

Hepatitis B

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Review team

J. Heathcote (Chair, Canada),
Z. Abbas (Pakistan), A. Alberti (Italy), Y. Benhamou (France),
C. Chen (Taiwan), A. Elewaut (Belgium), P. Ferenci (Austria),
C. Hui (Hong Kong), V. Isakov (Russia), H. Janssen (The Netherlands),
G. Lau (Hong Kong), S. Lim (Singapore), T. Okanou (Japan),
S. Ono-Nita (Brazil), T. Piratvisuth (Thailand), M. Rizzetto (Italy),
I. Sollano (Phillippines), W. Spearman (South Africa),
C-T. Yeh (Taiwan), M. Yuen (Hong Kong), J. Krabshuis (France)

Contents

- 1 Introduction
- 2 Epidemiology and transmission of hepatitis B
- 3 Pathogenesis and natural history
- 4 Laboratory diagnosis of hepatitis B
- 5 Long-term monitoring and screening of chronic hepatitis B
- 6 Treatment for chronic hepatitis B
- 7 Hepatitis B vaccination
- 8 Automatic searches, guidelines, further reading, and web sites
- 9 Queries and feedback

1 Introduction

Hepatitis B is a viral disease process caused by the hepatitis B virus (HBV). The virus is endemic throughout the world. It is shed in all body fluids by individuals with acute or chronic infection. When transmission occurs vertically (from mother to child) or horizontally between small children during play, the infection nearly always becomes chronic. By contrast, when transmission occurs in adolescents/adults—usually via sexual contact, contaminated needles (“sharps”), and less often from transfusion of blood products—the infection usually resolves unless the individual is immunocompromised (e.g., infected with human immunodeficiency virus). Providing education about how to avoid risky behavior can play an important role in prevention.

Health-care workers are an at-risk group because of the risk of needlestick injury, and they should therefore all be vaccinated before starting employment.

Individuals chronically infected with HBV are at increased risk of developing cirrhosis, leading to hepatic decompensation and hepatocellular carcinoma (HCC). Although most patients with chronic HBV infection do not develop hepatic complications, there is a potential for serious illness to develop during their lifetime, and it is more likely to occur in men.

Every individual chronically infected with HBV represents an opportunity for further cases to be prevented. It is important to take the time needed to educate patients and to explain the risks that the infection poses to the patients themselves and to others.

Hepatitis B vaccination is highly effective, and universal vaccination at a young age is desirable. At the very least, vaccination should be offered to all individuals who are at risk. Pregnant women must be screened for hepatitis B before delivery, as this offers an opportunity to prevent another generation of chronically infected persons.

Guidelines must not be resource-blind. This guideline therefore presents six cascades to provide resource-sensitive options for the prevention and treatment of hepatitis B.

2 Epidemiology and transmission of hepatitis B

Two billion people worldwide have serologic evidence of past or present HBV infection, and 350 million are chronically infected and at risk of developing HBV-related liver disease. Some 15–40% of chronically infected patients will develop cirrhosis, progressing to liver failure and/or HCC. HBV infection accounts for 500,000–1,200,000 deaths each year.

The prevalence of HBV varies markedly between different regions of the world (Fig. 1). In the literature, a distinction is usually made between areas of high, medium, and low endemicity; recently, the concept of “very low endemicity” has also been added. The prevalence of chronic infection ranges from over 10% of the population in South-East Asia, China, the Amazon area, and sub-Saharan Africa to less than 1% in western Europe and North America. Overall, approximately 45% of the global population lives in areas of high endemicity. Globalization processes mean that

individuals with hepatitis B who are new immigrants into areas where the chronic HBV infection rate is low may easily go unnoticed.

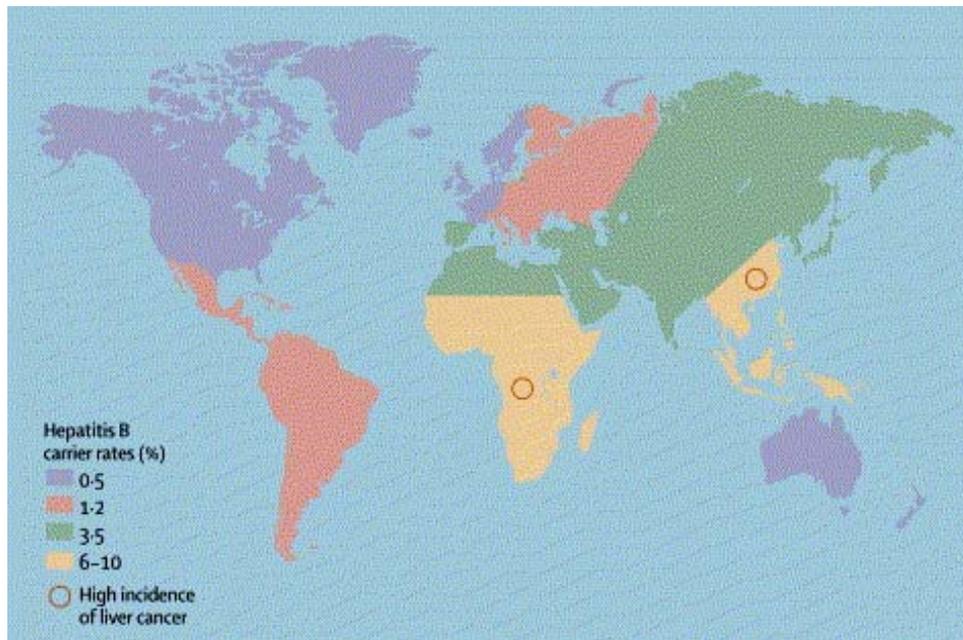


Fig. 1 Hepatitis B carrier rates in different regions of the world (courtesy of Dawson AJ, Lancet Inf Dis 2005;5;120–5).

The wide range of prevalence figures for chronic HBV infection is largely related to differences in age at infection. The chance that acute infection will become chronic is 70–90% for perinatally acquired (vertical) infection and 20–50% for (horizontal) infections acquired during early childhood (under the age of 5 years). The chance of developing chronic HBV ranges from 1% to 3% in adult-acquired HBV infections (unless the individual is immunosuppressed). Seven genotypes of hepatitis B virus have been identified, and their geographic distributions have been established (Table 1).

Table 1 Hepatitis B virus infection by genotype

Genotype	Geographic areas	Principal transmission mode	Chronic infection (%)	Median age of HB _e conversion
A	Western Europe North America South Africa	Sexual, intravenous drug use	< 1	20
B	Far East South-East Asia	Vertical	1–12	40
C	Far East South-East Asia	Vertical	1–10	30

Genotype	Geographic areas	Principal transmission mode	Chronic infection (%)	Median age of HB _e conversion
D	India Middle East Southern Europe	Vertical/"sharps." sexual, nosocomial	< 1–5	20
E	Africa	Horizontal, nosocomial	3–25	< 10
F	S America Polynesia	Sexual, vertical?	1	?

Adapted from Allain JP. Epidemiology of Hepatitis B virus and genotype. *J Clin Virol* 2006;36 Suppl 1:S12–7.

Increasing numbers of patients with chronic infection are developing HBV variants (caused by mutations in the core gene) that express no or little hepatitis B e antigen (HB_eAg); this HB_eAg-negative hepatitis B may require long-term therapy to reduce the likelihood that liver disease will progress, with relapse occurring when the patient is off treatment. A distinction is made between a precore mutation and a core promoter mutation. The prevalence of precore mutations is highest in the Mediterranean countries and most prevalent in genotype D, while the core promoter mutations are mostly found in genotype C (in the Far East and South-East Asia). However, the clinical manifestations are the same.

The combination of prevalence, route of transmission, and viral factors has implications for the vaccination strategy—vaccination of at-risk groups, infant vaccination, or adolescent vaccination. Studies suggest that universal vaccination at birth is cost-effective in countries with high and moderate prevalence, whereas Europe and North America, with very low incidence rates, have implemented either routine infant vaccination or vaccination for newborns of mothers who test positive for hepatitis B surface antigen (HB_sAg). Routine adolescent vaccination at the age of 10 and catch-up vaccination for at-risk adults (it is difficult to identify and/or access those who are “at risk”) are recommended in some countries, but this will have little effect on the rate of chronic infection.

