated interferon alfa is less commonly used than nucleos(t)ide analogues except in young HBeAg-positive patients who do not want to embark on a long or indefinite treatment course, particularly if they have genotype A infection.

### *Nucleos(t)ide analogues*

Six nucleos(t)ide analogues have been approved for oral use. Entecavir, TDF, and tenofovir alafenamide are preferred, because of their potent antiviral activity and low risk of viral resistance compared with the earlier nucleos(t)ide analogues: lamivudine, adefovir, and telbivudine. TDF or tenofovir alafenamide is preferred in patients with previous exposure to lamivudine or telbivudine, although entecavir or tenofovir alafenamide is preferred in patients with risk factors for renal impairment or osteoporosis. Some studies suggest that compared with entecavir, TDF is more efficacious in decreasing HCC incidence; however, these studies might be confounded.[107] Only 27–38% of HBeAg-positive patients clear HBeAg and only 3–5% of patients clear HBsAg after 10–year treatment (table).[98,100–102] Thus, nucleos(t)ide analogues are usually administered orally for many years and often for life, particularly in patients with cirrhosis, to prevent severe hepatitis flares due to viral relapse.

In patients without cirrhosis, nucleos(t)ide analogues can be discontinued in HBeAg-positive patients who

| | Pegylated interferon alfa 48–52 weeks (post therapy) | | Entecavir (on therapy) | | Tenofovir disoproxil fumarate (on therapy) | | Tenofovir alafenamide (on therapy) | |
|---|---|---|---|---|---|---|---|---|
| | 6 months | 3 years | 1 year | 7–10 years* | 1 year | 10 years† | 1 year | 5 years‡ |
| **HBeAg positive** | | | | | | | | |
| ALT normalisation | 32–41% | 57% | 68% | 78–79% | 68% | 78% | 72% | 76% |
| HBeAg seroconversion | 29–32% | 35% | 21% | 38% | 21% | 27% | 10% | 27% |
| HBV DNA undetectable§ | 7–14% | 25% | 67% | 80–97% | 76% | 98% | 64% | 93% |
| HBsAg clearance | 3–7% | 11% | 2% | 4% | 3% | 5% | 1% | 1% |
| **HBeAg negative** | | | | | | | | |
| ALT normalisation | 59% | 31% | 78% | 78–79% | 76% | 83% | 83% | 76% |
| HBV DNA undetectable§ | 19% | 23–26% | 90% | 80–97% | 93% | 100% | 94% | 93% |
| HBsAg clearance | 4% | 8–14% | 0 | 4% | 0 | 3% | 0 | 1% |

HBV definition: HBeAG=hepatitis B e-antigen. HBsAG=hepatitis B virus surface antigen. Results from randomised controlled trials or follow-up studies of these trials. Not direct comparison. Response rates reported during long-term follow-up are imprecise because not all patients in the original cohorts were followed up and some studies reported combined results for HBeAg-positive and HBeAg-negative patients. ALT=alanine aminotransferase. HBV=hepatitis B virus. *Entecavir year 7–10 response rates were mainly based on one study in Japan and included both HBeAg-positive and HBeAg-negative patients; HBeAg clearance, but not HBeAg seroconversion rates, were reported.[99] Another study from China provided combined virological response rates at year-10 in HBeAg-positive and HBeAg-negative patients.[100] †Tenofovir disoproxil fumarate year 10 response rates were based on follow-up of phase 3 trial cohort, but only 32% completed year-10 follow-up.[101] ‡Tenofovir alafenamide year-5 response rates were based on follow-up of phase 3 trial cohorts and included both HBeAg-positive and HBeAg-negative patients.[102] §Lower limit of detection of HBV DNA assays varied from 10 IU/mL to 80 IU/mL for studies on entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide. HBV DNA less than 2000 IU/mL was used as definition of virological response in pegylated interferon alfa trials.

*Table:* **Efficacy of approved hepatitis B therapies in patients with HBeAg-positive or HBeAg-negative chronic hepatitis B[99-102]**

