# Hepatitis B virus infection

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**Hepatitis B virus infection is a major public health problem worldwide; roughly 30% of the world's population show serological evidence of current or past infection. Hepatitis B virus is a partly double-stranded DNA virus with several serological markers: HBsAg and anti-HBs, HBeAg and anti-HBe, and anti-HBc IgM and IgG. It is transmitted through contact with infected blood and semen. A safe and effective vaccine has been available since 1981, and, although variable, the implementation of universal vaccination in infants has resulted in a sharp decline in prevalence. Hepatitis B virus is not cytopathic; both liver damage and viral control—and therefore clinical outcome—depend on the complex interplay between virus replication and host immune response. Overall, as much as 40% of men and 15% of women with perinatally acquired hepatitis B virus infection will die of liver cirrhosis or hepatocellular carcinoma. In addition to decreasing hepatic inflammation, long-term antiviral treatment can reverse cirrhosis and reduce hepatocellular carcinoma. Development of new therapies that can improve HBsAg clearance and virological cure is warranted.**

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## Introduction

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. An estimated 2 billion people have been infected, and more than 350 million are chronic carriers of the virus.[1] In the 2010 Global Burden of Disease study,[2] HBV infection ranked in the top health priorities in the world, and was the tenth leading cause of death (786 000 deaths per year). These data have led WHO to include viral hepatitis in its major public health priorities.

Safe and effective prophylactic vaccines and effective antiviral drugs are available to prevent and treat HBV infection, but the global burden will remain high without concerted efforts from governments, health-care providers, and communities to raise awareness and improve access to care.

## Epidemiology

Roughly 30% of the world's population shows serological evidence of current or past HBV infection.[3,4] About half the total liver cancer mortality in 2010 was attributed to HBV infection, and from 1990 to 2010, the worldwide mortality associated with liver cancer increased by 62% and that associated with cirrhosis increased by 29%.[2]

HBV is transmitted through contact with infected blood or semen. Three major modes of transmission prevail. In areas of high endemicity, HBV is transmitted mostly perinatally from infected mothers to neonates. In low endemic areas, sexual transmission is predominant. Risk of infection is higher in people with a high number of sexual partners, men who have sex with men, and people with histories of other sexually transmitted infections. The third major source of infection is unsafe injections, blood transfusions, or dialysis. Although screening of blood products has substantially reduced transfusion-associated HBV infection, infection in this manner is still frequent in developing countries. Other possible sources of HBV include nosocomial infection through contaminated medical, surgical, or dental instruments; needle-stick injuries; and organs donated by HBsAg-positive or HBV-DNA-positive donors. Household or intimate non-sexual contact and living in crowded conditions are also possible risks.

The outcome of acute HBV infection is age dependent. Roughly 95% of neonates, 20–30% of children (aged 1–5 years) and less than 5% of adults develop chronic infection.[5] The implementation of universal HBV vaccination in infants has resulted in a sharp fall in prevalence in many parts of the world (figure 1). However, vaccination coverage varies from 90% in the western Pacific and the Americas to 56% in southeast Asia,[6] and thus the global prevalence of HBV infection also varies widely. 45% of HBV-infected individuals live in highly endemic areas (ie, those with a prevalence ≥8%), which include China, southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon basin.[7] In these areas, most infections occur during infancy or childhood. As a result of universal vaccination of neonates, some highly endemic countries, such as China, now have overall prevalence of 7–8% and are expected to be in the intermediate prevalence category in the near future.

Roughly 43% of HBV-infected people live in regions of intermediate prevalence (2–7%), including south-central and southwest Asia, eastern and southern Europe, Russia, and Central and South America. In these areas, mixed

### Search strategy and selection criteria

We focused on advances in the management of hepatitis B in the past 5 years. We searched the Cochrane Library, PubMed, and Embase with the terms "hepatitis B", "chronic hepatitis B", and "hepatitis B virus", together with "epidemiology", "burden of disease", "immunopathogenesis", "prevention", "vaccination", "natural history", "treatment", "antiviral therapy", and "hepatocellular carcinoma" for articles published in English between Jan 1, 2008, and Dec 31, 2013. Landmark studies published before this date range were also included. We also searched the reference lists of articles identified by this search strategy and included any papers that we judged relevant. We excluded abstracts and studies with few patients.

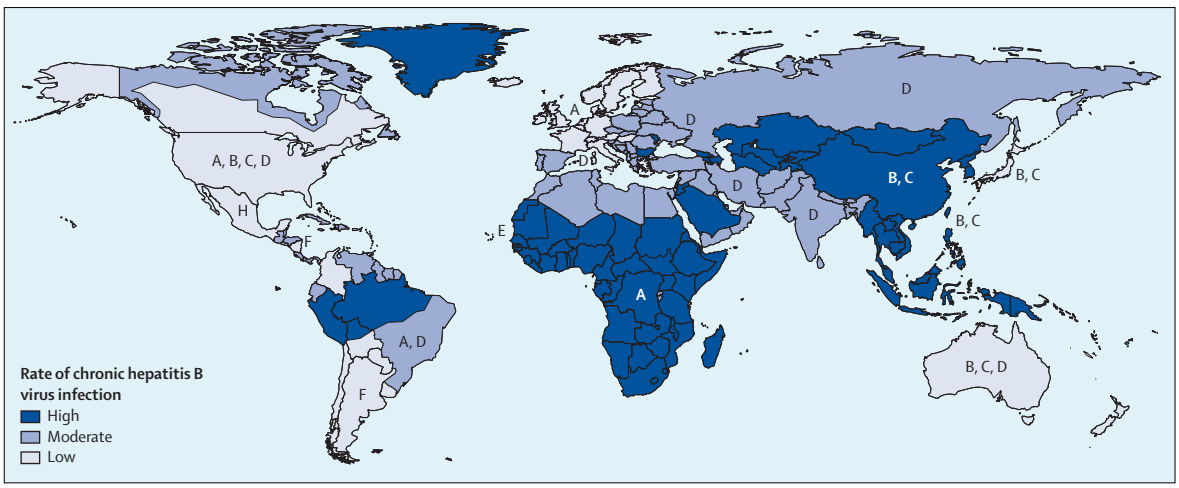


***Figure 1*: Geographical distribution of major hepatitis B virus genotypes and worldwide frequency of chronic hepatitis B virus infection**
Adapted from the US Centers for Disease Control and Infection.