3 Pathogenesis and natural history

Pathogenesis

HBV-related liver injury is largely caused by immune-mediated mechanisms, mediated via cytotoxic T-lymphocyte lysis of infected hepatocytes. The precise pathogenic mechanisms responsible for the HBV-associated acute and chronic necroinflammatory liver disease and the viral and/or host determinants of disease severity have only recently been established. The immune response of the host to HBV-related antigens is important in determining the outcome of acute HBV infection. The strength of the host’s immune response is crucial for clearing the virus,

but this simultaneously causes liver injury (i.e., a form of “hepatitis” manifested by a rise in transaminases occurs before clearance of the virus can be achieved). Those who become chronically infected are unable to sustain an immune response to HBV and thus undergo intermittent episodes of hepatocyte destruction (hepatitis).

Most studies of acute HBV infection are only initiated after the onset of symptoms, so that the critical early events following HBV infection go unnoticed. A recent study serially profiled the genomic changes during viral entry, spread, and clearance of the virus and showed that HBV does not induce any interferon-regulated genes in the early phase of the infection. In addition, no genes were up-regulated or down-regulated in the lag phase of the infection or during the phase of viral spread. This suggests that HBV may not induce the intrahepatic innate immune response. Hence, HBV may be a “stealth” virus early in the infection.

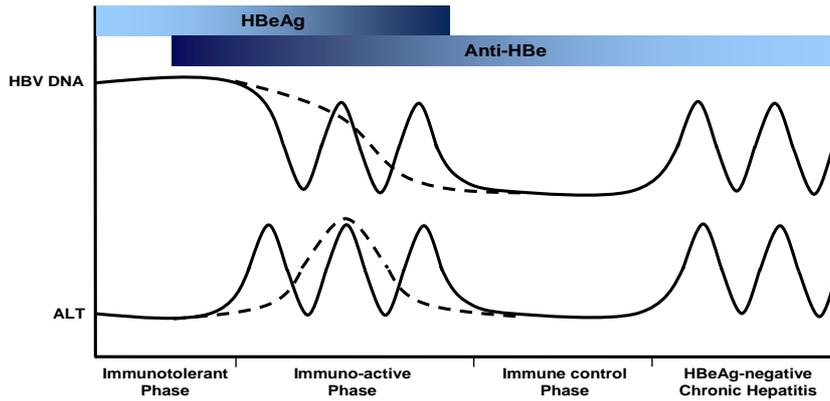
When neonates are infected during childbirth if their mother is HB_eAg-positive, immune tolerance is induced as the fetus becomes tolerized to the e antigen, a soluble viral protein that crosses the placenta in utero. This immune-tolerant phase continues for years to decades. Children born to mothers who are HB_eAg-negative but have ongoing viral replication more often develop an acute hepatitis in the neonatal period, which is cleared by the infant. However, the infectivity of many women who are HB_eAg-negative is often very low, so that only about 20% transmit hepatitis B to their offspring.

In summary, the outcome of HBV infection largely depends on the host–virus interaction, mediated by the adaptive immune response. The virus-specific T cell response is one of the key factors in the pathogenesis of HBV infection. Viral variants may influence the course and outcome of the disease. The effect of host factors in the progression of disease is underappreciated. Only very rarely (when there is profound immune suppression) does the hepatitis B virus become directly cytopathic.

Natural history (Table 2)

Table 2 Acute hepatitis B infection: the risk of chronicity is related to age at primary infection

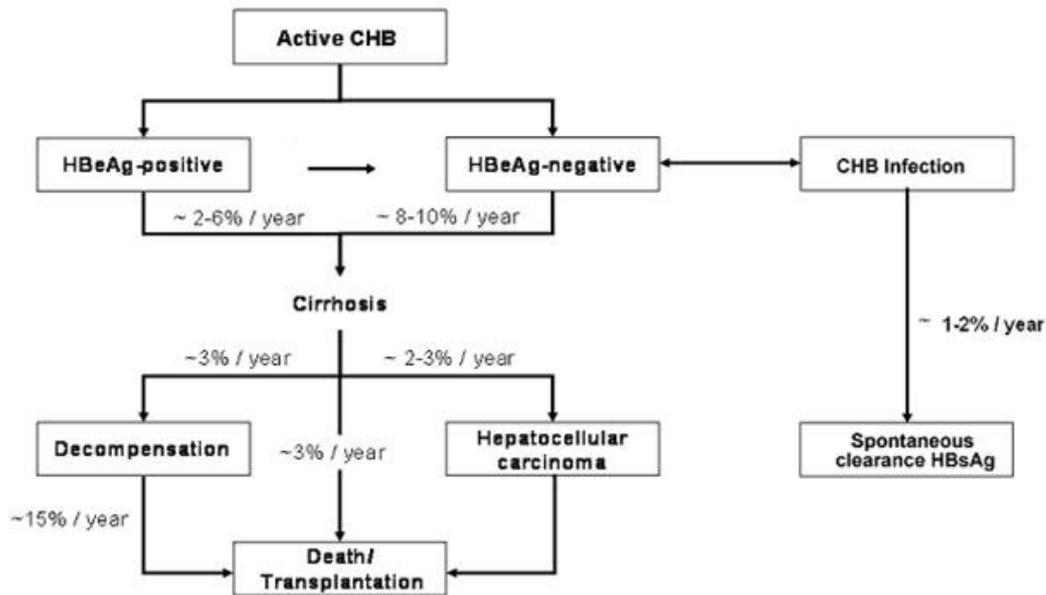
Outcome	Neonates	Children	Adults
Chronic infection	90%	30%	1%
Recovery	10%	70%	99%



Buster, Neth J Med 2006

Fig. 2 Chronic hepatitis B infection: phases of infection (from Buster EH, Janssen HL, Antiviral treatment for chronic hepatitis B virus infection—immune modulation or viral suppression? Neth J Med 2006;64:175–85).

Most cases of chronic hepatitis B in the reactivation phase are HBeAg-negative, but a few patients may be HBeAg-positive (Fig. 2). The rates of progression to cirrhosis and hepatocellular carcinoma, with the associated mortality rates, are shown in Fig. 3.



Adapted : De Franchis, J Hepatol 2003

Fig. 3 Progression to cirrhosis and hepatocellular carcinoma, with mortality rates (adapted from de Franchis et al., EASL International Consensus Conference on Hepatitis B. 13–14 September, 2002, Geneva, Switzerland. Consensus statement (long version), J Hepatol 2003;39(Suppl 1):S3–25).

4 Laboratory diagnosis of hepatitis B

Laboratory diagnosis

The diagnosis of *acute hepatitis B* is based on the detection of HB_sAg and anti-HB_c (IgM). During the initial phase of infection, markers of HBV replication—HB_eAg and HBV DNA—are also present. Recovery is accompanied by the disappearance of detectable HBV DNA, HB_eAg seroconversion to anti-HB_e, and subsequently clearance of HB_sAg with seroconversion to anti-HB_s with anti-HB_c (IgG). All this should take place within 3 months of the diagnosis.

Rarely, patients present during the window period when HB_sAg has already become negative but anti-HB_s is not yet positive. In this setting, which is more common in patients with fulminant hepatitis B, in whom viral clearance tends to be more rapid, IgM anti-HB_c is the sole marker of acute HBV infection.

Cascade 1 Laboratory diagnosis of acute hepatitis B

Level 1	HB _s Ag, anti-HB _c (IgM) and anti-HB _s ALT, bilirubin, and INR
Level 2	HB _s Ag, anti-HB _s , ALT
Level 3	HB _s Ag, ALT

ALT, alanine aminotransferase; HB_c, hepatitis B core (antigen); HB_sAg, hepatitis B surface antigen; IgM, immunoglobulin M; INR, international normalized ratio.

The differential diagnosis of HB_sAg-positive acute hepatitis includes exacerbations of chronic hepatitis B, which may occur at any time in any individual who is chronically infected (at these times, reversion back to anti-HB_c IgM may occur). Acute hepatitis may occur following withdrawal from immunosuppressive therapy or through superinfection of a person chronically infected with hepatitis B with either hepatitis C and/or D virus. Superimposed acute hepatitis due to drugs and other toxins administered to someone who has “silent” chronic hepatitis B infection may also present as acute hepatitis. A precipitating factor is sometimes not identified.

Past HBV infection. Previous HBV infection is characterized by the presence of anti-HB_s and IgG anti-HB_c (anti-HB_s sometimes becomes undetectable after many years). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HB_s.

