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Guideline

Guidelines for Prevention and Treatment of Chronic Hepatitis B

Guiqiang Wang[1*], Zhongping Duan[2*], Chinese Society of Infectious Diseases, Chinese Medical Association; Chinese Society of Hepatology, Chinese Medical Association

[1]Center for Liver Diseases, Department of Infectious Diseases, Peking University First Hospital; Department of Infectious and Liver Diseases, Peking University International Hospital, Beijing, China; [2]Center for Difficult and Complicated Liver Diseases and Artificial Liver, Beijing YouAn Hospital, Capital Medical University, Beijing, China

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Abstract

To achieve the goal of the World Health Organization to eliminate viral hepatitis as a major public health threat by 2030, the Chinese Society of Infectious Diseases and the Chinese Society of Hepatology convened an expert panel in 2019 to update the guidelines for the prevention and treatment of chronic hepatitis B (CHB). The current guidelines cover recent advances in basic, clinical, and preventive studies of CHB infection and consider the actual situation in China. These guidelines are intended to provide support for the prevention, diagnosis, and treatment of CHB.

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A Chinese expert panel led by the Chinese Society of Infectious Diseases and the Chinese Society of Hepatology developed the first edition of the guidelines for the prevention and treatment of chronic hepatitis B (CHB) in 2005, which were updated in 2010 and 2015, respectively. Over the past 4 years, significant progress has been made in basic and clinical research on chronic infection with the hepatitis B virus (HBV), both at home and abroad. The guidelines were updated again to standardize the prevention, diagnosis, and treatment of CHB and help to meet the goal to eliminate viral hepatitis as a major public health threat by 2030 that was proposed by the World Health Organization (WHO) in 2016.

The present guidelines aim to help clinicians make informed decisions for the prevention, diagnosis, and treatment of CHB; however, they are not intended to be mandatory standards and will probably not cover and solve all the issues associated with the diagnosis and treatment of CHB. Therefore, clinicians should use the best clinical evidence and their expertise, experience, and available medical resources to develop a comprehensive and reasonable diagnosis and treatment plan that addresses individual needs.

The quality of evidence in this guideline is divided into three levels: A, B, and C, and the strength of the recommendations is categorized into two levels, 1 and 2, as given in Table 1. (revised according to the Grades of Recommendation, Assessment, Development, and Evaluation classification system).

Epidemiology and prevention

Epidemiology

HBV is a global epidemic; however, its prevalence varies significantly between different regions. According to WHO, approximately 257 million people live with chronic HBV infection, 68% of whom live in Africa and the Western Pacific.[1] In 2015, approximately 887,000 people died from HBV infection-related diseases worldwide, and cirrhosis and hepatocellular carcinoma (HCC) accounted for 52% and 38% of the deaths, respectively. The prevalence of hepatitis B surface antigen (HBsAg) in the general population in Southeast Asia and the Western Pacific was 2% (39 million cases) and 6.2% (115 million cases), respectively. The endemicity of HBV in Asia is heterogeneous, and most of the region has a moderate to high prevalence of HBV infection, except for in a few low endemic areas.

In 2014, the Chinese Center for Disease Control and Prevention conducted a national seroepidemiological survey of hepatitis B among people aged 1–29 years. The results showed that the prevalence of HBsAg in people aged 1–4, 5–14, and 15–29 years was 0.32%, 0.94%, and 4.38%, representing a decrease of 96.7%, 91.2%, and 55.1%, respectively compared with the 1992 survey.[2] It was estimated that the current prevalence of HBsAg in the general population was from 5% to 6% in China, and approximately

Keywords: Hepatitis B; Chronic; Guidelines; Prevention; Treatment.

Abbreviations: ACLF, acute-on-chronic liver failure; ADV, adefovir dipivoxil; AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CT, Computerized tomography; DAA, direct-acting antiviral; ETV, entecavir; GFR, glomerular filtration rate; GGT, γ-glutamyl transferase; HBV, hepatitis B virus; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; Ig, immunoglobulin; LAM, lamivudine; LdT, telbivudine; MRI, Magnetic resonance imaging; PT, prothrombin activity time; PTA, prothrombin activity; TAF, tenofovir alafenamide fumarate tablets; TE, transient elastography; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; WHO, World Health Organization.

***Correspondence to:** Guiqiang Wang, Center for Liver Diseases, Department of Infectious Diseases, Peking University First Hospital; Department of Infectious and Liver Diseases, Peking University International Hospital, Beijing 100034, China. ORCID: https://orcid.org/0000-0003-0515-6806. Tel: +86-10-8357-2840, Fax: +86-10-6655-1680, E-mail: john131212@sina.com; Zhongping Duan, Center for Difficult and Complicated Liver Diseases and Artificial Liver, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China. ORCID: https://orcid.org/0000-0002-9397-6330. Tel: +86-10-8399-7349, Fax: +86-10-6329-5285, E-mail: duan2517@163.com

Table 1. Evidence level and recommendation strength

Level	Descriptions
Level of evidence	
High quality (A)	Further research will probably not change confidence in this assessment.
Medium quality (B)	Further research will probably have a significant impact on confidence in this assessment.
Low quality (C)	Further research will probably affect and change this assessment.
Recommended level	
Strong (1)	Quality of the evidence, possible outcomes, and potential results of prevention, diagnosis and treatment are all considered, with expected benefits outweighing estimated costs.
Weak (2)	Quality of evidence varies substantially, which results in a less certain recommendation, with expected benefits not necessarily outweighing estimated costs.