### *Panel 1*: Indications for vaccination against hepatitis B virus infection

- All neonates*
- All children and adolescents not vaccinated at birth
- High-risk adults
  - Men who have sex with men
  - People with multiple sexual partners
  - Injection drug users
  - Patients on haemodialysis
  - Patients in institutions
  - Health-care workers and public safety workers
  - Spouses, sexual partners, or household members of people who carry hepatitis B virus

*Infants born to carrier mothers are also given hepatitis B immunoglobulin.

patterns of transmission exist, including infant, childhood, and adult transmission. The remaining 12% of infected individuals live in low endemic areas (prevalence <2%), including North America, western Europe, Australia, and Japan. In these areas, most infections occur in adolescents and adults through sexual or parenteral routes.

Immigration has a pronounced effect on prevalence in high-income countries. A 2012 meta-analysis[8] showed that the prevalence of HBV infection was 7·2% in migrants and refugees, and that of previous immunity was 39·7%. In the USA, estimates suggest that immigrants account for 95% of newly diagnosed cases of chronic HBV infection.[9]

## Prevention

HBV infection can be prevented by avoiding transmission from infected people and by inducing immunity in unexposed people. Screening of blood donors for HBsAg and implementation of universal precautions resulted in a substantial reduction in transmission in health-care settings. The addition of HBV DNA testing to screening processes further decreases the incidence of transfusion-associated disease, but implementation is hampered by incremental cost.[10] Counselling infected people to prevent transmission; screening and vaccination of at-risk adults; and universal vaccination of neonates are the most important steps in the prevention of transmission and decreasing of the global burden of HBV infection.

A safe and effective vaccine against HBV infection has been available since 1981. Most vaccines in use are made from recombinant DNA that express HBsAg only. In addition to the monovalent vaccine, a combination vaccine that also protects against hepatitis A virus is also available, as is a multivalent vaccine that protects against diphtheria, tetanus, pertussis, and *Haemophilus influenza* type B. By the end of 2011, vaccination against HBV infection had been introduced into routine childhood vaccination schedules in 180 countries.[3]

Prevention of perinatal transmission of HBV is crucial, because the risk of progression from acute to chronic HBV infection is 90% when infection occurs in infants.[11] Despite the use of passive–active immunoprophylaxis with HBV immunoglobulin and HBV vaccine, babies born to mothers with high HBV DNA titres (>$10^7$ copies per mL) still carry a substantial risk of infection.[12] The risk of perinatal transmission might be further reduced by giving antiviral therapy to mothers with high viraemia during the third trimester of pregnancy.[13]

Panel 1 lists the groups for which HBV vaccine is recommended. Response to the vaccine—defined as an anti-HBs titre >10 mIU/mL—can be achieved in roughly 95% of immunocompetent people. Protection has been estimated to last more than 15 years. Over time, anti-HBs titres decrease; however, symptomatic acute infection or chronic infection is absent or rare in immunised people, suggesting the presence of immune memory.[14–16]

A position paper issued by WHO in 2009 stated that no compelling evidence showed the need to give boosters in routine immunisation programmes. This position was endorsed by the Viral Hepatitis Prevention Board in 2011.[14] Data from Taiwan have suggested a substantial proportion of people might have lost their immune memories against HBsAg 15 or more years after vaccination.[17] HBV vaccine is very safe. Reports of its association with multiple sclerosis and autism have not been substantiated, and current vaccines do not contain thiomersal. Although the need for booster doses remains controversial, in view of the high safety profile of the vaccine, booster doses to high-risk people might be appropriate.

The introduction of HBV vaccine led to a decrease in the incidence of not only HBV infection but also hepatocellular carcinoma. In Taiwan, the proportion of children who were carriers of HBsAg decreased from 10% in 1984, to 0·5% in 2009.[18] This fall was accompanied by a 70% reduction in the incidence of hepatocellular carcinoma in children and adolescents.[19] In the USA, the incidence of acute HBV infection decreased by 81% between 1990 and 2006.[20] Overall HBsAg carrier rates also fell from 0·38% to 0·27%, but this decrease occurred mainly in children and adolescents[21]—the relatively stable carrier rate in adults has been attributed to immigration of chronically infected people from endemic countries.[9]

47 European countries have adopted universal HBV vaccination programmes, and similar patterns in infection rates have been reported.[22,23] Six European countries (Denmark, Finland, Iceland, Norway, Sweden, and the UK) in which the prevalence of infection is low have targeted vaccination strategies, and vaccinate high-risk individuals only. Horizontal and sexual transmission from the immigrant community is a concern in these countries.