Chronic HBV infection. Diagnosis of chronic HBV infection is defined as the persistence of HB_sAg for more than 6 months. It needs to be established whether the individual is in the HB_eAg-positive or HB_eAg-negative phase of the infection (Table 3). Additional tests for markers of HBV replication—namely, HB_eAg and serial measurements of serum HBV DNA, in addition to alanine aminotransferase (ALT)—should be carried out. This will in part determine whether the patient should be considered for HBV therapy. Both HB_eAg-positive and HB_eAg-negative patients, even if they have normal serum ALT (women < 20 IU/L and men < 30 IU/L) and/or undetectable HBV DNA, still need to be monitored lifelong, as the condition may

change over time although they remain asymptomatic. Among individuals with chronic HB_sAg infection, those with elevated serum ALT concentrations should be followed more closely, preferably with serial HBV DNA measurements. It is important to know the lower limit of detection of the method used to measure HBV DNA, as values that are persistently $\geq 10^3$ IU/mL will prompt consideration of antiviral therapy. The decision on whether to initiate therapy depends on multiple factors (i.e., not just the level of HBV DNA and/or ALT). If the liver disease appears to be progressing (as judged by liver biopsy or noninvasive markers of inflammation and fibrosis), treatment should be considered. Additional tests for hepatitis C and hepatitis D should also be conducted in order to rule out superinfection with other hepatitis virus(es), particularly in patients with elevated ALT but undetectable HBV DNA.

Table 3 Differentiation of chronic hepatitis B infection

HB _s Ag (≥ 6 months)	ALT (normal range < 20 IU/L in women, < 30 IU/L in men)	HB _e Ag	Anti-HB _e	HBV-DNA LLD < 6–12 IU/mL
HB _e Ag-positive, immune-tolerant phase	Normal	Positive	Negative	$> 10^8$ c/mL $> 10^7$ IU/mL
HB _e Ag-positive chronic hepatitis B	Increased	Positive	Negative	$> 10^5$ c/mL $> 10^4$ IU/mL
Chronic hepatitis B, immune- control phase	Normal	Negative	Positive	$< 10^4$ c/mL $< 10^3$ IU/mL
Anti-HB _e -positive chronic hepatitis B	Increased (sustained or intermittent)	Negative	Positive	$> 10^4$ c/mL $> 10^3$ IU/mL
Hepatitis D	Increased	+/-	+/-	Negative/low
Coinfection with hepatitis C	Increased	+/-	+/-	Negative/low (HCV RNA- positive)

ALT, alanine aminotransferase; c/mL, copies per milliliter; HB_e, HB_eAg, hepatitis e antigen; HB_sAg, hepatitis B surface antigen; LLD, lower limit of detection.

Disclaimer: 1 IU/mL \approx 5 copies/mL. However, the error in the viral load test \approx 3-fold, or 0.51 g. To simplify for guidelines, therefore, 1 IU/mL \approx 10 copies/mL.

Occult HBV and HBV reactivation

Occult HBV infection can be defined as the persistence of HBV DNA in the liver tissue (and in some cases serum) of individuals in whom hepatitis B surface antigen (HB_sAg) is not detectable in the blood, with or without anti-HB_e.

Occult HBV infection is prevalent worldwide, but its frequency is related to the prevalence of overt HBV infection in a specific geographic area. Occult HBV is transmissible through blood transfusions and organ transplantation.

- Blood products should be screened for HB_sAg, anti-HB_e, and ideally HBV DNA.

- Organs from donors with anti-HB_c and/or anti-HB_s should preferably be used for recipients who test positive for anti-HB_s or HB_sAg.

Occult HBV infection is possibly an additional risk factor for HCC in anti-HCV–positive patients. It may also be associated with progression of chronic liver disease due to other causes than HBV.

HBV reactivation. Chronic HBV infection is frequently reactivated by cancer chemotherapy and other immunosuppressive or immunomodulator therapy (e.g., targeted immunotherapy) and may lead to a subclinical, icteric, or even fatal acute-on-chronic hepatitis.

Preemptive treatment with a nucleoside/nucleotide analogue is recommended in HB_sAg-positive patients who are going to receive anticancer or immunosuppressive drugs.

Occult HBV infection may be reactivated during prolonged cancer chemotherapy and immunosuppressive treatment, becoming overt chronic HBV infection. Pretreatment is not required, but these patients need to be monitored for ALT and HB_sAg during immunosuppressive therapy. In summary:

- The benefits of preemptive treatment for occult HBV reactivation remain unclear at the present time.
- Screening for HB_sAg and anti-HB_c is necessary before chemotherapy or immunosuppressive or immunomodulator therapy are started.
- For patients with evidence of HBV infection, as confirmed by positive anti-HB_c with or without anti-HB_s, a regular check-up for HBV-related markers is recommended during and after chemotherapy and immunosuppressive therapy.

Patients receiving chemotherapy or immunosuppression should follow the American Association for the Study of Liver Diseases (AASLD) and Asian-Pacific Association for the Study of the Liver (APASL) guidelines (Fig. 4).

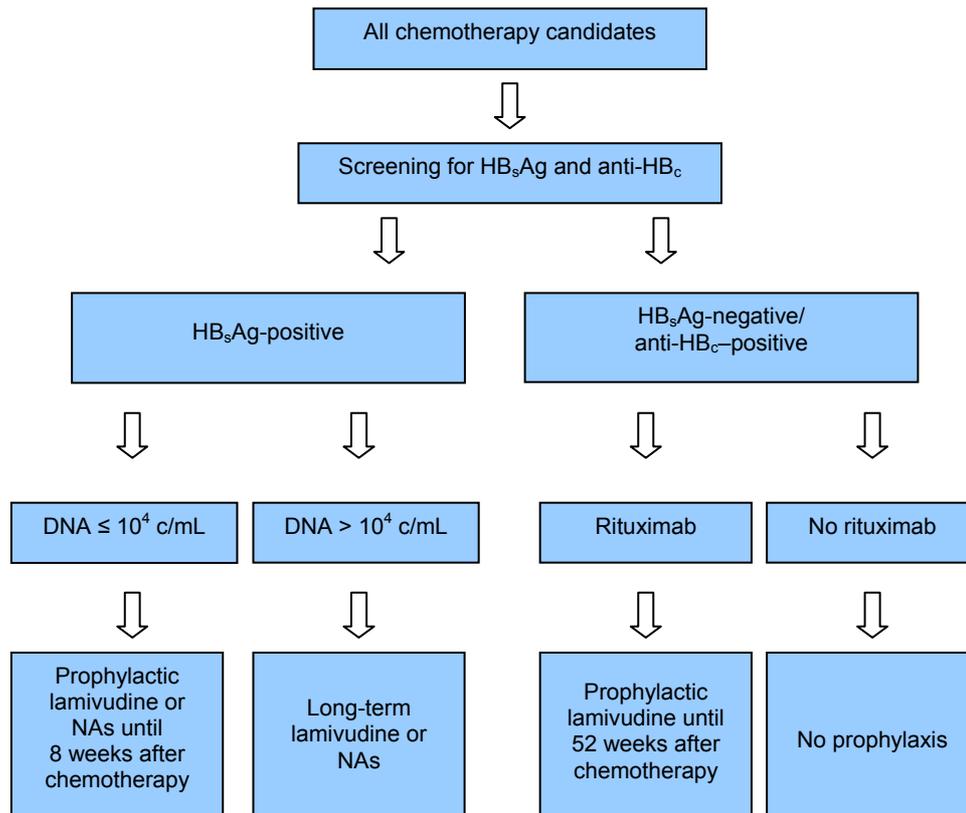


Fig. 4 Asian-Pacific Association for the Study of the Liver algorithm for all candidates for chemotherapy. c/mL, copies/mL; NA, nucleoside analogue.

5 Long-term monitoring and screening of chronic hepatitis B

Monitoring after cessation of therapy (Table 4)

Initial evaluation of patients with chronic HBV infection. Individuals with newly detected chronic HBV infection need to understand that long-term monitoring for the development of chronic hepatitis, cirrhosis, and HCC via a series of clinical examinations and laboratory tests is required even if they are asymptomatic. It is important to verify the stage of chronic hepatitis B (CHB) and decide the frequency of follow-up examinations needed. The initial examination should include:

- History and physical examination, especially skin and abdominal examination.
- HBV infection markers, including HB_eAg/anti-HB_e and HBV DNA to classify the phase of chronic HBV infection, as well as the HBV genotype if antiviral therapy with interferon is contemplated.
- Complete liver panel (ALT/AST to identify active inflammation, and bilirubin, prothrombin time, and albumin to check liver synthetic function to determine whether there is liver failure).
- Complete blood count, especially platelet count as a surrogate marker for portal hypertension.
- Abdominal ultrasonography for baseline screening for HCC.