Terminology	Definition
Chronic HBV infection	HBsAg, or HBV DNA seropositive, or both for ≥6 months.
CHB	Chronic liver disease caused by persistent HBV infection for ≥6 months.
HBV reactivation	Increase in HBV DNA ≥1 lg IU/mL from baseline, or detection of HBV DNA in patients with negative baseline HBV DNA, or HBsAg seroconversion from negative to positive in HBsAg-negative/anti-HBc-positive patients who receive immunosuppressive therapy or chemotherapy.
HBeAg clearance	Loss of HBeAg in HBeAg-positive patients.
HBeAg seroconversion	Loss of HBeAg and anti-HBe seroconversion from negative to positive in HBeAg-positive patients.
Resolved hepatitis B	Patients have a history of acute or CHB but are currently negative for HBsAg, positive or negative for anti-HBs, positive for anti-HBc, with undetectable HBV DNA and normal serum ALT levels.
Virological breakthrough	Increase in HBV DNA >1 lg IU/mL from nadir during treatment, or reversion to positive following conversion to negative, with or without elevated ALT, in patient with good compliance to NAs therapy, as confirmed 1 month later using the same reagent.
Virological relapse	Serum HBV DNA >2,000 IU/mL following the withdrawal of treatment in patients with virological response, confirmed 1 month later.
Drug resistance	
Genotypic resistance	Genetic mutations that confer resistance to HBV detected during antiviral therapy.
Phenotypic resistance	Decreased susceptibility (determined by *in vitro* testing) to antiviral drugs, which is associated with genotypic resistance.
Cross-resistance	Drug-resistant mutations that arise for one antiviral drug that can show resistance to other antiviral drugs (either one or several).
Multidrug resistance	Drug resistance to at least two different classes of NAs.

ALT, alanine aminotransferase; NAs, nucleos(t)ide analogs; HBeAg, hepatitis B e-antigen; anti-HBe, hepatitis B e-antibody; CHB, chronic hepatitis B; HBV, hepatitis B virus.

70 million people were chronically infected by HBV, which included approximately 20–30 million patients with CHB.[3]

HBV is transmitted from mother-to-child or through blood (which includes minor wounds on the skin and mucous membranes) and sexual contacts. Mother-to-child transmission is the most common route of transmission in China, which accounts for 30–50% of HBV infections.[4] It mainly occurs during the perinatal period through exposure to blood and body fluids of HBV-positive mothers. Maternal HBV DNA levels are closely correlated with the risk of HBV infection in infants. Mother-to-child transmission is more probable to occur in children born to HBeAg-positive mothers with high HBV DNA levels.[5] HBV is mainly transmitted through blood and sexual contact in adults. Patients with a history of drug injection, immunosuppressive therapy, blood transfusion or on hemodialysis, patients with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection, family members of HBsAg-positive people, healthcare workers and public safety workers at risk of occupational exposure to blood or body fluids in the work environment, prisoners, and diabetic patients who have not been vaccinated against hepatitis B have a higher risk of HBV infection.[6] Due to the strict screening for HBsAg and HBV DNA in blood donors and the adoption of safe injection practices, transmission through blood transfusion or blood products is rare. In addition, transmission could occur through damaged skin or mucous membranes, such as pedicures, tattoos, piercings, accidental exposure of healthcare workers during their work, and sharing of razors or toothbrushes.[6] Unprotected sexual contact with persons infected with HBV carries a high-risk of HBV infection, in particular, for those with multiple sexual partners and who are homosexual men.[7]

HBV does not spread through the respiratory or digestive tracts. Therefore, HBV cannot be transmitted via normal exposure in schools, workplaces, and other group settings, for example, working in the same office (which includes sharing

computers and other office supplies), contact through shaking hands and hugging, living in the same dormitory, dining in the same restaurant, toilet sharing, and other nonblood exposure contacts. No epidemiological or experimental studies have found that HBV can be transmitted via blood-sucking insects (e.g., mosquitoes and bedbugs).[8]

Prevention

Protecting susceptible people: HBV vaccination is the most effective measure to prevent HBV infections. Vaccination mainly targets newborns, followed by infants,[9] previously unvaccinated children and adolescents aged <15 years, and high-risk groups.[7–10]

The hepatitis B vaccine is administered in a series of three doses; the first dose is received immediately after birth, the second after 1 month, and the final dose at 6 months. The HBV vaccine should be administered as soon as possible after birth. The vaccine is administered by intramuscular injection into the deltoid muscle of the upper arm or the anterolateral aspect of the thigh for newborns and the middle deltoid muscle of the upper arm for children and adults. Newborns who suffer from severe diseases, such as very low birth weight, severe birth defects, severe asphyxia, and respiratory distress syndrome, should receive the first dose of hepatitis B vaccine as soon as possible after their vital signs have stabilized.