## Diagnosis

Serological markers for HBV infection include HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc IgM and IgG (figure 2; table 1). HBsAg is the hallmark of infection. During acute infection, anti-HBc (initially both IgM and IgG) appears 1–2 weeks after the appearance of HBsAg at the same time as raised aminotransferase concentrations and symptoms, while IgG persists during chronic infection. IgM anti-HBc can be present in some patients with severe exacerbations of chronic HBV infection but the titre is lower than that in acute infection.

The presence of anti-HBs represents immunity to HBV infection. It is the only HBV marker detected in people who have acquired immunity through vaccination, and is present in association with anti-HBc IgG in those who have recovered from previous HBV infection. Some HBsAg-negative people are positive for anti-HBc IgG but not anti-HBs, a serological pattern referred to as isolated anti-HBc. Most people with isolated anti-HBc have had previous exposure to HBV, many have detectable HBV DNA in the liver, and some also have detectable HBV DNA in the serum.[24] Such presentation is termed occult HBV infection.[25] HBsAg-negative, anti-HBc-positive people can experience reactivation of infection during chemotherapy or immunosuppressive therapy, with the reappearance of HBsAg.[26] HBeAg and anti-HBe had been used to show viral replication and infectivity in the past, but their use in this context has largely been superseded by HBV DNA testing.

HBV DNA is a direct measurement of the viral load, which shows the replication activity of the virus. Most HBV DNA assays in use are real-time PCR assays with a limit of detection of 10–20 IU/mL and a linear range of detection up to $10^9$ IU/mL. Serum HBV DNA concentrations can vary from undetectable to more than $10^9$ IU/mL during the course of chronic HBV infection.

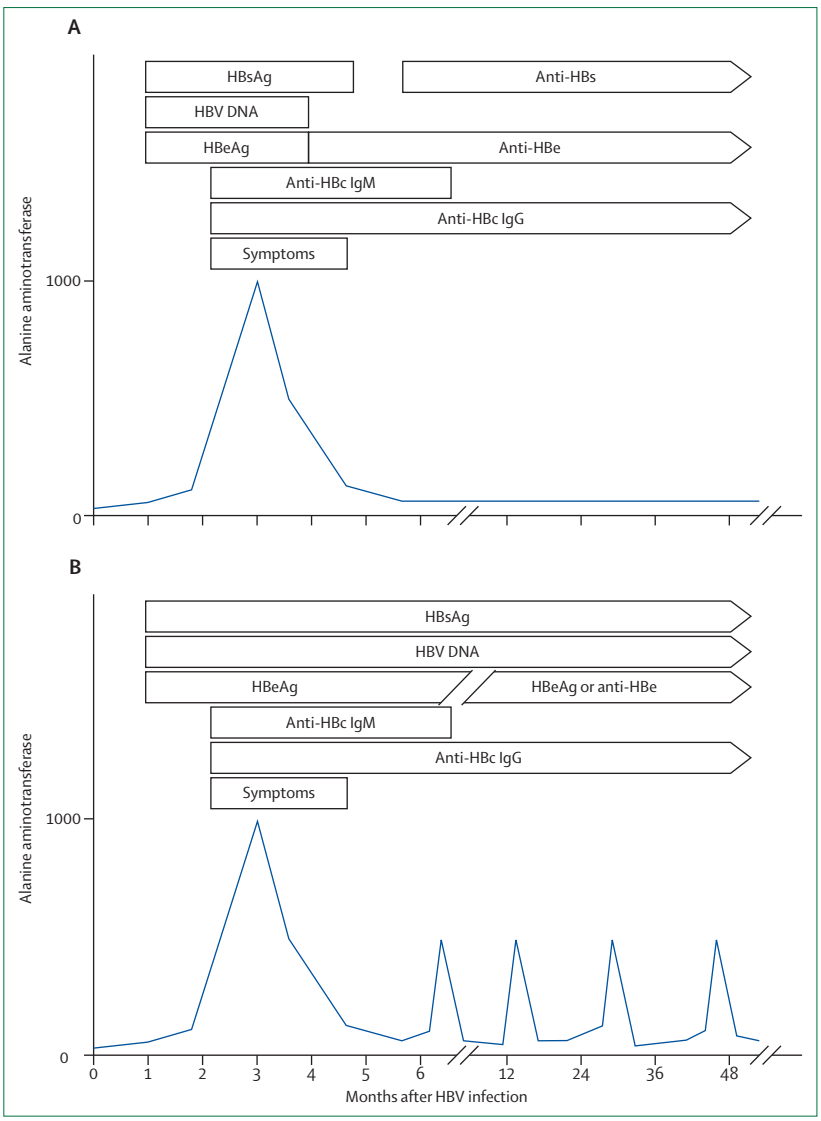


***Figure 2*: HBV markers during natural course resolved acute HBV infection (A) and transition of acute to chronic HBV infection (B)**
A subset of chronic patients might seroconvert from HBeAg to anti-HBe despite persistance of HBV DNA. HBV=hepatitis B virus.

| | Clinical interpretation |
|---|---|
| HBsAg | Hallmark of infection<br>Positive in early phase of acute infection and persistently positive in chronic infection |
| Anti-HBs | Recovery from acute infection or immunity from vaccination |
| HBeAg | Immune tolerance phase or immune clearance phase<br>Usually associated with high viral load |
| Anti-HBe | Low replicative phase if hepatitis B virus DNA is low<br>HBV variants if hepatitis B virus DNA is high |
| IgM anti-HBc | Acute infection; only positive serological marker in the serological window between disappearance of HBsAg and appearance of anti-HBs<br>Might be positive during severe exacerbation of chronic infection |
| IgG anti-HBc | Exposure to infection<br>Present in association with HBsAg in chronic infection<br>Present in association with anti-HBs after recovery from acute infection<br>Isolated presence might signify occult infection |