- Other viral infection markers, including HCV and HDV, particularly if ALT is elevated but HBV DNA is low or undetectable.
- Before oral antiviral therapy is introduced, all patients should be screened for human immunodeficiency virus (HIV).
- Liver biopsy if required.

Table 4 Risk factors associated with progression of chronic hepatitis B

Male gender
Older age
Unrelenting HBeAg-seropositive hepatitis
Sustained elevation in serum HBV DNA
Sustained elevation in serum ALT
Coinfection with HIV
HBV genotypes C and D
Coinfection with HCV and HDV
Cigarette smoking
Excess alcohol intake
Family history of HCC
Host genetic polymorphisms
Aflatoxin exposure

ALT, alanine aminotransferase; HB_eAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

Long-term follow-up monitoring of CHB patients. The aim in CHB monitoring is to assess the progression of liver disease and clarify the indication for treatment. In evaluating the response to therapy, the frequency of monitoring and types of laboratory testing depend on the CHB phase, disease severity, and treatment protocol.

HCC screening

The aim is to detect tumors smaller than 3 cm in diameter, and preferably less than 2 cm, in order to offer a potential for curative treatment. Screening for HCC is advocated in all cirrhotic patients, as they are at the highest risk of developing HCC. However, in Africa and South-East Asia, where HBV infection is acquired early in life, HCC may develop in a noncirrhotic liver.

The AASLD recommends HCC surveillance using ultrasonography in the following types of patient with chronic hepatitis B:

- Asian men over the age of 40 and Asian women over the age of 50
- All patients with cirrhosis, regardless of age
- Patients with a family history of HCC; any age
- Africans over the age of 20
- Any individuals with HBV/HIV coinfection

For hepatitis B carriers not included in this list, the risk of HCC varies depending on the severity of the underlying liver disease and current and past hepatic inflammatory activity. Those with high HBV DNA concentrations and ongoing hepatic inflammatory activity (evidenced by elevated ALT values) are at high risk for HCC.

6 Treatment for chronic hepatitis B

Introduction

Before any form of HBV therapy is started, and optimally at the time of first presentation, the patient needs to be provided with information about the natural history of chronic hepatitis B infection and the fact that most infections remain entirely without symptoms even in those with severe disease, so that there is a need for regular lifelong monitoring, and this information should be discussed with the patient. Possible transmission to contacts, the timing of the start of treatment, and the need for absolute compliance with follow-up examinations when the patient is either on or off treatment, need to be explained. In women of childbearing age, only drugs that are considered safe in pregnancy should be used, since once a nucleoside or nucleotide has been prescribed it cannot be stopped abruptly in those who remain HB_eAg-positive. The patient needs to understand that cessation of treatment may precipitate acute liver failure even if there is no cirrhosis.

Gold standard and cascades

The current gold standards are shown in Figs. 5 and 6 below. Table 5 provides an overview of currently approved treatment regimens for chronic hepatitis B, and Table 6 lists recommended treatments. Cascades are included to reflect resource-sensitive options.

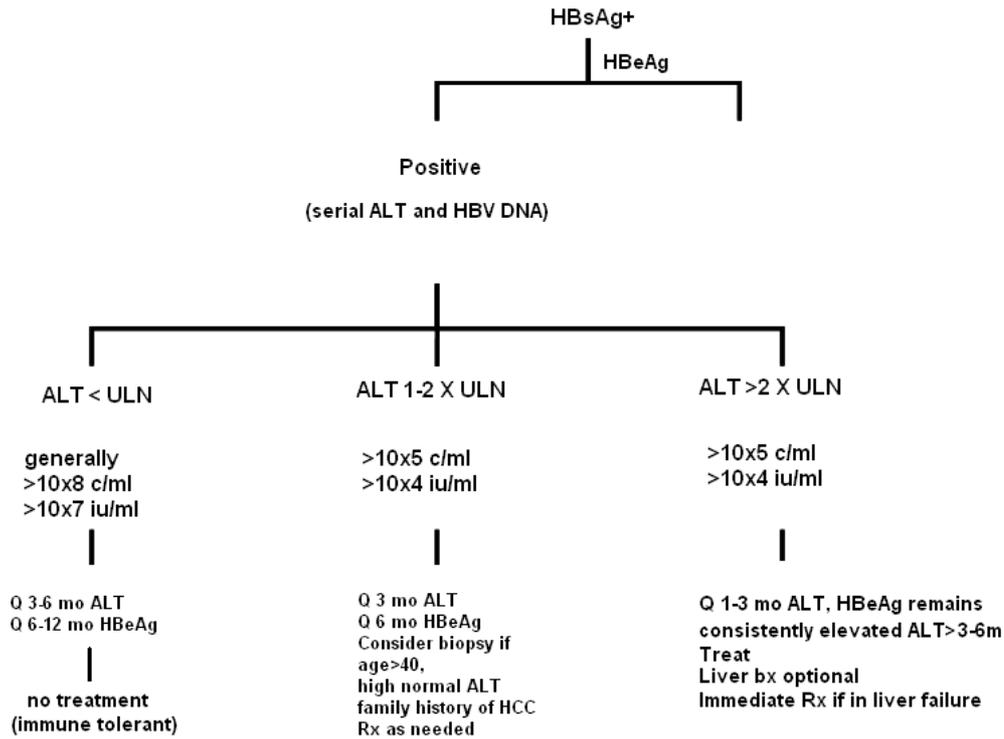


Fig. 5 Management of chronic HB_eAg-positive infection. Surveillance for hepatocellular carcinoma should be carried out if indicated (depending on age, sex, severity of liver disease, and family history). (Adapted from Lok AS, McMahon BJ, Chronic hepatitis B, *Hepatology* 2007;45:507–39.) ALT, alanine aminotransferase; bx, biopsy; HB_eAg, hepatitis b e antigen; HB_sAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; Rx, treatment; ULN, upper limit of normal.

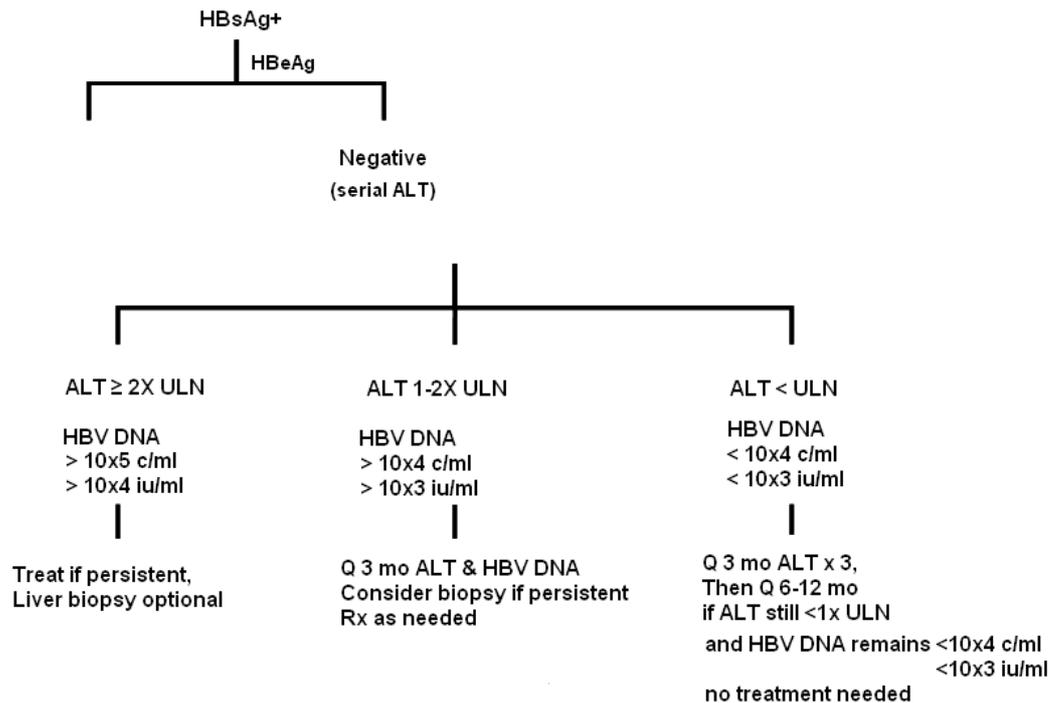


Fig. 6 Management of chronic HB_eAg-negative infection. Surveillance for hepatocellular carcinoma should be carried out if indicated (depending on age, sex, severity of liver disease, and family history). (Adapted from Lok AS, McMahon BJ, Chronic hepatitis B, *Hepatology* 2007;45:507–39.). ALT, alanine aminotransferase; HB_eAg, hepatitis b e antigen; HB_sAg, hepatitis B surface antigen; HBV, hepatitis B virus; Rx, treatment; ULN, upper limit of normal.