seroconverted to anti-HBe and completed an additional 12 months consolidation therapy.[10,11,62] Approximately 40% of patients will remain in the inactive carrier phase, although others might revert to HBeAg-positive or progress to HBeAg-negative CHB. Nucleos(t)ide analogues can be discontinued in HBeAg-negative patients who cleared HBsAg. Given the rarity of HBsAg clearance and the observation that, whereas viral relapse is universal when nucleos(t)ide analogue is stopped, only 40–60% experience clinical relapse within 2 years of stopping nucleos(t)ide analogue,[108] the Asian Pacific Association for the Study of the Liver and the European Association for the Study of the Liver guidelines recommend that nucleos(t)ide analogues can be stopped in selected HBeAg-negative patients who have completed more than 2–3 years of treatment with undetectable HBV DNA and agree to close follow-up.[11,62,109] Paradoxically, patients who stopped nucleos(t)ide analogues had higher HBsAg clearance rates than patients who continued nucleos(t)ide analogues.[110,111] Two randomised controlled trials in Europe (>85% White) of HBeAg-negative patients confirmed higher HBsAg clearance rates among patients who stopped, versus patients who continued nucleos(t)ide analogues,[112,113] but a similarly designed trial in Canada (96% Asian) showed no benefit in increasing HBsAg clearance.[114] The difference in outcomes might be due to differences in race, HBV genotypes, or duration of HBV infection. A retrospective study including patients from North America, Europe, and Asia found that non-Asian people had 8·3-fold higher odds of HBsAg clearance compared with Asians who stopped nucleos(t)ide analogues. Low HBsAg level at nucleos(t)ide analogue withdrawal is the strongest predictor of HBsAg clearance.[115] Some studies found that compared with entecavir, relapse occurs earlier after TDF withdrawal, but the overall relapse rates were similar.[116,117] Despite careful patient selection and exclusion of patients with cirrhosis, severe hepatitis flares and decompensations have been reported occasionally,[111] and the decision to withdraw nucleos(t)ide analogues should be made jointly between patients and physicians.

Nucleos(t)ide analogues have excellent long-term safety. TDF is associated with a small risk of renal impairment and decreased bone mineral density. Tenofovir alafenamide, a new formulation of tenofovir, has improved renal and bone safety.[118] Nucleos(t)ide analogues are dosed daily in patients with normal renal function. Entecavir and TDF are dosed at reduced frequencies if creatinine clearance is less than 50 mL/min. Tenofovir alafenamide does not require dose adjustment in patients with creatinine clearance of at least 15 mL/min and should not be used in patients with creatinine clearance of less than 15 mL/min who are not on haemodialysis. For patients on haemodialysis, TAF should be dosed after each dialysis. Viral resistance is manifested as virological breakthrough defined as more than 1 log increase in HBV DNA levels during treatment and can be accompanied by ALT increase and even hepatic failure. Resistance to entecavir after 5 years is observed in approximately 1% of lamivudine-naive and in up to 50% of lamivudine-experienced patients.[119] Resistance was not observed in patients receiving TDF for up to 10 years[100] or tenofovir alafenamide for up to 3 years.[120] TDF and tenofovir alafenamide are active against lamivudine-resistant, telbivudine-resistant, entecavir-resistant, and adefovir-resistant HBV. TDF monotherapy has similar efficacy in suppressing these resistance variants as combination of TDF and entecavir or emtricitabine.[121,122]

*Factors associated with response*

High pretreatment ALT and low pretreatment HBV DNA are associated with high rates of HBeAg and HBsAg responses to both pegylated interferon alfa and nucleos(t)ide analogues.[123–125] HBV genotype A is associated with the highest rate of HBeAg and HBsAg clearance after pegylated interferon alfa therapy,[27] but HBV genotype is not predictive of response to nucleos(t)ide analogues.

## HBV reactivation and HBV–HIV coinfection

Patients with chronic or past HBV infection receiving immunosuppressive or immunomodulatory therapies are at risk of HBV reactivation, which could lead to potentially fatal hepatitis flares. All patients who will be initiating these therapies should be screened for HBsAg and IgG anti-HBc. HBsAg-positive and HBsAg-negative, anti-HBc-positive patients who require therapies with moderate-to-high HBV reactivation risk should receive nucleos(t)ide analogue prophylaxis before or simultaneously with the start of these therapies; nucleos(t)ide analogues should be continued for 6–12 months after completion of most such therapies,[10,11,20,62,126] and for at least 12 months after completion of B-cell depleting therapies due to their prolonged immunosuppressive effects. Patients who require therapies with low HBV reactivation risk can be monitored with ALT or HBV DNA in HBsAg positive patients and with ALT, HBsAg or HBV DNA in HBsAg negative, anti-HBc positive patients with initiation of nucleos(t)ide analogue at the first sign of HBV reactivation.