***Table 1*: Clinical interpretation of serological markers of hepatitis B virus infection**

See Online for appendix

During the past few years, commercial assays to quantify HBsAg concentrations have been approved in Europe and many countries in Asia. A correlation has been shown between serum HBsAg concentrations and the amount and transcription activity of covalently closed circular DNA (cccDNA) in the liver, particularly in HBeAg-positive patients.[27] HBsAg monitoring predicts response to interferon and which HBeAg-negative patients with normal alanine aminotransferase concentrations will have progressive disease.[27,28]

## Immunopathogenesis

HBV is not cytopathic: both liver damage and viral control are immunomediated. The clinical outcome of infection is dependent on the complex interplay between HBV replication and host immune response.[29–31] HBV is a weak inducer of the innate immune response.[32] Resolution of acute infection is mainly mediated through the adaptive immune response. People with serological recovery from acute HBV infection have strong T-cell responses to several epitopes in different regions of the HBV genome. By contrast, patients chronically infected with HBV have weak T-cell responses to a few epitopes.[33,34] Recovery of immune function has been reported in patients who underwent spontaneous HBeAg seroconversion and in those with virological responses to antiviral therapy,[35,36] suggesting that sequential treatment with antiviral therapy followed by immunotherapy could increase the chance of viral clearance.[37,38]

Immune responses to HBV can have negative effects. Overly aggressive immune response is thought to be the cause of fulminant HBV infection, and exacerbations of chronic disease with flares in alanine aminotransferase concentrations are mediated by immune responses. Although some flares are accompanied by falls in HBV DNA concentrations and subsequent HBeAg to anti-HBe seroconversion (representing successful immune clearance of infected hepatocytes),[39] other flares are accompanied by transient falls in HBV DNA concentrations, representing ineffective immune clearance.[40] Recurrent alanine aminotransferase flares increase the risk of cirrhosis and hepatocellular carcinoma. Besides the hepatic manifestations mediated by cellular immune responses, extrahepatic manifestations—mainly glomerulonephritis and vasculitis including polyarteritis nodosa—can develop as a result of an imbalance of humoral responses generating circulating immune complexes.[41]

## Virology

HBV belongs to the Hepadnaviridae family. It is a partly doublestranded DNA virus with approximately 3200 base pairs. The transcriptional template of HBV is the cccDNA, which resides inside the hepatocyte nucleus as a mini-chromosome.[42] The maintenance of cccDNA is essential for the persistence of the virus. The replication of HBV implicates reverse transcription of the pregenomic RNA intermediate into HBV DNA. Reverse transcriptase is error prone and the mutation rate is high (appendix). The receptor for HBV entry into hepatocytes is sodium taurocholate polypeptide.[43]

The most common HBV mutations include a single nucleotide change at position 1896 in the precore region, which creates a stop codon, and a double nucleotide change at positions 1762 and 1764 in the basal core promoter region, which decreases the transcription of the precore mRNA.[44] These mutations abolish or downregulate the production of HBeAg without affecting the replication capacity of the virus and cause HBeAg-negative chronic HBV infection. The precore and basal core promoter mutations can occur alone or together.

The geographical prevalence of these HBeAg-negative mutants is related to the prevalence of their associated HBV genotypes. The virus can be classified into at least ten genotypes, labelled A–J.[45] Genotype A is frequent in North America, northern Europe and Africa, genotypes B and C are prevalent in Asia, and genotype D is detected mostly in Mediterranean countries, the Middle East, and India (figure 1). HBV genotypes can affect disease progression and response to interferon.[46]

## Natural history

The occurrence of symptoms during acute HBV infection and the outcome depend on age at infection. Infants and children are mostly asymptomatic, whereas roughly 70% of adults have subclinical or anicteric hepatitis and 30% have icteric hepatitis. Less than 1% of acute HBV infection in adults progresses to fulminant hepatitis, which has a mortality of around 80% without liver transplantation.

HBsAg appears in the serum 2–10 weeks after exposure to HBV, before onset of symptoms and increases in aminotransferases, and it usually disappears in 4–6 months. Anti-HBs can appear several weeks before or after HBsAg seroclearance (figure 2A) in people who recover. Persistence of HBsAg beyond 6 months is used to define progression to chronic

infection (figure 2B). When HBV infection is acquired during infancy or early childhood, the initial phase of chronic infection is characterised by positive HBeAg, very high HBV DNA (>$10^7$ IU/mL) and normal alanine aminotransferase concentrations, and minimum inflammation and fibrosis on histology (figure 3, table 2).[47] HBsAg concentrations are also high (>$10^5$ IU/mL).[48] This phase can last for 20–40 years with minimum disease progression, and the rate of spontaneous HBeAg seroconversion is very low. An absence of liver disease despite high viraemia is because of immune tolerance, which is probably a result of clonal deletion of T cells against HBV in the fetus induced by in-utero exposure to HBeAg.[49]

Loss of immune tolerance triggers the second phase or immune clearance phase (HBeAg-positive chronic HBV infection; figure 3, table 2),[50] which is characterised by a decrease in HBV DNA and an increase in alanine aminotransferase concentrations. HBsAg concentrations are also lower ($10^3$–$10^4$ IU/mL).[48] Roughly 10–20% of patients will lose HBeAg and develop anti-HBe—ie, HBeAg seroconversion—in a year.[51] Persistent or recurrent increases in alanine aminotransferase with unsuccessful immune clearance increase the risk of liver cirrhosis and hepatocellular carcinoma.[52] Patients infected with genotype C HBV undergo HBeAg seroconversion at an older age than do patients infected with other HBV genotypes,[53] which might account for the higher incidence of hepatocellular carcinoma in genotype-C-infected patients.