The dosing regimen for hepatitis B vaccine for newborns is: (1) 10 μg of recombinant yeast hepatitis B vaccine per injection, regardless of whether the mother is HBsAg-positive or not, and (2) recombinant Chinese hamster ovary (commonly known as CHO) cell hepatitis B vaccine, 10 μg for newborns of HBsAg-negative mothers or 20 μg for newborns of HBsAg-positive mothers per injection.

It is recommended that adults should be vaccinated with three doses of 20 μg recombinant yeast hepatitis B vaccine or 20 μg recombinant CHO cell hepatitis B vaccine. For immunocompromised people or non-responders, the dose (e.g., 60 μg) and the number of injections should be increased; for those who do not respond to the three-dose series (0, 1, and 6 months), one additional dose of 60 μg or three doses of 20 μg hepatitis B vaccine could be administered. Serum anti-HBs should be tested 1–2 months after the second-round vaccination. If there was no response, another dose of 60 μg recombinant yeast hepatitis B vaccine should be administered. The protection conferred by vaccination with hepatitis B vaccine generally lasts for ≥30 years in responders.[11] Therefore, anti-HBs monitoring or booster immunization is not required for the general population; however, anti-HBs should be monitored for high-risk groups or immunocompromised people. Another dose of the hepatitis B vaccine should be administered if anti-HBs levels were <10 mIU/mL.

Women who have not been infected with HBV can safely receive the hepatitis B vaccine during pregnancy.[12,13] In addition to the standard vaccination procedure, the accelerated vaccination schedule (0, 1, and 2 months) has been proven to be feasible and efficacious.[14]

Accidentally-exposed people refer to those whose damaged skin or mucous membranes have encountered the blood or body fluids from HBsAg-positive or HBsAg-unknown sources, or who have been stabbed by needles that are contaminated by such blood or body fluids.

Management of the sources of infection: People who have been identified as HBsAg-positive for the first time should be reported to local disease control and prevention centers, as required, if they meet the reporting standards for infectious diseases. In addition, it is recommended that their family members are tested for serum HBsAg, anti-HBs, and anti-hepatitis B core (HBc). Susceptible people should be vaccinated against HBV. The infectivity of HBV-infected people is mainly determined by serum HBV DNA levels, instead of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels. It is recommended that HBV infection markers should be tested during health examinations and medical activities that do not involve school admission or job recruitment. The aim is to facilitate early diagnosis and early treatment and to mitigate the harm caused by HBV infection. For the follow-up of people with chronic HBV infection, refer to section XV, "Monitoring and follow-up management of people with chronic HBV infection." Individuals with chronic HBV infection should avoid sharing dental appliances, razors, syringes, and blood collection needles. In addition, they are not allowed to donate blood, organs, or sperm, and it is suggested that they receive regular medical follow-ups. Their family members or sexual partners should be vaccinated against hepatitis B as soon as possible.

Blocking transmission routes: The promotion of safe injection (which includes blood collection needles and tools for acupuncture and moxibustion) is critical and standard precaution principles for hospital infection management should be followed. The equipment used in service industries, including hairdressing, shaving, pedicuring, puncturing, and tattooing, should be strictly disinfected. People whose sexual partners are HBsAg-positive should receive the HBV vaccine or use condoms. When the health condition of the sexual partner is unknown, condoms must be used to prevent HBV and other blood-borne or sexually transmitted diseases. For pregnant women who are HBsAg-positive, amniocentesis should be avoided whenever possible to ensure the placenta is intact and to minimize the chance of the newborn's exposure to maternal blood.

Recommendation 1: Hepatitis B vaccination for newborns

1. Infants born to HBsAg-negative mothers should receive 10 μg of recombinant yeast hepatitis B vaccine as soon as possible within 12 h of birth, the second dose at 1 month, and the third dose at 6 months (A1).
2. Infants born to HBsAg-positive mothers should receive 100 IU of hepatitis B immunoglobulin (HBIG) and concurrent recombinant yeast HBV vaccine (10 μg) at different sites as soon as possible within 12 h of birth, followed by the second and third doses of HBV vaccine at 1 and 6 months, respectively. Infants born to HBsAg-positive mothers should be tested for HBsAg and anti-HBs 1–2 months after the third dose of hepatitis B vaccine. If HBsAg is negative and anti-HBs levels are <10 mIU/mL, three additional doses of hepatitis B vaccine can be given according to the 0, 1, and 6 months immunization program. If HBsAg is positive, it means that the vaccination has failed, and the infants should be monitored regularly (A1).
3. Premature infants and low-weight infants born to mothers with unknown HBsAg status should receive the first dose of hepatitis B vaccine and HBIG as soon as possible within 12 h of birth; after 1 month, three doses of hepatitis B vaccine can be administered according to the 0, 1 and 6 month immunization program (A1).
4. Newborns who are vaccinated with hepatitis B vaccine and HBIG within 12 h of birth can breastfeed from HBsAg-positive mothers (B1).