All patients coinfected with HBV and HIV should receive combination antiviral therapy that has activity against both viruses, regardless of HBV DNA and ALT levels, and any changes in antiretroviral regimen must ensure that the new regimen is effective in inhibiting both viruses.[10,11,62,127]

## New therapies in development

Nucleos(t)ide analogues are safe and effective in suppressing HBV replication but rarely clear HBsAg, and long-term treatment is needed to prevent relapse. Thus, several classes of direct-acting antivirals and immunomodulatory therapies are in development (figure 2) with the goal of functional cure defined as sustained undetectable HBsAg and HBV DNA after a finite course of treatment.[128] HBsAg clearance is associated with lower HCC risk compared with HBV DNA suppression without HBsAg clearance, and minimal risk of relapse after treatment discontinuation.[129] There are no data from phase 3 trials for these new drugs, and their safety, clinical efficacy, and optimal dose regimens are being studied.

Entry inhibitors such as bulevirtide block HBV entry into hepatocytes. Bulevirtide alone and in combination with pegylated interferon alfa has shown promise in chronic HDV but data in chronic HBV mono-infection are scarce.[130,131] Capsid-assembly modulators can act at multiple steps in the HBV lifecycle, including assembly of aberrant or empty capsids (thereby inhibiting HBV DNA replication) and interference with disassembly of incoming virions and intracellular recycling of capsids (thereby inhibiting cccDNA establishment and replenishment). Combination of capsid-assembly modulators and nucleos(t)ide analogues has an additive effect in decreasing HBV DNA and HBV RNA levels, but it has a minimal effect on HBeAg and HBsAg concentrations.[132,133]

Translation inhibitors silence HBV RNA, thereby decreasing viral antigen production. Translation inhibition can be achieved using small interfering RNAs or antisense oligonucleotides. Both approaches can decrease HBsAg levels, with effects lasting more than 6 months after completion of dosing, but sustained HBsAg clearance is rare.[134,135,136] Upregulation of HBV-specific immune responses has been observed in some patients following decline in HBsAg concentrations.

Nucleic acid polymers in combination with pegylated interferon alfa have resulted in sustained HBsAg clearance in one small study, but most patients had marked ALT flares.[137]

Previous approaches to stimulate or remove blockade of HBV-specific immune responses have not been successful.[138–140] Recent studies suggest that therapeutic vaccines expressing antigens from HBV core or polymerase regions might be more effective than those from the surface region and addition of immune checkpoint inhibitors might augment the effect of these vaccines.[141,142]

Multiple steps need to be satisfied to achieve the goal of functional HBV cure: complete suppression of HBV DNA replication, inhibition of HBsAg production, and restoration of innate and HBV-specific immune response. As such, combination of several classes of drugs will be necessary to achieve this goal in a high percentage of patients. Nucleos(t)ide analogues will remain a backbone in suppressing HBV DNA replication and pegylated interferon alfa could continue to have a role in HBsAg clearance.

## Future directions

HBV infection remains a major global health problem. Although many tools are available, achievement of WHO's goals will require concerted efforts of community health providers, physicians, health authorities, and industry researchers to ensure universal vaccination—in particular birth-dose vaccination—is implemented worldwide; increase screening, diagnosis, and linkage to care of those infected; and remove the stigma of HBV infection. Race is a social construct and could reflect unmeasured confounders; however, race in the context of HBV is associated with mode of transmission, age at infection, and genotypes, factors that influence the course of chronic infection and outcomes. Future studies should examine whether social determinants of health, timing of infection, HBV genotypes, or host biology account for the race-specific observations.

**Contributors**
ASFL conceptualised the study concept. W-JJ conducted the literature search. W-JJ, GVP, and ASFL conducted data collection, manuscript writing, revisions, and approved final manuscript.

**Declaration of interests**
W-JJ has served as advisor and lecturer for Bristol Myers Squibb and Gilead; and received grants for research and attendance of meetings from Chang Gung Medical Foundation and National Science Council of Taiwan. GVP has served as advisor and lecturer for Amgen, Gilead, GlaxoSmithKline, Ipsen, Janssen, Novo Nordisk, Roche, and Takeda; received support for attendance of meetings from Gilead Sciences, Ipsen, Janssen, Merck Sharp & Dohme, Novo Nordisk, Roche, and Takeda; and received research grants from Gilead. ASFL has received research grants from Bristol Myers Squibb, Gilead, and TARGET Pharma, and royalties from Wolters Kluwer (UpToDate) and Wiley (textbooks); and served as advisor and consultant for Ambys, Amgen, Arbutus, Chroma, CLEAR-B, Eli Lilly, Enanta, Enochian, GlaxoSmithKline, GNI, Huahui, Janssen, TARGET, and Virion.