Successful HBeAg seroconversion with suppression of HBV DNA and normalisation of alanine aminotransferase concentration marks transition to the inactive phase, during which serum HBV DNA concentration tends to be low (generally <2000 IU/mL) or undetectable and the HBsAg concentration falls gradually to $10^2$–$10^3$ IU/mL. HBeAg seroconversion before age 30 years is associated with a lower risk of hepatocellular carcinoma and better survival than is seroconversion later in life.[54,55] The yearly rate of spontaneous HBsAg seroclearance is about 0·5–1%.[56] Patients in the inactive phase with HBsAg concentrations of less than 1000 IU/mL are more likely to undergo spontaneous HBsAg seroclearance[57] and less prone to cirrhosis and hepatocellular carcinoma than are those who have high HBsAg concentrations.[58] Patients who achieve HBsAg seroclearance before age 50 years and before cirrhosis develops have excellent outlooks compared with those who do so after age 50 years, have cirrhosis, or are co-infected with hepatitis C virus.[59,60]

Roughly 20–30% of patients will experience reactivation of HBV infection with raised viral DNA or alanine aminotransferase concentrations, or both, after HBeAg seroconversion. These patients are in the HBeAg-negative chronic HBV infection phase, during which precore mutations or basal core promoter mutations, or both, can be detected in most patients.[61] HBeAg-negative patients with active disease have increased risk of liver cirrhosis and hepatocellular carcinoma, whereas the outlook for those who remain in the inactive phase is excellent.[52]

Overall, up to 40% of men and 15% of women with perinatally acquired HBV infection will die of liver cirrhosis or hepatocellular carcinoma.[62] In a population-based study[63] of 3342 untreated non-cirrhotic HBsAg-positive people in Taiwan, the incidence of liver cirrhosis was 838·1 per 100 000 person-years and that of hepatocellular carcinoma was 306·3 per 100 000 person-years. In people with cirrhosis, the incidence of

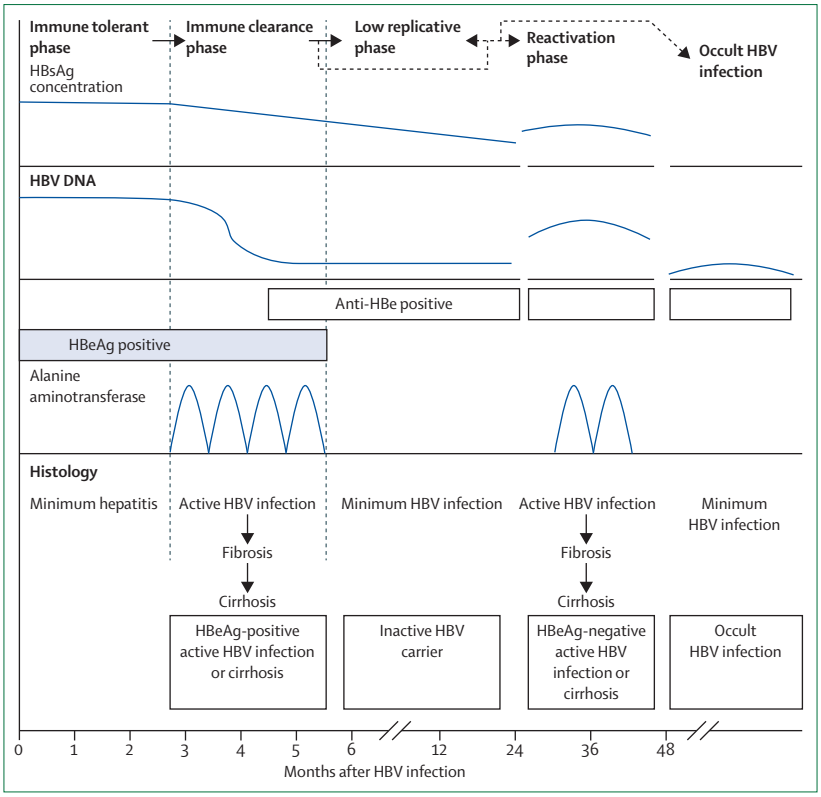


***Figure 3*: Schematic depiction of the natural phases of chronic HBV infection**
HBV=hepatitis B virus.

| | Definition |
|---|---|
| Immune tolerant phase | Chronic HBV infection, HBeAg positive, HBV DNA >20 000 IU/mL, persistently normal aminotransferase concentrations |
| HBeAg-positive chronic HBV infection | Chronic HBV infection, HBeAg positive, HBV DNA >20 000 IU/mL, abnormal or fluctuating aminotransferase concentrations |
| Inactive HBV carrier | Chronic HBV infection, HBeAg negative, anti-HBe positive, HBV DNA undetectable or <2000 IU/mL, persistently normal aminotransferase concentrations |
| HBeAg-negative chronic HBV infection | Chronic HBV infection, HBeAg negative, HBV DNA >2000 IU/mL, persistent or intermittently increased aminotransferase concentrations |
| Acute exacerbation of chronic HBV infection | Abrupt rise of aminotransferase concentrations to >5 times the upper limit of normal and more than twice the baseline concentration |
| Resolved HBV infection | Previous known history of acute or chronic HBV infection, HBsAg negative, undetectable HBV DNA in serum, and normal aminotransferase concentrations with anti-HBc and anti-HBs |

HBV=hepatitis B virus.