Recommendation 2: Catch-up vaccination should be administered for children who have not been vaccinated with the hepatitis B vaccine or who have not completed the full vaccination series. The interval between the first dose and the second dose should be ≥28 days, and the interval between the second dose and the third dose should be ≥60 days (A1).

Recommendation 3: For immunocompromised or non-responsive adults, the vaccination dose (e.g., 60 μg) and

the number of doses should be increased; for those who do not respond to the three-dose procedure (0, 1, and 6 months), one additional dose of 60 μg or three doses of 20 μg hepatitis B vaccine should be administered, and serum anti-HBs should be tested 1–2 months after the second-round vaccination. If there is still no response, another dose of 60 μg recombinant yeast hepatitis B vaccine should be administered (A1).

Recommendation 4: People who are accidentally exposed to HBV should be treated as follows:

1. Gently squeeze around the wound to drain blood from the wound, rinse the wound with 0.9% NaCl solution, and then treat the wound with disinfectant (A1).
2. HBV DNA and HBsAg should be tested immediately and rechecked after 3–6 months (A1).
3. No treatment is required for those who have been vaccinated with hepatitis B vaccine and are known to be positive for anti-HBs (≥10 mIU/mL). For those who have not been vaccinated against hepatitis B or those who have been vaccinated against HBV but have anti-HBs levels <10 mIU/mL or unknown anti-HBs levels, 200–400 IU HBIG and concurrent hepatitis B vaccine (20 μg) should be administered immediately at different sites, followed by second and third doses of hepatitis B vaccine (20 μg) 1 and 6 months later (A1).

Recommendation 5: HBsAg, anti-HBc, and anti-HBs should be screened for during health examinations or medical treatments that do not involve school admission or job recruitment. HBsAg, anti-HBc, and anti-HBs should be screened in high-risk groups, pregnant women, and patients who receive antitumor treatment (chemotherapy or radiotherapy) or immunosuppressive agents or direct-acting antiviral (DAA) therapy for HCV, and in HIV-infected people. Hepatitis B vaccination is recommended for those who are negative for all the three HBV markers (B1).

Etiology

HBV belongs to the Hepapadnaviridae family. It is an enveloped DNA virus with a genome length of approximately 3.2 kb and contains a partially double-stranded circular DNA. Its genome encodes HBsAg, HBc antigen (HBcAg), hepatitis B e antigen (HBeAg), viral polymerase, and HBV X protein (HBx). HBV is highly resistant but can be inactivated at 65°C for 10 h, at 100°C for 10 min, or by high-pressure steam. In addition, HBV can effectively be inactivated by ethylene oxide, glutaraldehyde, peroxyacetic acid, and iodophors.

HBV enters liver cells by binding to sodium-taurocholate cotransporting polypeptide (commonly referred to as NTCP) on the liver cell membrane.[15] After HBV invasion of liver cells, the partially double-stranded circular DNA uses the negative strand as a template and extends the positive strand into the cell nucleus to repair the nick in the positive strand, which forms a covalently closed circular DNA (cccDNA). cccDNA plays an important role in chronic infection because it has a long half-life and is difficult to completely remove from the body. HBV can integrate into the host genome. HBV uses cccDNA as a template to transcribe viral mRNAs with different lengths, which include the 3.5 kb pregenomic RNA (commonly referred to as pgRNA) that can be released into the peripheral blood. Serum HBV RNA levels can reflect the activity of cccDNA in liver tissue and might be related to virological responses and the prognosis of patients.[16–18] HBV can be divided into at least nine genotypes, from A to I;[19] genotypes B and C are the most prevalent in China. The incidence of mother-to-child transmission in HBV patients with type B and C was higher than that of other genotypes, and genotype C is associated with earlier progression to HCC. HBV genotypes are associated with disease progression and responses to interferon-α (IFN-α) therapy.[20–22] The response rate of HBeAg-positive patients to IFN-α treatment was higher in type B than in type C and higher in type A than in type D.[23]

Natural history and pathogenesis

Natural history

The natural history of HBV infection depends mainly on the interaction between the virus and the host. The age when HBV infection is acquired is one of the most critical factors that determine whether the HBV infection will become chronic. The risk of chronic HBV infection in newborns and infants aged <1 year is 90%.[24] Most people with HBV infection in China are infected during the perinatal period or infancy. The world has achieved significant success in blocking HBV mother-to-child transmission.[25] A universal immunization program that combines hepatitis B vaccine and HBIG has been adopted for newborns of HBsAg-positive mothers in China; however, approximately 5–7% of newborns are still infected with HBV due to mother-to-child transmission. This occurs in 7–11% of HBeAg-positive pregnant women and 0–1% in HBeAg-negative pregnant women.[26,27]