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**References**

1 WHO. Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis. 2016. https://apps.who.int/iris/handle/10665/246177 (accessed Sept 23, 2022).
2 WHO. Hepatitis B. 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed March 25, 2022).
3 GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol* 2022; **7:** 796–829.
4 Thomas DL. Global elimination of chronic hepatitis. *N Engl J Med* 2019; **380:** 2041–50.
5 Iqbal K, Klevens RM, Kainer MA, et al. Epidemiology of acute hepatitis B in the United States from population-based surveillance, 2006–2011. *Clin Infect Dis* 2015; **61:** 584–92.
6 Ott JJ, Horn J, Krause G, Mikolajczyk RT. Time trends of chronic HBV infection over prior decades—a global analysis. *J Hepatol* 2017; **66:** 48–54.
7 Wong RJ, Brosgart CL, Welch S, et al. An updated assessment of chronic hepatitis B prevalence among foreign-born persons living in the United States. *Hepatology* 2021; **74:** 607–26.
8 Choi HSJ, Brouwer WP, Zanjir WMR, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. *Hepatology* 2020; **71:** 539–48.
9 Wong GL, Wong VW, Yuen BW, et al. An aging population of chronic hepatitis B with increasing comorbidities: a territory-wide study from 2000 to 2017. *Hepatology* 2020; **71:** 444–55.
10 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:** 1560–99.
11 Lampertico P, Agarwal K, Berg T, et al. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370–98.
12 Zhou M, Li L, Han L, Sun F, Yi N. Breast-feeding is not a risk factor of mother-to-child transmission of hepatitis B virus. *Int J Gen Med* 2021; **14:** 1819–27.
13 Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995; **20:** 992–1000.
14 Papatheodoridi M, Papatheodoridis GV, Valenti L. Is hepatitis delta underestimated? *Liver Int* 2021; **41** (suppl 1)**:** 38–44.
15 WHO. Global hepatitis report, 2017. Geneva, Switzerland: World Health Organization 2017.
16 Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management. *Ann Gastroenterol* 2015; **28:** 221–28.
17 Weldemhret L. Epidemiology and challenges of HBV/HIV co-infection amongst HIV-infected patients in endemic areas: review. *HIV AIDS* 2021; **13:** 485–90.
18 Li W, Urban S. Entry of hepatitis B and hepatitis D virus into hepatocytes: basic insights and clinical implications. *J Hepatol* 2016; **64** (suppl)**:** S32–40.
19 Martinez MG, Boyd A, Combe E, Testoni B, Zoulim F. Covalently closed circular DNA: the ultimate therapeutic target for curing HBV infections. *J Hepatol* 2021; **75:** 706–17.
20 Raimondo G, Locarnini S, Pollicino T, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. *J Hepatol* 2019; **71:** 397–408.
21 Wooddell CI, Yuen MF, Chan HL, et al. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg. *Sci Transl Med* 2017; **9:** eaan0241.
22 Bousali M, Papatheodoridis G, Paraskevis D, Karamitros T. Hepatitis B virus DNA integration, chronic infections and hepatocellular carcinoma. *Microorganisms* 2021; **9:** 1787.
23 Liu CJ, Kao JH. Global perspective on the natural history of chronic hepatitis B: role of hepatitis B virus genotypes A to J. *Semin Liver Dis* 2013; **33:** 97–102.
24 Ghany MG, Perrillo R, Li R, et al. Characteristics of adults in the hepatitis B research network in North America reflect their country of origin and hepatitis B virus genotype. *Clin Gastroenterol Hepatol* 2015; **13:** 183–92.
25 Lin CL, Kao JH. Natural history of acute and chronic hepatitis B: the role of HBV genotypes and mutants. *Best Pract Res Clin Gastroenterol* 2017; **31:** 249–55.
26 Viganò M, Grossi G, Loglio A, Lampertico P. Treatment of hepatitis B: is there still a role for interferon? *Liver Int* 2018; **38** (suppl 1)**:** 79–83.
27 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:** 459–67.
28 Chan HL, Hussain M, Lok AS. Different hepatitis B virus genotypes are associated with different mutations in the core promoter and precore regions during hepatitis B e antigen seroconversion. *Hepatology* 1999; **29:** 976–84.
29 Lau DTY, Ganova-Raeva L, Wang J, et al. Precore and basal core promoter hepatitis B virus (HBV) variants are present from a young age and differ across HBV genotypes. *Hepatology* 2021; **73:** 1637–51.
30 Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. *J Viral Hepat* 2002; **9:** 52–61.
31 Yang HI, Yeh SH, Chen PJ, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100:** 1134–43.
32 Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. *Nat Rev Immunol* 2022; **22:** 19–32.
33 Fisicaro P, Barili V, Rossi M, et al. Pathogenetic mechanisms of T cell dysfunction in chronic HBV infection and related therapeutic approaches. *Front Immunol* 2020; **11:** 849.
34 Boni C, Laccabue D, Lampertico P, et al. Restored function of HBV-specific T cells after long-term effective therapy with nucleos(t)ide analogues. *Gastroenterology* 2012; **43:** 963–73.e9.
35 Vanwolleghem T, Groothuismink ZMA, Kreefft K, Hung M, Novikov N, Boonstra A. Hepatitis B core-specific memory B cell responses associate with clinical parameters in patients with chronic HBV. *J Hepatol* 2020; **73:** 52–61.
36 WHO. Hepatitis B vaccines: WHO position paper—July 2017. *Wkly Epidemiol Rec* 2017; **92:** 369–92.
37 CDC. Viral hepatitis—hepatitis B Information. October 12, 2021. https://www.cdc.gov/hepatitis/hbv/ (accessed March 25, 2022).
38 Pattyn J, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B vaccines. *J Infect Dis* 2021; **224** (suppl 2)**:** S343–51.
39 Muhoza P, Danovaro-Holliday MC, Diallo MS, et al. Routine vaccination coverage—worldwide, 2020. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 1495–500.
40 Chang MH, You SL, Chen CJ, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 2016; **151:** 472–480.e1.
41 Centers for Disease Control and Prevention. Immunization schedule-recommendations for ages 19 years or older, United States. February 17, 2022. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html (accessed March 25, 2022).
42 Are booster immunisations needed for lifelong hepatitis B immunity? European Consensus Group on Hepatitis B Immunity. *Lancet* 2000; **355:** 561–65.