***Table 2*: Phases of chronic HBV infection**

*Panel 2*: **Factors associated with increased risk of hepatocellular carcinoma**

**Host factors**
- Age older than 50 years
- Male sex
- Presence of cirrhosis
- Family history of hepatocellular carcinoma
- African or Asian race
- Obesity
- Diabetes mellitus

**Virus factors**
- High levels of replication of hepatitis B virus
- Genotype (C>B)
- Basal core promoter variant

**Environmental factors**
- Concurrent infection with hepatitis C virus or hepatitis D virus
- Alcohol
- Aflatoxin

hepatocellular carcinoma can be as high as 8000 cases per 100 000 person-years.[64] The incidence of hepatocellular carcinoma is lower in white people with chronic HBV infection than in chronically infected Asian people. A review[65] of published work worldwide estimated that the annual incidence of hepatocellular carcinoma is 2–3% for HBsAg-positive people with cirrhosis and less than 1% for those without cirrhosis.

Most HBV-related hepatocellular carcinomas develop in cirrhotic livers but roughly 20% do not. Various factors have been associated with increased risk of hepatocellular carcinoma (panel 2); coffee seems to be protective. Large-scale longitudinal studies[66–68] in Asia showed that HBeAg and high serum HBV DNA concentrations are associated with increased risk of liver cirrhosis and hepatocellular carcinoma. These studies also showed an association between genotype C (compared with genotype B) and the presence of basal core promoter mutations and hepatocellular carcinoma. However, these studies cannot be extrapolated to young Asian patients because only people aged 30–65 years were enrolled, nor do they apply to patients who acquired HBV infection in adult life. HBeAg-negative patients with HBV DNA concentrations of lower than 2000 IU/mL have reduced risk of hepatocellular carcinoma, especially when HBsAg concentrations are also low.[58]

## Management

### General

Acute HBV infection is self-limiting in more than 95% of immunocompetent adults. Therefore management is supportive, and so far antiviral therapy is indicated only for patients with protracted or severe acute disease. Management of chronic infection should include assessment of HBV replication status; screening for HIV, hepatitis C virus, and hepatitis D virus co-infection; and assessment of severity of liver disease. Clinical assessment, blood counts, analysis of liver enzymes, and liver histology are used to establish the severity of liver disease. Non-invasive methods (blood tests and measurement of liver stiffness) to assess inflammation and fibrosis have been developed, which complement and increasingly could replace liver histology.[69,70] Although results are promising, these methods need further assessment before they can be applied in clinical practice. Non-invasive assessment is particularly useful in patients with normal alanine aminotransferase concentrations to exclude clinically significant fibrosis because the risk–benefit trade-off does not favour liver biopsy in these patients. That said, liver biopsy is important in patients with slightly raised or fluctuating alanine aminotransferase concentrations to establish whether antiviral therapy is indicated.

Patients should be counselled on measures to prevent transmission and lifestyle changes, such as limiting alcohol intake to decrease the risk of liver damage. Patients should also be educated about disease outcomes, treatment options, and the importance of long-term monitoring. Patients older than 40 years, with cirrhosis, or with a family history of hepatocellular carcinoma should undergo ultrasonography and α-fetoprotein testing.[71] This surveillance for hepatocellular carcinoma should be continued during antiviral therapy because the risk persists even in patients with virological responses.

The main goals of antiviral therapy are sustained suppression of HBV replication and hepatic inflammation, thereby preventing progression to cirrhosis and hepatocellular carcinoma. Response to treatment is assessed on the basis of biochemical (normalisation of alanine aminotransferase), virological (suppression of HBV DNA to undetectable concentrations by a sensitive PCR assay), serological (loss of HBeAg or HBsAg and seroconversion to anti-HBe or anti-HBs), and histological (decreased inflammation on liver biopsies with no worsening of fibrosis) measures. Seven antiviral agents are approved for treatment of chronic HBV infection: two formulations of interferon alfa (conventional and pegylated), and five nucleos(t)ide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir; appendix).[72,73]

### Interferon

Interferon has both antiviral and immunomodulatory activity and is given by subcutaneous injection. It has many side-effects, including influenza-like symptoms, fatigue, bone marrow suppression, depression, and exacerbation or unmasking of autoimmune illnesses. Interferon is contraindicated for patients with liver failure, and should be used with caution in patients with compensated cirrhosis. A 1 year course of pegylated interferon with or without lamivudine in HBeAg-positive

patients resulted in HBeAg seroconversion in 29–32% of patients and HBsAg loss in 3–7% of patients 24 weeks after completion of treatment.[74,75] On follow-up, HBeAg seroconversion was durable in 80% of patients, and HBsAg loss occurred in 58% of patients infected with genotype A and 11% of those infected with other genotypes who had HbeAg seroconversion.[76] In HBeAg-negative patients, a 1 year course of pegylated interferon with or without lamivudine resulted in sustained response, which was defined as normalisation of alanine aminotransferase concentrations and suppression of HBV DNA below 10 000 IU/mL in 25% of patients and HBsAg loss in 9% of patients 3 years after completion of treatment.[77] Addition of lamivudine to pegylated interferon did not improve responses.