In general, the natural history of chronic HBV infection is divided into four phases based on its natural progression,[28–30] namely the immune tolerance phase (chronic HBV carrier state), immune clearance phase (HBeAg-positive CHB), immune control phase (inactive HBsAg carrier state), and reactivation phase (HBeAg-negative CHB) (Table 2). For more details, refer to section IX, "Clinical Diagnosis". Not all patients with chronic HBV infection will experience all four phases. Patients who are infected with HBV during adolescence and adulthood usually experience no immune tolerance phase and directly enter the immune clearance phase.

Spontaneous HBeAg seroconversion might occur during the immune clearance phase, with an annual incidence of 2–15%. Patients with age <40 years, elevated ALT, HBV genotype A and genotype B had higher incidence.[28,31] After HBeAg seroconversion, the HBsAg clearance rate was 0.5–1.0% annually.[32] Ten years after HBsAg disappeared, cccDNA was still detectable in the liver of approximately 14% of these patients.[33] Patients with either age >50 years, cirrhosis, or concomitant HCV or hepatitis D virus (HDV) infections can still progress to HCC even if HBsAg has disappeared; however, the incidence rate is low.[34]

The annual incidence of cirrhosis in CHB patients without antiviral therapy is 2–10%,[35] and risk factors include host (older age, male, age >40 years when HBeAg seroconversion occurs, and persistently elevated ALT levels[36,37]), the virus (HBV DNA >2,000 IU/mL), persistently positive HBeAg status,[38] genotype C, coinfection with HCV, HDV, or HIV, and other liver injury-inducing factors (e.g., alcohol or obesity).[35] The annual incidence of decompensated cirrhosis from compensated cirrhosis is 3–5%, and the 5-year survival rate of the patients with decompensated cirrhosis is 14–35%.[35] The annual incidence of HCC in patients with HBV infection without cirrhosis is 0.5–1.0%.[35] The annual incidence of HCC in patients with cirrhosis is 3–6%.[39–41] Also, cirrhosis, diabetes, immediate relatives with HCC, high serum HBsAg levels, and exposure to aflatoxin are all associated with a high incidence of HCC.[35,42–46] Lower HBsAg levels often suggest that hosts have exerted good immune control over HBV replication and infection. Studies have shown that even if HBeAg is negative and HBV DNA levels are low, patients with higher HBsAg levels (≥1,000 IU/mL) are still at a higher risk of HCC, regardless of genotype B or C.[45,46]

Table 2. Stages of chronic HBV infection

Markers	Immune tolerance phase (chronic HBV carrier status)	Immune clearance phase (HBeAg-positive CHB)	Immune control phase (inactive HBsAg carrier status)	Reactivation phase (HBeAg-negative CHB)
HBV serological markers				
HBsAg (IU/mL)	$>1\times10^4$	+	$<1\times10^3$	+
anti-HBs	–	–	–	–
HBeAg	+	+	–	+/–
anti-HBe	–	–	+	+/–
anti-HBc	+	+	+	+
HBV DNA (IU/mL)	$>2\times10^7$	$>2\times10^4$	$<2\times10^3$	$\geq2\times10^3$
ALT	Normal	Persistent or recurrent increase	Normal	Persistent or recurrent increase
Liver pathology	No obvious necroinflammation or fibrosis	Obvious necroinflammation, or fibrosis, or both	No or mild inflammation, with varying degrees of fibrosis	Obvious necroinflammation, or fibrosis, or both

CHB, chronic hepatitis B; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Pathogenesis

The pathogenesis of chronic HBV infection is complicated and is not fully understood. HBV does not directly kill liver cells. The immune response caused by the virus is the main mechanism that leads to liver cell damage and necroinflammation. Persistent or recurrent necroinflammation is an important factor for patients with chronic HBV infection progressing to cirrhosis and even HCC.

The nonspecific (innate) immune response plays an important role in the initial stages of HBV infection and initiates the subsequent specific (adaptive) immune response.[47,48] HBV uses its proteins, such as HBeAg and HBx, to interfere with antiviral signaling pathways that involve Toll-like receptors and retinoic acid-inducible gene I-like receptors; therefore, the level of the nonspecific immune response is suppressed. CHB patients often present with decreased frequencies of myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs) in the peripheral blood. The ability of mDCs to mature and the ability of pDCs to produce IFN-α are significantly impaired, which make it more difficult for the body to eliminate the virus and induce HBV-specific T lymphocytes, which impedes viral elimination.