43 Dynavax Technologies Corporation. Heplisav-B package insert. May, 2022. https://www.heplisavb.com/assets/pdfs/HEPLISAV-B-Prescribing-Information.pdf (accessed March 25, 2022).

44 European Medicines Agency. Heplisav B. https://www.ema.europa.eu/en/medicines/human/EPAR/heplisav-b (accessed March 25, 2022).

45 Jackson S, Lentino J, Kopp J, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. *Vaccine* 2018; **36:** 668–74.

46 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:** 455–58.

47 VBI Vaccines Inc. Package insert—PREHEVBRIO. 13 December, 2021. https://www.fda.gov/vaccines-blood-biologics/prehevbrio (accessed March 25, 2022).

48 Vesikari T, Langley JM, Segall N, et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. *Lancet Infect Dis* 2021; **21:** 1271–81.

49 Vesikari T, Finn A, van Damme P, et al. Immunogenicity and safety of a 3-antigen hepatitis B vaccine vs a single-antigen hepatitis B vaccine: a phase 3 randomized clinical trial. *JAMA Netw Open* 2021; **4:** e2128652.

50 Nelson NP, Jamieson DJ, Murphy TV. Prevention of Perinatal Hepatitis B Virus Transmission. *J Pediatric Infect Dis Soc* 2014; **3:** (suppl 1): S7–12.

51 Lee WM, King WC, Schwarz KB, Rule J, Lok ASF. Prevalence and clinical features of patients with concurrent HBsAg and anti-HBs: evaluation of the hepatitis B research network cohort. *J Viral Hepat* 2020; **27:** 922–31.

52 Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130:** 678–86.

53 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.

54 Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. *Hepatology* 2015; **61:** 292–302.

55 Ji D, Chen Y, Shang Q, et al. Unreliable estimation of fibrosis regression during treatment by liver stiffness measurement in patients with chronic hepatitis B. *Am J Gastroenterol* 2021; **116:** 1676–85.

56 Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. *JHEP Rep* 2020; **2:** 100067.

57 Chan HL, Wong GL, Choi PC, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2009; **16:** 36–44.

58 Branchi F, Conti CB, Baccarin A, Lampertico P, Conte D, Fraquelli M. Non-invasive assessment of liver fibrosis in chronic hepatitis B. *World J Gastroenterol* 2014; **20:** 14568–80.

59 Boursier J, Vergniol J, Sawadogo A, et al. The combination of a blood test and Fibroscan improves the non-invasive diagnosis of liver fibrosis. *Liver Int* 2009; **29:** 1507–15.

60 Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. *Gastroenterology* 2019; **156:** 355–68.

61 Liaw YF. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. *Nat Rev Gastroenterol Hepatol* 2019; **16:** 631–41.

62 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.

63 Ghany MG, King WC, Lisker-Melman M, et al. Comparison of HBV RNA and hepatitis B core related antigen with conventional HBV markers among untreated adults with chronic hepatitis B in North America. *Hepatology* 2021; **74:** 2395–409.