Predictors of response in HBeAg-positive patients include high pretreatment alanine aminotransferase concentrations, low HBV DNA concentrations, and viral genotype A.[78,79] The results of a 2013 study suggest that an on-treatment fall in HBsAg concentration is a strong predictor of response to interferon, but different stopping rules apply according to HBV genotype.[80] For HBeAg-negative patients, no consistent pretreatment predictor of response exists but a decrease in HBsAg concentration after the first 12–24 weeks of treatment is predictive of sustained response.[81] Interferon lambda3/IL28B polymorphisms have also been reported to predict response in some but not all studies.[82,83]

## Nucleos(t)ide analogues

Nucleos(t)ide analogues mainly act by inhibiting reverse transcription of the pregenomic RNA into HBV DNA and have no direct effect on cccDNA, which explains why viral relapse is common after treatment is stopped. A 1 year course of nucleos(t)ide analogues in HBeAg-positive patients resulted in suppression of serum HBV DNA to undetectable concentrations in 21–76% of patients, normalised alanine aminotransferase concentrations in 41–77%, HBeAg seroconversion in 12–22%, and HBsAg loss in 0–3% (appendix). Extension of the duration of treatment to 4–5 years increased the rate of HBeAg seroconversion to 31–48%, with minimum increase in the rate of HBsAg loss (0–10%).[84,85] In HBeAg-negative patients, a year of treatment with nucleos(t)ide analogues resulted in suppression of serum HBV DNA to undetectable concentrations in 51–93% of patients, normalised alanine aminotransferase in 62–78%, and HBsAg loss in less than 1% (appendix). Extension of the duration of treatment to 4–5 years maintained viral suppression in 67–99% of patients but the rate of HBsAg loss remained low (0–5%).[85]

A major drawback with earlier nucleos(t)ide analogues is the high rate of antiviral resistance but the new drugs—entecavir and tenofovir—have low rates of resistance (1·2% and 0% after 5 years' treatment).[85,86] Antiviral resistance because of selection of drug-resistance mutations shown by increased serum HBV DNA concentrations can trigger flares of alanine aminotransferase and liver failure. Patients infected with HBV resistant to one drug are at increased risk of resistance to other drugs that share the same resistance mutations. Therefore, the choice of the initial drug is important to prevent multidrug resistance.

Nucleos(t)ide analogues are given orally once daily, with dose adjustment for patients with impaired renal function. They are generally safe, but myopathy and neuropathy had been reported in patients taking telbivudine,[87] and nephrotoxic effects and renal tubular dysfunction in those on adefovir or tenofovir.[88] These uncommon adverse events might increase with duration of exposure. High pretreatment alanine aminotransferase is the most important predictor of response in HBeAg-positive patients.[89] HBeAg-positive patients with normal or slightly raised alanine aminotransferase concentrations have lower rates of undetectable HBV DNA and HBeAg seroconversion.[90] No predictors of response to nucleos-(t)ide analogues including HBV or host IL28B genotypes have been identified for HBeAg-negative patients.

In addition to decreasing hepatic inflammation, long-term antiviral treatment can also reverse cirrhosis. In a study[85] in which paired biopsies were compared at baseline and after 5 years of tenofovir treatment, 176 (51%) of 348 patients had decreases in their Ishak fibrosis score of one unit or more (range 0–6), and 71 (74%) of 96 patients with cirrhosis at baseline had regression of cirrhosis. Reversal of fibrosis and cirrhosis during long-term treatment with other nucleos(t)ide analogues has also been reported.[91,92] Antiviral treatment improved clinical outcomes in a double-blind, randomised, placebo-controlled trial of lamivudine in 651 patients with advanced fibrosis or cirrhosis and high HBV DNA concentrations. After a median of 32 months, disease progression occurred in 7·8% and hepatocellular carcinoma in 3·9% of the treatment group compared with 17·7% and 7·4% in the control group.[93] Other studies of patients receiving antiviral treatment in clinical practice have also shown a decrease in hepatocellular carcinoma;[94,95] however, the risk persists in patients with advanced fibrosis or cirrhosis even after complete viral suppression or HBsAg seroclearance.[96]

## Who should be treated?

Current treatments for HBV infection suppress replication but do not eradicate the virus. Most patients will need long-term treatment to maintain viral suppression. The American, European, and Asian Pacific liver associations' guidelines recommend starting treatment as soon as possible in patients with life-threatening liver disease—ie, acute liver failure, decompensated cirrhosis, or severe exacerbation of chronic HBV infection.[71,97,98] All guidelines recommend starting treatment in patients with compensated cirrhosis irrespective of alanine amino-transferase concentration but the cutoff HBV DNA concentration for treatment initiation varies.

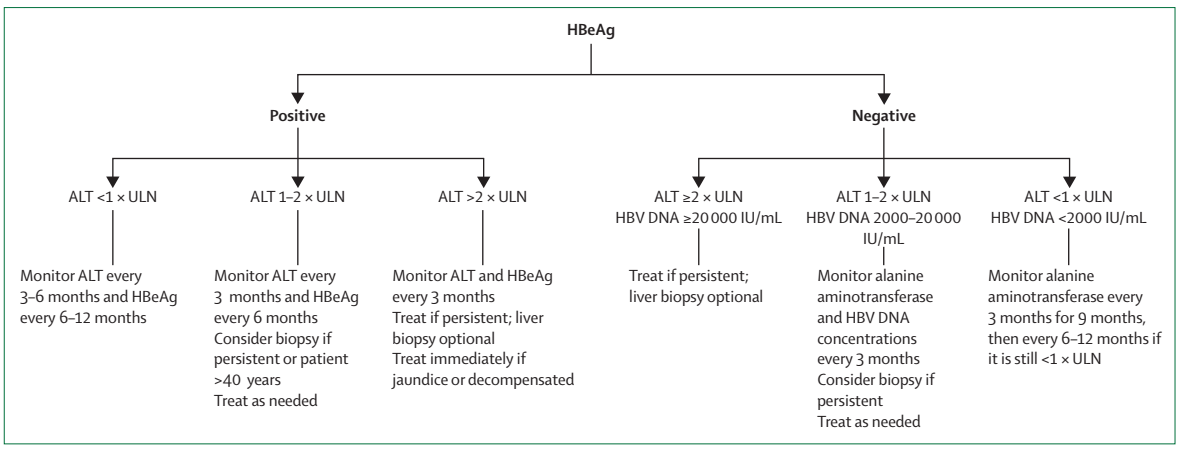


***Figure 4*: Indications for treatment of patients with chronic HBV who have not progressed to cirrhosis and monitoring of those in whom treatment is not indicated at presentation**

Adapted from American Association for the Study of Liver Diseases guidelines.[71] HCC surveillance should be done if indicated.[96] HBV=hepatitis B virus. ULN=upper limit of normal. ALT=alanine aminotransferase.