N.B. The upper limit of normal for alanine aminotransferase (ALT) is 19 IU/L in women and 30 IU/L in men. Monitoring HBV DNA every 3 months in patients with ALT one to two times the upper limit of normal is expensive and not practical when economic resources are limited; see the cascades below for further solutions.

Cascade 2a Immunotolerant phase (no therapy)

Level 1	Annual HB _e Ag and HBV DNA 6-monthly ALT
Level 2	Annual HB _e Ag 6-monthly ALT
Level 3	6-monthly ALT

Cascade 2b Immunoactive phase monitoring (off therapy)

Level 1	3-monthly ALT and HBV DNA 6-monthly HB _e Ag and CBC Prior to any treatment, do HIV test
Level 2	3-monthly ALT 6-monthly HB _e Ag, HBV DNA, and CBC Prior to any treatment, do HIV test

Level 3	3-monthly ALT 6-monthly recheck on HB _e Ag and CBC Prior to any treatment, do HIV test
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Cascade 2c Immune-control phase monitoring (off therapy)

Level 1	Annual HB _s Ag and anti-HB _e Ag 6-monthly ALT, HBV DNA, and CBC
Level 2	6-monthly ALT, HBV DNA, and CBC
Level 3	6-monthly ALT and CBC
Level 4	Annual ALT and CBC

Cascade 2d Reactivation phase, HB_eAg-negative (off therapy)

Level 1	3-monthly ALT and HBV DNA 6-monthly CBC Prior to treatment, do HIV test
Level 2	6-monthly ALT and HBV DNA 6-monthly CBC Prior to treatment, do HIV test
Level 3	6-monthly ALT 6-monthly CBC Prior to treatment, do HIV test

ALT, alanine aminotransferase; CBC, complete blood count; HB_eAg, hepatitis B e antigen; HB_sAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Table 5 Comparison of approved treatments for chronic hepatitis B

	IFN or peginterferon alfa	Lamivudine (LAM)	Adefovir (ADF)	Entecavir (ETV)	Telbivudine (LdT)	Tenofovir (TDF)
HB _e Ag+, normal ALT	No therapy	No therapy	No therapy	No therapy	No therapy	No therapy
HB _e Ag-positive chronic hepatitis	Indicated	Indicated *	Indicated	Indicated	Indicated *	Indicated
HB _e Ag-negative chronic hepatitis	Indicated	Indicated *	Indicated	Indicated	Indicated *	Indicated

	IFN or peginterferon alfa	Lamivudine (LAM)	Adefovir (ADF)	Entecavir (ETV)	Telbivudine (LdT)	Tenofovir (TDF)
<i>Duration of treatment</i>						
HB _e Ag-positive chronic hepatitis	4–12 mo [†]	Until HB _e Ab-positive [‡]	Until HB _e Ab-positive [‡]	Until HB _e Ab-positive [‡]	Until HB _e Ab-positive [‡]	Until HB _e Ab-positive [‡]
HB _e Ag-negative chronic hepatitis	1–2 y	Unknown; ? until loss of HB _s Ag	Unknown; ? until loss of HB _s Ag	Unknown; ? until loss of HB _s Ag	Unknown; ? until loss of HB _s Ag	Unknown; ? until loss of HB _s Ag
Route	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Side effects	Many	Negligible	Potential nephrotoxicity	Negligible	Negligible	Negligible
Drug resistance	None	≈ 20%, yr 1 ≈ 70%, yr 5	None, yr 1 29%, yr 5	< 1% at 1 y ? 30% if LAM-R	2–5% in yr 1; 8–22% yr 2; never give for LAM-R	None at yr 1
Cost	Initially high (but finite duration)	Lowest	Intermediate high particularly as long term therapy needed	Very high, particularly as long-term therapy needed	Intermediate high, particularly as long-term therapy needed	Intermediate high, particularly as long term therapy needed

ALT, alanine aminotransferase; HB_eAb, HB_e antibody; HB_eAg, hepatitis B e antigen; HB_sAg, hepatitis B surface antigen; IFN, interferon; LAM-R, lamivudine-resistant/resistance.

* There is a high rate of resistance, particularly in patients with a baseline viral load $\geq 10^4$ IU/mL, $\geq 10^5$ c/mL.

[†] Peginterferon approved for 12 months.

[‡] Treatment for as long as the patient remains HB_eAg-positive and for at least 6 months after anti-HBe seroconversion.

Table 6 Recommendations for when to treat chronic hepatitis B

	HBV DNA (PCR)	ALT	Treatment strategy
HB _e Ag-positive	$\geq 10^4$ IU/mL $\geq 10^5$ c/mL	$\leq 2 \times$ ULN	Low efficacy with current treatments —Observe; consider treatment when ALT becomes more elevated —Consider biopsy in persons > 40 years, with ALT persistently high normal to $2 \times$ ULN, or with family history of HCC —Treatment if HBV DNA $\geq 10^4$ IU/mL, $\geq 10^5$ c/mL and biopsy shows moderate/severe inflammation or significant fibrosis

HBV DNA (PCR)	ALT	Treatment strategy
$\geq 10^4$ IU/mL $\geq 10^5$ c/mL	$> 2 \times$ ULN	<p>—Observe for 3–6 months and treat if spontaneous HB_eAg loss fails to occur. Consider liver biopsy prior to treatment if no liver failure present</p> <p>—Immediate treatment if icteric or if there is clinical decompensation</p> <p>—IFN-α/PEG-IFN-α, LAM, ADV, ETC, LdT, or TDF may be used as initial therapy (do <i>not</i> use IFN in decompensated disease)</p> <p>—LAM and LdT are not preferred due to the high rate of drug resistance</p> <p>—End point of treatment: seroconversion from HB_eAg to anti-HB_e</p> <p>—Duration of therapy:</p> <ul style="list-style-type: none"> • IFN-α: 16–24 weeks; if no antiviral response, stop; if HBV DNA becomes undetectable, sufficient • PEG-IFN-α: 24–48 weeks; if no antiviral response, stop; if HBV DNA becomes undetectable, sufficient • LAM/ADV/ETV/LdT/TDF: minimum 1 year, continue for at least 6 months after HB_eAg seroconversion; <i>cannot</i> stop unless seroconversion occurs (n.b., TDF not licensed everywhere for hepatitis B mono-infection)
HB _e Ag-negative $\geq 10^4$ IU/mL $\geq 10^5$ c/mL	$> 2 \times$ ULN	<p>—End point of treatment not defined</p> <p>—Liver biopsy preferred before initiation of therapy to evaluate severity of fibrosis</p> <p>Duration of therapy:*</p> <ul style="list-style-type: none"> • IFN-α/PEG-IFN-α: 1 year or more • LAM/ADV/ETV/LdT/TDF: until loss of HB_sAg
HB _e Ag-negative $\geq 10^3$ IU/mL $\geq 10^4$ c/mL	$1-2 \times$ ULN	Consider liver biopsy and treat if liver biopsy shows moderate/severe necroinflammation
HB _e Ag-negative $\geq 10^3$ IU/mL $\geq 10^4$ c/mL	\leq ULN	Observe; treat if HBV DNA or ALT becomes higher
Detectable $< 10^3$ IU/mL $< 10^4$ c/mL	\leq ULN	<i>Compensated cirrhosis</i> : no treatment if ALT $<$ ULN
HB _e Ag-negative $< 10^3$ IU/mL $< 10^4$ c/mL	\leq ULN	<i>Decompensated cirrhosis</i> : coordinate treatment with transplant center. At this level of HBV DNA, any nucleoside/nucleotide acceptable (monitor renal function carefully)
HB _e Ag-negative Undetectable	\leq ULN	<i>Compensated cirrhosis</i> : observe

HBV DNA (PCR)	ALT	Treatment strategy
Undetectable	≤ ULN	<i>Decompensated cirrhosis: refer for liver transplant</i>

ADV adefovir; ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B; HCC, hepatocellular carcinoma; IFN- α , interferon alfa; LAM, lamivudine; LdT, telbivudine; PCR, polymerase chain reaction; PEG-IFN- α , peginterferon alfa; TDF, tenofovir (not yet licensed for hepatitis B mono-infection); ULN, upper limit of normal.

* Note: there is no strong evidence currently for the use of on-treatment HBV DNA levels as a stopping rule in interferon or peginterferon therapy.