64 Kennedy PTF, Sandalova E, Jo J, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. *Gastroenterology* 2012; **143:** 637–45.

65 Park JJ, Wong DK, Wahed AS, et al. Hepatitis B virus-specific and global T-cell dysfunction in chronic hepatitis B. *Gastroenterology* 2016; **150:** 684–95.e5.

66 Lee HA, Lee HW, Kim IH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. *Aliment Pharmacol Ther* 2020; **52:** 196–204.

67 Lee HW, Kim EH, Lee J, et al. Natural history of untreated HBeAg-positive chronic HBV infection with persistently elevated HBV DNA but normal alanine aminotransferase. *Clin Transl Gastroenterol* 2020; **11:** e00140.

68 Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. *Gut* 2018; **67:** 945–52.

69 Liaw YF, Chu CM, Huang MJ, Sheen IS, Yang CY, Lin DY. Determinants for hepatitis B e antigen clearance in chronic type B hepatitis. *Liver* 1984; **4:** 301–06.

70 Marx G, Martin SR, Chicoine JF, Alvarez F. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. *J Infect Dis* 2002; **186:** 295–301.

71 Yang HI, Hung HL, Lee MH, et al. Incidence and determinants of spontaneous seroclearance of hepatitis B e antigen and DNA in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2012; **10:** 527–34.

72 Lee WM, King WC, Janssen HLA, et al. Hepatitis B e antigen loss in adults and children with chronic hepatitis B living in North America: a prospective cohort study. *J Viral Hepat* 2021; **28:** 1526–38.

73 Sheen IS, Liaw YF, Tai DI, Chu CM. Hepatic decompensation associated with hepatitis B e antigen clearance in chronic type B hepatitis. *Gastroenterology* 1985; **89:** 732–35.

74 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:** 493–96.

75 Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. *Hepatology* 2010; **51:** 435–44.

76 Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35:** 1522–27.

77 Tai DI, Lin SM, Sheen IS, Chu CM, Lin DY, Liaw YF. Long-term outcome of hepatitis B e antigen-negative hepatitis B surface antigen carriers in relation to changes of alanine aminotransferase levels over time. *Hepatology* 2009; **49:** 1859–67.

78 Kumada T, Toyoda H, Yasuda S, Ito T, Tanaka J. Mortality of inactive hepatitis B virus carriers in Japan is similar to that of the general population. *Hepatol Res* 2022; **52:** 81–92.

79 Di Bisceglie AM, Lombardero M, Teckman J, et al. Determination of hepatitis B phenotype using biochemical and serological markers. *J Viral Hepat* 2017; **24:** 320–29.

80 Yapali S, Talaat N, Fontana RJ, Oberhelman K, Lok AS. Outcomes of patients with chronic hepatitis B who do not meet criteria for antiviral treatment at presentation. *Clin Gastroenterol Hepatol* 2015; **13:** 193–201.

81 Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. *Hepatology* 2007; **45:** 1187–92.

82 Yeo YH, Tseng TC, Hosaka T, et al. Incidence, factors, and patient-level data for spontaneous HBsAg seroclearance: a cohort study of 11,264 patients. *Clin Transl Gastroenterol* 2020; **11:** e00196.

83 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:** 463–72.

84 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:** 361–70.

85 Tong MJ, Nguyen MO, Tong LT, Blatt LM. Development of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. *Clin Gastroenterol Hepatol* 2009; **7:** 889–93.

86 Huang YT, Jen CL, Yang HI, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. *J Clin Oncol* 2011; **29:** 3643–50.

87 Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol* 2011; **26:** 628–38.

88 Chen CF, Lee WC, Yang HI, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. *Gastroenterology* 2011; **141:** 1240–48.

89 Sinn DH, Kang D, Guallar E, et al. Alcohol intake and mortality in patients with chronic viral hepatitis: a nationwide cohort study. *Am J Gastroenterol* 2021; **116:** 329–35.

90 El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142:** 1264–73.

91 Lee YB, Moon H, Lee JH, et al. Association of metabolic risk factors with risks of cancer and all-cause mortality in patients with chronic hepatitis B. *Hepatology* 2021; **73:** 2266–77.

92 Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Risk scores for hepatocellular carcinoma in chronic hepatitis B: a promise for precision medicine. *Hepatology* 2020; **72:** 2197–205.

93 Duberg AS, Lybeck C, Falt A, Montgomery S, Aleman S. Chronic hepatitis B virus infection and the risk of hepatocellular carcinoma by age and country of origin in people living in Sweden: a national register study. *Hepatol Commun* 2022; published online May 3. https://doi.org/10.1002/hep4.1974.