For patients who have not progressed to cirrhosis, all guidelines agree that treatment should be begun in patients with HBV DNA concentrations of greater than 20 000 IU/mL and persistently increased alanine aminotransferase concentrations or histological evidence of moderate or severe inflammation or fibrosis (figure 4). The guidelines vary in their recommendations for patients with HBV DNA concentrations between 2000 and 20 000 IU/mL and for those with alanine aminotransferase concentrations between one time or twice the upper limit of normal. All guidelines recommend that the patient's age (lower threshold for those older than 40 years), HBeAg status, family history of hepatocellular carcinoma, occupational requirements (eg, health-care providers engaged in exposure-prone procedures), family planning, and preferences should be considered when making treatment decisions. Several studies showed that patients with normal alanine aminotransferase concentrations can have substantial liver fibrosis, especially when concentrations are at the high end of the normal range, HBV DNA concentrations are high (>10 000 IU/mL), or when they are older than 40 years.[99] Guidelines recommend liver biopsies in these patients and antiviral treatment in those with moderate-to-severe inflammation or fibrosis.

To prevent reactivation of HBV replication, which can lead to hepatitis and liver failure, guidelines also recommend prophylactic antiviral therapy in HBsAg-positive patients who will be receiving immunosuppressive therapy. Prophylactic antiviral therapy is also recommended for patients who are HBsAg negative and anti-HBc positive and who will be receiving potent immunosuppressive therapies such as anti-CD20 or myeloablation before haemopoietic stem cell transplantation, to prevent reappearance of HBsAg.[100] Because babies born to mothers with high HBV DNA concentrations have a substantial risk of infection despite passive–active immunoprophylaxis, guidelines recommend the consideration of nucleos(t)ide analogues with low resistance and safety data, such as tenofovir, during pregnancy to reduce the risk of mother-to-infant transmission. However, there is no consensus on the cutoff HBV DNA concentration for recommending antiviral therapy and when antiviral therapy should be started.

Selection of first-line treatment should be based on the safety and efficacy of the drug, risk of resistance, cost, and patient's preference. The main advantages of interferon are a finite duration of treatment and a higher rate of HBeAg and HBsAg loss, particularly in HBeAg-positive patients with genotype A. However, injectable interferon is associated with many side-effects. Nucleos-(t)ide analogues are given orally and well tolerated but most patients require lifelong treatment. Guidelines recommend pegylated interferon, entecavir, or tenofovir as first-line treatment.[71,97,98]

All guidelines recommend pegylated interferon for 48–52 weeks in both HBeAg-positive and HBeAg-negative patients. For nucleos(t)ide analogues, guidelines recommend that treatment can be stopped when HBeAg-positive patients have completed 6–12 months consolidation therapy after HBeAg seroconversion. According to the American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines, treatment can be stopped when HBeAg-negative patients have lost HBsAg. Because of cost concerns, the Asian Pacific Association for the Study of the Liver recommends consideration of stopping treatment in patients in whom HBV DNA is undetectable after two years' treatment; however, in a 2013 study, 45% of patients who met this criterion relapsed clinically, and an additional 13% had virological relapse within 1 year of stopping treatment.[101] All guidelines recommend lifelong nucleos(t)ide analogues in patients with cirrhosis before treatment. Irrespective of the underlying liver disease

and the treatment used, patients need to be closely monitored when treatment is stopped, so that treatment can be reinitiated promptly in patients with increased alanine aminotransferase concentrations associated with viral relapse.

Despite advances in vaccination and treatment, the global burden of HBV remains high because vaccination coverage is low in some countries and many infected people have not been diagnosed. Educational programmes to raise awareness in the public and health-care providers and innovative strategies to overcome barriers to diagnosis, care, and treatment should go hand in hand with the development of new therapies that can achieve sustained control of HBV. WHO's renewed focus on viral hepatitis provides hope for low-income countries that are disproportionately affected by HBV. Lessons learned from successful programmes supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria should be extended to HBV infection. Development of new treatments that can improve the rate of HBsAg loss allowing virological cure will greatly increase treatment uptake.

#### Contributors

All authors contributed equally to the development of the outline; the search of published work and review of data; and the drafting, editing, and approval of this Seminar.

#### Declaration of interests

CT is on advisory boards for Janssen and Flamel Technologies and has received research grants from MSD, Roche, Janssen, and Flamel Technologies. HLYC is on advisory boards for Bristol-Myers Squibb, Gilead, MSD, Roche, and Novartis; has received speaker fees from Bristol-Myers Squibb, Gilead, MSD, Roche, Novartis, GlaxoSmithKline, and Echosens; and received an unrestricted grant from Roche for HBV research. AL is on advisory boards for Gilead, GlaxoSmithKline, and Merck and has received research grants from Bristol-Myers Squibb, Gilead, and Merck.

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