Cascade 3a Immunoactive phase: HB_eAg-positive—monitoring when the patient is on treatment

Level 1	ALT and HBV DNA at 3 and 6 months Thereafter every 6 months (unless cirrhotic; then HBV DNA 3-monthly) HB _e Ag 6-monthly CBC and creatinine annually
Level 2	ALT 3-monthly HBV DNA at 3 and 6 months into treatment Then 6-monthly HB _e Ag annually CBC and creatinine annually
Level 3	ALT 3-monthly HB _e Ag annually CBC and creatinine annually

Cascade 3b Reactivation phase: HB_eAg-negative hepatitis—monitoring when the patient is on treatment

Level 1	ALT and HBV DNA at 3 months Thereafter every 6 months (unless cirrhotic; then 3-monthly) HB _s Ag annually CBC and creatinine annually
Level 2	ALT and HBV DNA at 3 months Then ALT 6-monthly HBV DNA annually HB _s Ag, CBC and creatinine annually
Level 3	ALT every 3 months HB _s Ag, CBC and creatinine annually

ALT, alanine aminotransferase; CBC, complete blood count; HB_eAg, hepatitis B e antigen; HB_sAg, hepatitis B surface antigen; HBV, hepatitis B virus.

HB_eAg-positive hepatitis (Tables 7, 8)

Recommendations. As a general rule, HB_eAg-positive patients with persistent ALT $\geq 2 \times$ upper limit of normal, and with HBV DNA $\geq 10^4$ IU/mL or $\geq 10^5$ c/mL, should be considered for treatment.

- In patients who have had a liver biopsy, treatment should be started for those with moderate to severe inflammation or significant fibrosis.
- Treatment should be initiated in those who have cirrhosis and those who have experienced a hepatitis B flare.
- Any of the approved therapies can be chosen, and the decision regarding the selection of therapy should include an assessment of efficacy, safety, and genetic barrier (low resistance rate).
- Patients should be monitored regularly during therapy at 3–6-monthly intervals, or more frequently if they are on interferon-based therapy to monitor for efficacy, safety, and early evidence of resistance (only if they are taking nucleoside/nucleotide analogues).
- Ideally, patients should be monitored with ALT, HB_eAg, anti-HB_e, and HBV DNA, but this may not be possible in countries where these tests are not available or are prohibitively expensive, in which case ALT will have to suffice.
- *Virologic breakthrough*: an increase in HBV DNA > 1 log above the nadir after a virologic response has been achieved during continued treatment (for nucleoside/nucleotide analogues).
- *Biochemical breakthrough*: an increase in ALT above the upper limit of normal after normalization has been achieved during continued treatment.
- Patients with resistance should be considered for rescue therapy with nucleosides/nucleotides that do not have a cross-resistant profile (LAM, LdT, ETV same profile).
- Oral agents should be continued until at least 6 months after the end point of HB_eAg seroconversion occurs in HB_eAg-positive hepatitis.
- Interferon-based therapies have the advantage of a fixed course of therapy, rather than relying on the occurrence of HB_eAg seroconversion, as seroconversion may take place up to 6 months after discontinuation of interferon. The advantage of interferon is that it can be stopped abruptly with no fear of flare-up (e.g., in women of childbearing age, in whom caution is needed with oral antiviral therapy as some agents appear to be safer than others).
- Close monitoring is recommended after oral therapy has been stopped or withdrawn.
- It is advisable to check for HIV coinfection before treatment.

Table 7 Responses to oral antiviral therapies approved by the United States Food and Drug Administration (FDA) in treatment-naïve HB_eAg-positive patients with chronic hepatitis B

	Lamivudine 100 mg/day 48–52 weeks	Adefovir dipivoxil 10 mg/day 48 weeks	Entecavir 0.5 mg/day 48 weeks	Telbivudine 600 mg/day 52 weeks	Placebo
Loss of serum HBV DNA*	44%	21%	67%	60%	0–16%
Serum HBV DNA reduction from baseline	5 log	4 log	7 log	6 log	0–0.6 log
Normalization of serum ALT	41–75%	48%	68%	77%	7–24%
Histologic improvement	49–56%	53%	72%	65%	25%
HB _e Ag loss	17–32%	24%	22%	26%	6–11%
HB _e Ag seroconversion	16–21%	12%	21%	22%	7%

* The percentages for lamivudine were determined using a branched-chain hybridization assay, and those for adefovir and telbivudine by polymerase chain reaction assay.

Table 8 The response at the end of treatment in HB_eAg-positive patients with chronic hepatitis B with peginterferon alfa as monotherapy or dual therapy (with the addition of lamivudine)

	Peginterferon alfa 2a for 48 weeks	Peginterferon alfa 2b for 52 weeks	Peginterferon alfa 2b plus lamivudine
Loss of serum HBV DNA	25%	NA	33%
Serum HBV DNA reduction from baseline	4 log	2 log	5 log
Normalization of serum ALT	32–44%	46%/44%*	51%/35%*
Histologic improvement	38%	53%	33%
HB _e Ag loss	30%/34%*	40%/49%*	44%/35%*
HB _e Ag seroconversion	27%/32%*	30%/39%*	25%/29%*

* Responses at the end of treatment/at the end of follow-up (24 weeks after stopping therapy).

HB_eAg-negative hepatitis

HB_eAg-negative CHB represents a late phase in the course of chronic HBV infection.

Recommendations for HBV treatment

HBV DNA $\geq 10^4$ IU/mL or $\geq 10^5$ c/mL and serum ALT $> 2 \times$ ULN

- Consider liver biopsy in patients with HBV DNA $\geq 10^4$ IU/mL or $\geq 10^5$ c/mL and serum ALT $< 2 \times$ ULN or HBV DNA $\geq 10^3$ IU/mL or $\geq 10^4$ c/mL and serum ALT $>$ ULN; treat if liver biopsy shows moderate/severe necroinflammation or significant fibrosis
 - HBV DNA $\geq 10^3$ IU/mL or $\geq 10^4$ c/mL in patients with compensated cirrhosis
 - Detectable HBV DNA in patients with decompensated cirrhosis
- 1 The treatment regimen can be conventional interferon (not in the presence of liver failure), peginterferon alfa, or nucleoside/nucleotide analogues.
 - 2 In patients with contraindications to interferon such as decompensated cirrhosis or autoimmune disease, oral nucleoside/nucleotide analogues are recommended.
 - 3 The duration of interferon or peginterferon therapy is 1 year.
 - 4 For antiviral therapy, agents with a low resistance rate such as adefovir, entecavir, or tenofovir are preferred, particularly in patients with cirrhosis. However, where economic constraints are a consideration, therapy can be started with lamivudine (or telbivudine), with early adefovir add-on therapy when drug resistance is detected or when HBV DNA remains at $\geq 10^4$ IU/mL or $\geq 10^5$ c/mL at week 24 of therapy.
 - 5 The optimal duration of anti-viral therapy for HB_eAg-negative CHB is not known, but long-term therapy for more than 1 year is required—possibly lifelong or until loss of HB_sAg.
 - 6 Monitoring both biochemistry and HBV DNA every 3–6 months is recommended for assessing the treatment response and for early detection of drug resistance.
 - 7 A nonresistant drug should be added or switched to when drug resistance is detected. Add-on therapy is preferred, particularly in patients with advanced fibrosis or with HBV DNA $\geq 10^5$ IU/mL or $\geq 10^6$ c/mL.
 - 8 Before treatment with nucleoside/nucleotide analogues is started, the patient should be tested for HIV.

Drug resistance

The following strategies can be used to prevent resistance:

- For the first-line therapy, choose a potent antiviral drug and/or one with a low incidence of resistance (high genetic barrier) over time.
- The viral load should be monitored frequently (every 3–6 months) during treatment, and resistance testing (genotyping) should be carried out in case of viral breakthrough or suboptimal viral suppression, so as to allow genotypic resistance to be detected before clinical consequences develop.
- If HBV DNA is $> 10^5$ IU/mL or $\geq 10^6$ c/mL and/or ALT has become elevated at the time when resistance is first detected, then adding another antiviral agent is preferable to switching to another antiviral. (No drug resistance to interferon has been described, although some individuals do not show any reduction in HBV DNA, in which case therapy should be stopped.)

Coinfection

HBV–HDV. Hepatitis D virus (HDV) is a defective virus with a circular RNA genome and a single structured protein, hepatitis delta antigen. The virus requires HBV surface antigen to envelop its delta antigen. This helper function of HBV is important for HDV assembly and propagation. Up to 5% of the world's population is infected with HBV, and probably 5% of those chronically infected with HBV have HDV infection. However, some endemic areas in the developing world may have much higher rates. The virus simultaneously coinfects with HBV, or superinfects in someone already chronically infected with HBV. Coinfection evolves to chronicity only in 2%, while superinfection leads to progressive disease and cirrhosis in more than 80% of cases. Cirrhosis develops at a younger age than in patients with chronic HBV mono-infection.