94 Kennedy K, Graham SM, Arora N, Shuhart MC, Kim HN. Hepatocellular carcinoma among US and non-US-born patients with chronic hepatitis B: risk factors and age at diagnosis. *PLoS One* 2018; **13:** e0204031.

95 Yang M, Wei L. Impact of NAFLD on the outcome of patients with chronic hepatitis B in Asia. *Liver Int* 2022; **42:** 1981–90.

96 Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol* 2013; **177:** 333–42.

97 Loomba R, Liu J, Yang HI, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2013; **11**: 1636-45 e1-3.

98 Jeng WJ, Lok AS. Should treatment indications for chronic hepatitis B be expanded? *Clin Gastroenterol Hepatol* 2021; **19:** 2006–14.

99 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: 182–93.

100 Hou JL, Zhao W, Lee C, et al. Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a randomized trial in 24 countries. *Clin Gastroenterol Hepatol* 2020; 18: 457–67.e21.

101 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: 1868–75.

102 Chan HLY, Ferret MAB, Agarwal K, et al. Maintenance of high levels of viral suppression and improved safety profile of tenofovir alafenamide (TAF) relative to tenofovir disoproxil fumarate (TDF) in chronic hepatitis B patients treated for 5 years in 2 ongoing phase 3 studies. *Hepatology* 2020; 72: 490A (abstract).

103 Lee SK, Kwon JH, Lee SW, et al. Sustained off therapy response after peglyated interferon favours functional cure and no disease progression in chronic hepatitis B. *Liver Int* 2021; **41:** 288–94.

104 Sun J, Ding H, Chen G, et al. Sustained serological and complete responses in HBeAg-positive patients treated with peginterferon alfa-2b: a 6-year long-term follow-up of a multicenter, randomized, controlled trial in China. *BMC Gastroenterol* 2019; **19:** 65.

105 Marcellin P, Bonino F, Yurdaydin C, et al. Hepatitis B surface antigen levels: association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients. *Hepatol Int* 2013; **7:** 88–97.

106 Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. *Gastroenterology* 1993; **104:** 1116–21.

107 Tseng CH, Hsu YC, Chen TH, et al. Hepatocellular carcinoma incidence with tenofovir versus entecavir in chronic hepatitis B: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 1039–52.

108 Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. *Hepatology* 2016; **63:** 1481–92.

109 Kao JH, Jeng WJ, Ning Q, et al. APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients. *Hepatol Int* 2021; **15:** 833–51.

110 Chen CH, Hu TH, Wang JH, et al. Comparison of HBsAg changes between HBeAg-negative patients who discontinued or maintained entecavir therapy. *Hepatol Int* 2020; **14:** 317–25.

111 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:** 425–34.

112 Berg T, Simon KG, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients—FINITE study. *J Hepatol* 2017; **67:** 918–24.

113 van Bömmel F, Stein K, Heyne R, et al. Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg negative patients: results of the Stop-NUC trial. *J Hepatol* 2020; **73:** S118–19.

114 Liem KS, Fung S, Wong DK, et al. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). *Gut* 2019; **68:** 2206–13.

115 Sonneveld MJ, Chiu SM, Park JY, et al. Probability of HBsAg loss after nucleo(s)tide analogue withdrawal depends on HBV genotype and viral antigen levels. *J Hepatol* 2022; **76:** 1042–50.

116 Kuo MT, Hu TH, Hung CH, et al. Hepatitis B virus relapse rates in chronic hepatitis B patients who discontinue either entecavir or tenofovir. *Aliment Pharmacol Ther* 2019; **49:** 218–28.

117 Hall SAL, Burns GS, Anagnostou D, et al. Stopping nucleot(s)ide analogues in non-cirrhotic HBeAg-negative chronic hepatitis B patients: HBsAg loss at 96 weeks is associated with low baseline HBsAg levels. *Aliment Pharmacol Ther* 2022; **56:** 310–20.

118 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:** 672–81.

119 Colonno RJ, Rose R, Baldick CJ, et al. Entecavir resistance is rare in nucleoside naïve patients with hepatitis B. *Hepatology* 2006; **44:** 1656–65.

120 Hou J, Ning Q, Duan Z, et al. 3-year Treatment of tenofovir alafenamide *vs.* tenofovir disoproxil fumarate for chronic HBV infection in China. *J Clin Transl Hepatol* 2021; **9:** 324–34.

121 Fung S, Kwan P, Fabri M, et al. Tenofovir disoproxil fumarate (TDF) vs. emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: a 5-year randomised study. *J Hepatol* 2017; **66:** 11–18.