The HBV-specific immune response plays a leading role in HBV clearance.[49] Major histocompatibility complex class I-restricted $CD8^+$ cytotoxic T lymphocytes can induce the apoptosis of infected hepatocytes and can secrete IFN-γ and suppress the expression and replication of HBV genes in liver cells in a noncytolytic fashion.[50] During chronic infection, HBV-specific T cells are susceptible to apoptosis. Their ability to produce cytokines and proliferate is significantly impaired, and their functions become exhausted, which might be one of the mechanisms that lead to persistent HBV infection.[51] Currently, it is believed that there are large amounts of HBsAg in serum and liver tissue, and the lack, or dysfunction, or both of HBsAg-specific cytotoxic T lymphocytes is an important cause of immune tolerance in patients with chronic HBV infection.[52]

Laboratory tests

Serological testing for HBV

Traditional serum markers for HBV include HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and anti-HBc immunoglobulin (Ig)M. Serum HBsAg can be produced by cccDNA-derived mRNA or an HBV DNA sequence that is integrated into the human genome. HBsAg positivity indicates HBV infection. Anti-HBs is a protective antibody, and anti-HBs positivity indicates immunity to HBV, which can be seen in people with a resolved hepatitis B infection or who have been inoculated with the hepatitis B vaccine. Anti-HBc-IgM positivity is mostly found in patients with acute hepatitis B. Anti-HBc-IgM is usually mildly positive in patients with reactivation of chronic HBV infection. The main subtype of anti-HBc is IgG. The IgG subtype is positive in most HBV cases, whether the virus is eliminated or not.

Recently, the quantitative detection of HBsAg has been widely used in clinical practice. Its level is indicative of the stage of the disease and the risk of disease progression. In addition, it can be used to guide the use of recombinant human IFN and peginterferon-α (peg-IFN-α).

Virological testing for HBV

HBV DNA quantification: This is mainly used to assess the level of virus replication in HBV-infected patients. In addition, it can be used as a crucial component to select the indications and assess the efficacy of antiviral therapy. During antiviral therapy, obtaining a sustained virological response could significantly control the progression of cirrhosis and lower the risk of HCC.[53,54] The quantitative detection of HBV DNA utilizes real-time quantitative polymerase chain reaction; however, the detection limit varies between manufacturers' reagents.

HBV genotyping: To date, at least nine HBV genotypes (A to I) and one undefined genotype (J) have been identified. Some genotypes are further divided into subtypes. The detection of HBV genotypes could help to predict the efficacy of IFN and determine the disease prognosis.[55–58]

Detection of resistant mutants: HBV is a highly mutable virus. During reverse transcription and replication, a mutation might occur to one or more nucleotides during replication, due to the lack of proofreading ability in RNA polymerase and reverse transcriptase. HBV can naturally mutate during chronic persistent infection. Viral mutation can be induced by antiviral treatment. In both cases, mutated HBV might become less susceptible to antiviral drugs.[59]

The appropriate detection of drug-resistant mutant strains could help clinicians to identify drug resistance and adjust the treatment plan as required. Commonly used clinical tests for drug resistance include gene sequencing that uses reverse transcriptase and reverse hybridization-based line probe assays (INNO-LIPA kit).

Detection of new HBV markers

Anti-HBc quantification (qAnti-HBc): A novel double-antigen sandwich enzyme-linked immunosorbent assay (commonly known as ELISA) can quantitatively determine serum anti-HBc levels. In natural history studies, the quantitative (q)anti-HBc levels in patients during the immune clearance and reactivation phases were significantly higher than those in the immune tolerance and low replication phases.[60,61] The baseline qAnti-HBc levels of HBeAg-positive CHB patients could predict the efficacy of peg-IFN-α and nucleos(t)ide analogues (NAs).[62,63] In addition, qAnti-HBc levels are strongly correlated with ALT levels and are associated with the degree of necroinflammation in liver tissue in patients with normal ALT levels.[64]

HBV RNA quantification: HBV RNA levels are related to the transcriptional activity of cccDNA in liver cells, and further study is required to assess the risk of recurrence after withdrawal of NAs.[65,66] Its use is limited, because the detection methods used by different research teams are different.

Hepatitis B core-related antigen (HBcrAg): This is a composite marker that contains HBcAg, HBeAg, and p22. It is related to the transcriptional activity of cccDNA in liver cells. Studies have examined its usefulness to determine disease progression, predict the antiviral efficacy of peg-IFN-α and NAs, and assess the risk of HBV recurrence and HCC development with the discontinuation of treatment.[67–70]

Serum biochemical testing[71]

ALT and AST: Serum ALT and AST levels can partially reflect the degree of liver cell injury. An increase in ALT levels in patients with long-term virus suppression requires further tests to identify the possible causes.[72]

Total bilirubin: This is related to the production, uptake, metabolism, and excretion of bilirubin. Bilirubin elevation is caused by liver cell damage, intrahepatic and extrahepatic biliary obstruction, abnormal bilirubin metabolism, and hemolysis. In patients with liver failure, total bilirubin levels might be >171 μmol/L or could increase by >7.1 μmol/L daily.