Recommendations

- Universal HBV vaccination should be implemented to prevent the HDV infection in the community and thereby decrease its prevalence.
- HB_sAg-positive patients should be evaluated to rule out HDV infection, particularly if hepatitis is present in the face of little or no HBV viral replication (i.e., a low HBV viral load).
- HDV infection can be diagnosed by detection of HDV RNA in serum by PCR, or indirectly by detection of antibodies against hepatitis D antigen (anti-HD) of the IgG and IgM classes.
- Chronic hepatitis D should be treated with interferon (preferably pegylated interferon) for at least 12 months.

HBV–HCV. Infection with HBV and hepatitis C (HCV) viruses may occur, as the two share similar risk factors and modes of transmission. As a consequence, coinfection with the two agents occurs quite frequently, particularly in geographic areas where both agents are more endemic. For the same reasons, HBV and HCV coinfection and even triple infection with HBV, HCV and HIV and potentially quadruple (HDV in addition) may be observed in high risk populations.

The interferons (and pegylated interferons) are well-established therapeutic agents for both HBV and HCV and represent the treatment of choice for coinfecting patients (in the absence of HIV). When HCV predominates (detectable HCV-RNA and low or undetectable HBV DNA) combination therapy with peginterferon and ribavirin is recommended. When HBV predominates (high HBV DNA levels), hepatitis C has often been cleared (i.e., undetectable HCV-RNA). Peginterferon monotherapy may be preferred. In the case of contraindications to interferon-based therapy, oral nucleosides/nucleotides active against HBV can be used when it is the latter that is actively replicating. Regular monitoring of ALT and of HCV RNA and HBV DNA during and after therapy is required, as suppression of the dominant virus by antiviral therapy may result in reactivation of the previously suppressed virus.

HBV–HIV. An estimated 40 million persons throughout the world are infected with HIV. Chronic infection with HBV may be present due to the common modes of transmission of the viruses—parenteral, vertical, and sexual.

The prevalence of CHB infection among HIV-infected persons may be ten times or more higher than that of the background population. Chronic HBV infection occurs in 6–14% of HIV-infected persons in western Europe and the United States overall. In

the risk groups, infection rates are 4–6% among heterosexuals, 9–17% of men who have sex with men, and 7–10% of injection drug users.

The absence of controlled trials and the dual activity of some agents complicate the management of CHB infection in patients with HIV coinfection. Treatment regimens depend on the clinical status of both HIV and HBV, but monotherapy with an agent that is effective against both HIV and HBV should be avoided, otherwise resistance to both HIV and HBV will rapidly occur. All patients with CHB should therefore always be checked for HIV coinfection before antiviral treatment is initiated.

The principal objectives of anti-HBV treatment (Figs. 7, 8) are to stop or decrease the progression of liver disease, and to prevent cirrhosis and HCC. Seroconversion to anti-HB_e is not a realistic goal in HIV-coinfected patients. Prolonged suppression of HBV replication leads to histologic improvement, significant decrease or normalization of aminotransferases, and prevention of progression to cirrhosis and end-stage liver disease.

Sustained viral control requires long-term maintenance therapy. Treatment discontinuation in particular may be associated with HBV reactivation and ALT flares. The drawback of long-term therapy is the risk of HBV resistance. To reduce drug resistance, most coinfecting patients require HBV combination therapy.

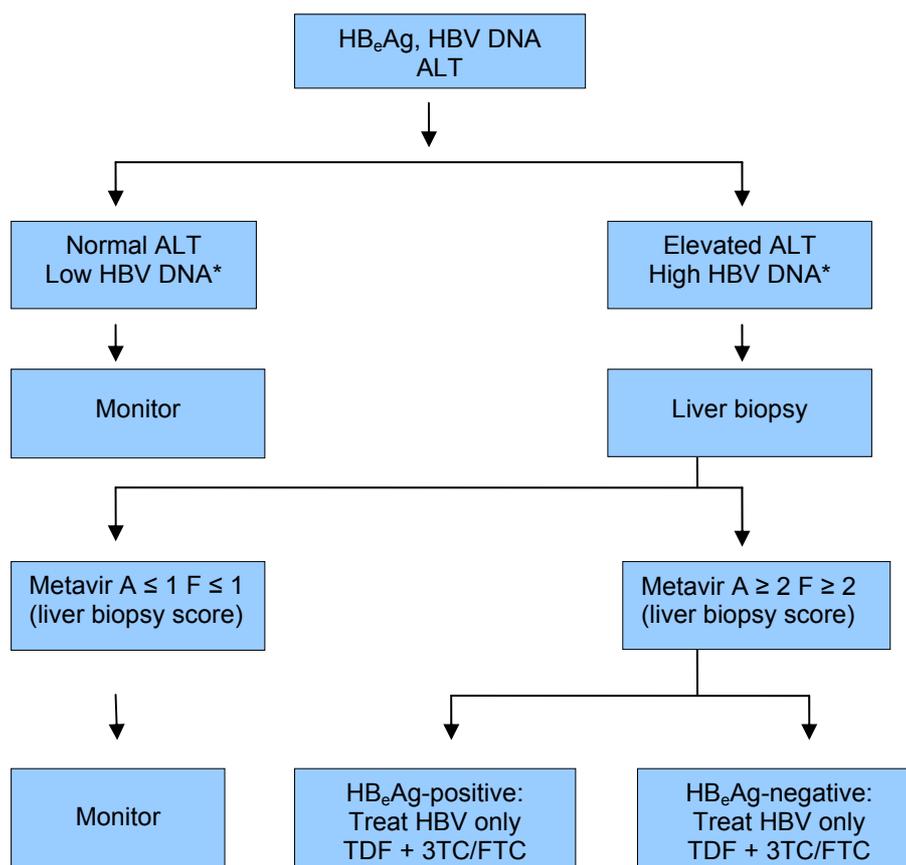


Fig. 7 Summarized treatment algorithm for chronic hepatitis B in patients coinfecting with human immunodeficiency virus (HIV). Patients with *no* indication for anti-HIV therapy. ALT, alanine aminotransferase; FTC, emtricitabine; HB_eAg, hepatitis B e antigen; HBV, hepatitis B virus; 3TC, lamivudine; TDF, tenofovir.

* HBV DNA: $\geq 10^4$ IU/mL (or $> 10^5$ c/mL) in HB_eAg-positive or HB_eAg-negative patients.

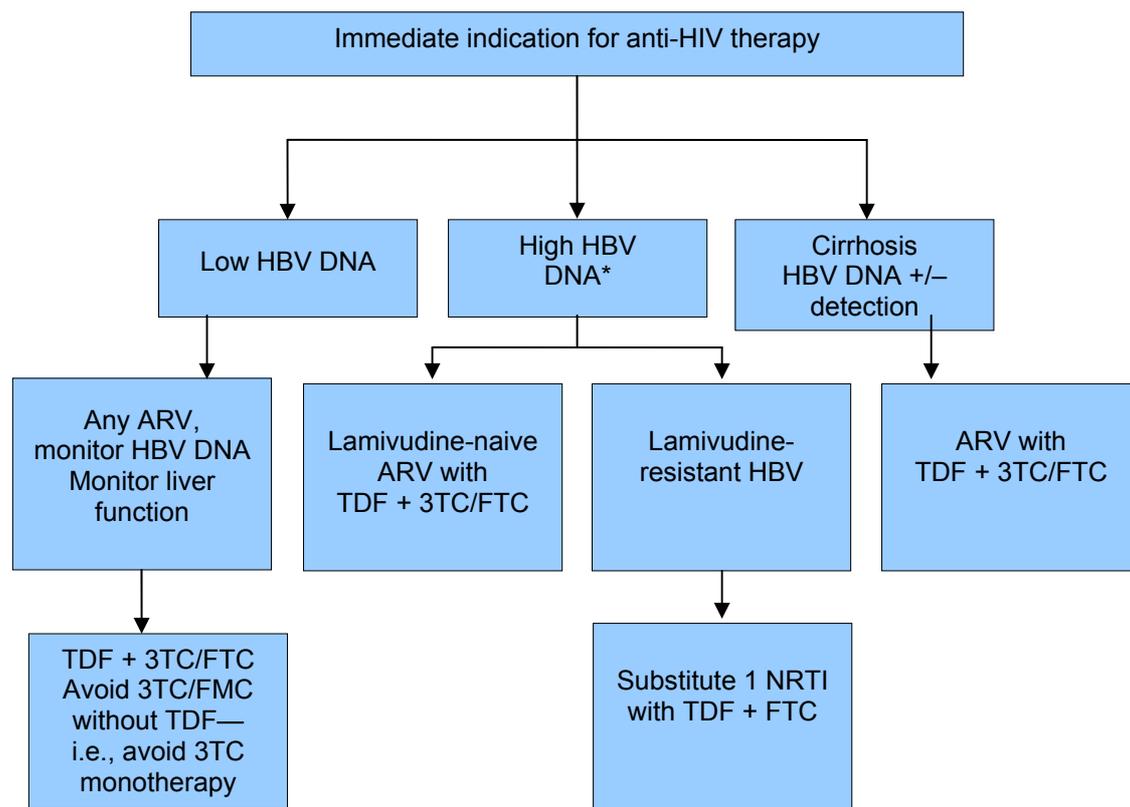


Fig. 8 Immediate indication for anti-HIV therapy. ARV, antiretroviral agent; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; 3TC, lamivudine; TDF, tenofovir.