122 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.

123 Peng CW, Jeng WJ, Chien RN, Liaw YF. The impact of hepatitis flare on HBeAg loss was effective mainly in the first year of nucleot(s)ide therapy in chronic hepatitis B. *J Viral Hepat* 2021; **28:** 475–83.

124 Jeng WJ, Chen YC, Chang ML, Liaw YF. α-Fetoprotein level-dependent early hepatitis B surface antigen decline during entecavir therapy in chronic hepatitis B with hepatitis flare. *J Antimicrob Chemother* 2016; **71:** 1601–08.

125 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:** 2002–09.

126 Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014; **11:** 209–19.

127 Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. https://health.gov/healthypeople/tools-action/browse-evidence-based-resources/guidelines-use-antiretroviral-agents-adults-and-adolescents-living-hiv (accessed March 25, 2022).

128 Cornberg M, Lok AS, Terrault NA, et al. Guidance for design and endpoints of clinical trials in chronic hepatitis B—report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. *J Hepatol* 2020; **72:** 539–57.

129 Kim MA, Kim SU, Sinn DH, et al. Discontinuation of nucleos(t)ide analogues is not associated with a higher risk of HBsAg seroreversion after antiviral-induced HBsAg seroclearance: a nationwide multicentre study. *Gut* 2020; **69:** 2214–22.

130 Loglio A, Ferenci P, Uceda Renteria SC, et al. Safety and effectiveness of up to 3 years' bulevirtide monotherapy in patients with HDV-related cirrhosis. *J Hepatol* 2022; **76:** 464–69.

131 Lok AS, Negro F, Asselah T, Farci P, Rizzetto M. Endpoints and new options for treatment of chronic hepatitis D. *Hepatology* 2021; **74:** 3479–85.

132 Taverniti V, Ligat G, Debing Y, Kum DB, Baumert TF, Verrier ER. Capsid assembly modulators as antiviral agents against HBV: molecular mechanisms and clinical perspectives. *J Clin Med* 2022; **11:** 1349.

133 Yuen MF, Agarwal K, Gane EJ, et al. Safety, pharmacokinetics, and antiviral effects of ABI-H0731, a hepatitis B virus core inhibitor: a randomised, placebo-controlled phase 1 trial. *Lancet Gastroenterol Hepatol* 2020; **5:** 152–66.

134 Yuen MF, Heo J, Jang JW, et al. Safety, tolerability and antiviral activity of the antisense oligonucleotide bepirovirsen in patients with chronic hepatitis B: a phase 2 randomized controlled trial. *Nat Med* 2021; **27:** 1725–34.

135 Gane E, Yuen MF, Kim DJ, et al. Clinical study of single-stranded oligonucleotide RO7062931 in healthy volunteers and patients with chronic hepatitis B. *Hepatology* 2021; **74:** 1795–808.

136 Yuen MF, Lim SG, Plesniak R, et al; B-Clear Study Group. Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. *Nat N Engl J Med* 2022; **387:** 1957–1968.

137 Bazinet M, Pântea V, Placinta G, et al. Safety and efficacy of 48 weeks REP 2139 or REP 2165, tenofovir disoproxil, and pegylated interferon alfa-2a in patients with chronic HBV infection naïve to nucleos(t)ide therapy. *Gastroenterology* 2020; **158:** 2180–94.

138 Boni C, Vecchi A, Rossi M, et al. TLR7 Agonist increases responses of hepatitis B virus-specific T cells and natural killer cells in patients with chronic hepatitis B treated with nucleos(t)Ide analogues. *Gastroenterology* 2018; **154:** 1764–77.

139 Janssen HLA, Brunetto MR, Kim YJ, et al. Safety, efficacy and pharmacodynamics of vesatolimod (GS-9620) in virally suppressed patients with chronic hepatitis B. *J Hepatol* 2018; **68:** 431–40.

140 Agarwal K, Ahn SH, Elkhashab M, et al. Safety and efficacy of vesatolimod (GS-9620) in patients with chronic hepatitis B who are not currently on antiviral treatment. *J Viral Hepat* 2018; **25:** 1331–40.

141 Gane E, Verdon DJ, Brooks AE, et al. Anti-PD-1 blockade with nivolumab with and without therapeutic vaccination for virally suppressed chronic hepatitis B: a pilot study. *J Hepatol* 2019; **71:** 900–07.

142 Ma H, Lim TH, Leerapun A, et al. Therapeutic vaccine BRII-179 restores HBV-specific immune responses in patients with chronic HBV in a phase Ib/IIa study. *JHEP Rep* 2021; **3:** 100361