Serum albumin: This reflects the synthetic functions of the liver. Patients with cirrhosis and liver failure present with decreased serum albumin levels. In addition, serum albumin levels are affected by nutritional status.

Prothrombin activity time (PT), prothrombin activity (PTA), and international normalized ratio: These indicators reflect the synthetic functions of coagulation factors in the liver and are valuable to predict disease progression and prognosis.

Serum γ-glutamyl transferase (GGT): The serum GGT in healthy people mainly comes from the liver. This enzyme is significantly increased in alcoholic liver disease, drug-induced liver disease, cholangitis, and intrahepatic and extrahepatic cholestasis.

Serum alkaline phosphatase (ALP): This is not a liver-specific indicator, although cholestasis can stimulate ALP synthesis. If ALP levels are elevated, elevated GGT or ALP isoenzyme levels are required to confirm whether ALP elevation has occurred in the liver. The dynamic changes in ALP levels are often used clinically to assess disease progression, prognosis, and efficacy.

Alpha-fetoprotein (AFP) and its isoform AFP-L3: AFP is an important indicator for the diagnosis of HCC. The magnitude and dynamic changes in AFP increase, and its correlation with the increase and decrease of ALT and AST levels require special attention. In addition, clinical manifestations and liver imaging examinations need to be carried out to offer a comprehensive analysis.[73]

Protein induced by vitamin K absence or antagonist-II (PIVKA-II): This is known as des-γ-carboxy prothrombin (DCP) and it is another important indicator for the diagnosis of HCC, and can be used to complement AFP.[74]

Noninvasive tests for liver fibrosis

AST to platelet ratio index (APRI)

APRI is an index that has been developed based on the data from chronic HCV infections to assess the degree of HCV-related liver fibrosis. The formula for APRI is as follows: [upper limit of normal (ULN) of AST/AST×100]/platelet count ($\times 10^9$/L). An APRI score ≥2 indicates the presence of cirrhosis and an APRI score <1 suggests the absence of cirrhosis in adults. However, recent studies have suggested that this index is less accurate to evaluate the degree of HBV-related liver fibrosis.[75–77]

Fibrosis 4 (FIB-4) score

FIB-4 was developed based on the data from chronic HCV infections and is used to assess the degree of HCV-related liver fibrosis. The formula for FIB-4 is as follows: age (years)×AST (IU/L)/[platelet count ($\times 10^9$/L)×√ALT (IU/L)]. A FIB-4 value ≥3.25 or a Metavir score ≥F3 suggest the presence of liver fibrosis; a FIB-4 value <1.45 suggests the absence of liver fibrosis. Recent studies have shown that an FIB-4 value ≥0.25 has a 97% specificity for the diagnosis of fibrosis in people with chronic HBV infection,[76] and an FIB-4 value ≤0.70 has a negative predictive value of 96% for the exclusion of hepatitis B cirrhosis in people aged >30 years.[78]

Other indicators

Extracellular matrix components, such as hyaluronic acid, type III procollagen peptide, type IV collagen, and laminin, can indicate the presence of liver fibrosis, but no generally accepted cutoffs are available for clinical application. GGT to platelet ratio (GPR) [=GGT/GGT ULN/platelet count ($\times 10^9$/L)×100] and red cell distribution width-platelet ratio (RPR) [=red cell distribution width (%)/platelet count ($\times 10^9$/L)] are composed of routine lab indicators, but stable diagnostic cutoffs need to be defined.[79,80] Serum Golgi glycoprotein 73 (commonly referred to as GP73) used in combination with AST and GGT levels can reflect moderate to severe liver inflammation.[81] Serum chitinase 3-like protein 1 (commonly referred to as CHI3L1 or YKL-40) can predict moderate to severe liver fibrosis in patients with normal or mildly elevated ALT levels.[82,83]

Liver stiffness measurement

Liver stiffness can be measured using transient elastogra-

phy (TE), ultrasound-based acoustic radiation force impulse (ARFI), and magnetic resonance elastography (MRE). ARFI includes two techniques, namely point shear wave elastography (p-SWE) and 2D shear wave elastography (2D-SWE). ARFI and MRE are still undergoing clinical research.