* HBV DNA: $\geq 10^4$ IU/mL (or $> 10^5$ c/mL) in HB_eAg-positive or HB_eAg-negative patients.

7 Hepatitis B vaccination

Introduction

A program for universal vaccination of all newborns is a key step toward effective control of HBV infection throughout the world. Hepatitis B vaccination is highly cost-effective, in that it prevents infection with HBV and thus reduces the incidence of chronic hepatitis, cirrhosis, and HCC in the vaccinated population.

Active vaccination with hepatitis B vaccine

HB_sAg is the antigen used in the formulation of the hepatitis B vaccine. It is produced from yeast through recombinant DNA technology. It is available as a single-agent preparation or as a fixed combination with other vaccines.

Passive vaccination with hepatitis B immunoglobulin (HBIG)

HBIG is prepared from plasma of individuals who have a high concentration of anti-HB_s. The standard dose of HBIG is 0.06 mL/kg for all applications in adults. In standard doses, it provides temporary protection (i.e., for approximately 3–6 months)

against HBV infection. HBIg is administered by intramuscular injection, preferably into the deltoid or gluteal muscle. If given with hepatitis B vaccine, administration of the HBIg vaccine should be in a different location.

Preexposure prophylaxis

A comprehensive strategy for eliminating HBV transmission should start with a preexposure vaccination program. This should include universal vaccination of:

- All infants at birth, particularly those born to pregnant women who test positive when screened for hepatitis B surface antigen.
- Postexposure immunoprophylaxis to children born to mothers whose HB_sAg status is unknown.
- Catch-up vaccination of all children and adolescents who have not previously been vaccinated.
- Vaccination of unvaccinated adults exposed to risks of HBV infection (however, typically “high-risk” individuals frequently do not access or inform health-care facilities; hence the need for universal childhood vaccination).

Vaccination schedules

- Primary vaccination, consisting of three or more intramuscular doses of hepatitis B vaccine administered at 0, 1, and 6 months, results in a positive antibody response in 30–55% of adults aged ≤ 40 years after the first dose, 75% after the second dose, and $> 90\%$ after the third dose. These response rates decline when the vaccine is given to older individuals (e.g., $< 90\%$ in persons > 40 years old, 75% in those over 60 years old).
- Other innovative vaccination schedules (e.g. 0, 1, and 4 months or 0, 2, and 4 months) are able to produce dose-specific and final rates of protection similar to those obtained with the 0, 1, 6-month schedule, and may be more practical for newborns.
- Host factors (e.g., smoking, obesity, cirrhosis, genetic factors, immune suppression, renal failure, etc.) are known to result in decreased vaccine response.
- For persons ≥ 18 years old who do not live in an area endemic for hepatitis A, both hepatitis A and B, a combined hepatitis A–hepatitis B vaccine (Twinrix) is available.

Postexposure prophylaxis

Postexposure prophylaxis should be considered for individuals who have had recent exposure (either parenteral or sexual) to blood or other body fluids, if it can be carried out in a timely fashion. Evaluation of the hepatitis B surface antigen status of the infective source and the anti-HB_s status of the exposed person should be carried out before the vaccine is administered. Individuals without prior vaccination should receive both HBIg and hepatitis B vaccine soon after exposure (preferably within 24 h). Hepatitis B vaccine administered simultaneously with HBIg must be at a different injection site. Completion of the hepatitis B vaccine series is again at 0, 1, and 6 months.

Persons who are in the process of being vaccinated (but who have not completed the vaccine series) should receive the appropriate dose of HBIg and should be advised to complete the hepatitis B vaccination series.

Vaccine responders tend to maintain protective anti-HB_s levels for a long time. Individuals who respond to hepatitis B vaccination are protected for at least 20 years (perhaps lifelong), even if vaccinees lack detectable anti-HB_s at the time of a recent exposure.

Thus, immunocompetent persons who are known to have responded to hepatitis B vaccination with anti-HB_s concentrations of ≥ 10 mIU/mL (preferably higher than this) do not require additional passive or active immunization after an HBV exposure. In addition, they do not need further periodic testing to assess anti-HB_s concentrations.

Booster doses are not recommended routinely for immunocompetent individuals, whether they have received the vaccination as infants, adolescents, or adults. Likewise, serologic testing to assess antibody concentrations in any age group is not recommended, except perhaps in certain circumstances—e.g., a booster dose should be administered when the anti-HB_s level is < 10 mIU/mL. It is prudent to recommend booster doses to individuals with a clear, ongoing risk of HBV infection (e.g., when the sexual partner is HB_sAg-positive, or in health-care personnel).

Pregnancy

There are no teratogenic or other risks to the fetus if hepatitis B vaccine is administered to pregnant women. There are no contraindications for hepatitis B vaccination or HBIg administration in pregnant or lactating mothers.

8 Automatic searches, guidelines, further reading, and web sites

Introduction and automatic searches for PubMed

This section provides the best options for obtaining further information and help about hepatitis B.

PubMed/Medline (www.pubmed.org) is the best source for keeping up to date with new evidence for hepatitis B. The two links below are preprogrammed automatic searches in PubMed for evidence-based hepatitis B literature from the last 3 years (link #1) and from the last 3 months (link #2). Just click the link.

- Link 1: [Hepatitis B in the last 3 years](#)
- Link 2: [Hepatitis B in the last 3 months](#)

Guidelines and consensus statements

- Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palù G, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005;42:615–24 (PMID: 15916745).
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- Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep* 2005;54(RR-16):1–31 (available at http://www.ngc.org/summary/summary.aspx?doc_id=8526, accessed 30 August 2008).
- Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006;55(RR-16):1–33; quiz CE1–4 (available at: http://www.ngc.org/summary/summary.aspx?doc_id=10245, accessed 30 August 2008).
- World Gastroenterology Organisation. World Digestive Health Day 29 May 2007. Vade mecum: hepatitis B (available at <http://www.worldgastroenterology.org/videmecum/>, accessed 30 August 2008).

Further reading

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- Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005;34:1329–39 (PMID: 16259217).
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- Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev* 2006;28:112–25 (PMID: 16754644).

Web sites

- American Association for the Study of Liver Diseases
www.aasld.org/
- International Association for the Study of the Liver
<http://www.iaslonline.com/>
- Viral Hepatitis Prevention Board
www.vhpb.org
- American Liver Foundation
www.liverfoundation.org
- Hepatitis Foundation International
www.hepfi.org/
- American Hepato-Pancreato-Biliary Association
www.ahpba.org
- European Association for the Study of the Liver
www.easl.ch
- International Liver Transplantation Society
www.ilts.org
- Safe Injection Global Network (SIGN)
www.injectionsafety.org
- World Health Organization hepatitis B information
http://www.who.int/immunization/topics/hepatitis_b/en/index1.html
- Centers for Disease Control and Prevention
<http://www.cdc.gov/ncidod/diseases/hepatitis/b/>
- Hepatitis B Foundation
<http://www.hepb.org/>
- Advanced Immunization Management (AIM)/ Program for Appropriate Technology in Health(PATH): hepatitis B–specific resources
<http://aim.path.org/en/vaccines/hepb/resources/hepb/index.html>

9 Queries and feedback

The Practice Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some procedures are associated with extra risk? Tell us about your own experience. You are welcome to click on the linked e-mail icon below and let us know your views.