TE has been approved for use in the USA, Europe, and the Asia-Pacific region. It can accurately identify advanced liver fibrosis and early cirrhosis,[84,85] but its results are susceptible to liver necroinflammation, cholestasis, and severe steatosis. TE results should be interpreted in combination with ALT and bilirubin levels.[86–88] The combined use of TE and other serological indicators could improve diagnostic accuracy.[84,89–91] A multicenter study carried out by Chinese researchers suggested a cutoff of 21.3 kPa for the diagnosis of hepatitis B cirrhosis (specificity: 95%; positive likelihood ratio: 8.5), a cutoff of 12.4 kPa for the diagnosis of advanced liver fibrosis (specificity: 95%; positive likelihood ratio: 11.8), a cutoff of 9.1 kPa for diagnosis of significant liver fibrosis (specificity: 95%; positive likelihood ratio: 6.4); a cutoff value of 8.2 kPa for the exclusion of cirrhosis (sensitivity: 95%; positive likelihood ratio: 0.07), and a cutoff value of 5.8 kPa for the exclusion of advanced liver fibrosis (sensitivity: 95%; positive likelihood ratio: 0.10).[92] For guidance on the clinical application of TE, see "Expert consensus on the use of transient elastography for diagnosing liver fibrosis (2018 update)."[85]

Imaging diagnosis

The aim of imaging examination in patients with chronic HBV infection is to monitor clinical progression by the identification of signs of cirrhosis and portal hypertension, and to detect and differentiate space-occupying lesions to make an early diagnosis of HCC.[93,94]

Abdominal US

Abdominal US is the most commonly used liver imaging technique, because it offers a noninvasive, inexpensive, real-time imaging solution that is easy to repeat. US can demonstrate the size, shape, and parenchymal echogenicity of the liver and spleen, and can determine the calibrator and blood flow of the portal, splenic, and hepatic veins. In addition, it can identify the presence and severity of ascites which suggests the presence of cirrhosis and portal hypertension. Regular US surveillance is essential for the identification of early HCC. Contrast-enhanced ultrasonography can be used to better differentiate the nature of space-occupying lesions. The downside of US is that the image quality and results are susceptible to several factors, such as equipment performance, gas in the gastrointestinal tract, and the operator's skills.

Computerized tomography (CT)

In patients with CHB, CT is mainly used to investigate the imaging changes of the liver to determine the presence of cirrhosis and portal hypertension and identify/differentiate the space-occupying lesions. Contrast-enhanced multiphase CT scanning has a high sensitivity and specificity for the diagnosis of HCC.

Magnetic resonance imaging (MRI)

MRI is a preferred imaging modality for the liver due to its avoidance of radiation exposure. In general, MRI with enhanced multiphase scans and with hepatobiliary-specific contrast agents is outperformed to contrast-enhanced CT in differentiating benign from malignant space-occupying lesions in the liver.

Pathological diagnosis

The aim of liver biopsy in people with chronic HBV infection is to evaluate the degree of necroinflammation and fibrosis, to determine the presence or absence of cirrhosis, to exclude other liver diseases, thereby providing information on the diagnosis, prognosis, and efficacy assessment.

The main pathological features of CHB are portal and periportal necroinflammation and fibrosis. The inflammatory cells infiltrating the portal area are predominantly lymphocytes with a few plasma cells and macrophages. The aggregation of inflammatory cells often destroys the limiting plate and leads to interface hepatitis (previously called piecemeal necrosis). Degeneration, necrosis (e.g., spotted, bridging, and confluent necrosis) and apoptosis of hepatocytes can be seen in the lobules. Ground glass hepatocytes and apoptotic bodies can be formed by apoptotic hepatocytes, which is proportional to inflammation activity. Chronic necroinflammation in the liver can cause the excessive deposition of extracellular matrix, especially collagen, which results in fibrosis that is manifested by varying degrees of portal fibrous expansion and fibrous septum formation. Masson's trichromatic staining and reticulin staining can help to determine the degree of liver fibrosis and lobular disarray. Then, cirrhosis develops, which is, by definition, the combination of diffuse fibrosis and regenerative nodules (pseudolobules). In addition, immunohistochemical staining for HBsAg and HBcAg as well as *in situ* hybridization or PCR for HBV DNA or cccDNA in liver tissue can be exploited.

The scoring systems developed by Knodell, Scheuer, Metavir, or Ishak are widely used to grade hepatic necroinflammation and stage fibrosis in persons with chronic HBV infection.[95–98] The Laennec system further subclassifies Metavir stage 4 (cirrhosis) into stages 4A, 4B, and 4C, based on the size of the regenerative nodules and the thickness of fibrous septa.[99] In addition, Chinese researchers have proposed a histopathological grading and staging system for viral hepatitis B.[100] Comparisons of the various grading and staging systems are shown in Tables 3 and 4.

Computer image analysis can be used to determine the collagen proportional area of the stained sections of liver tissue. Quantitative assessment of liver fibrosis (qFibrosis) based on two-photon second harmonic generation can automatically measure the collagen area and the morphological features in unstained liver tissue sections, with high reproducibility and accuracy.[101] Chinese researchers recently developed a P-I-R classification for liver fibrosis. Based on the width and shape of fibrous septa, this system qualitatively subdivides fibrosis with an Ishak score ≥3 into predominantly progressive (P), intermediate (I), and predominantly regressive (R) liver fibrosis. Therefore, the merit of this classification is to judge the dynamic trend of liver fibrosis evolution.[102]

Clinical diagnosis

According to the results of serological, virological, biochemical, imaging, and pathological tests as well as other auxiliary examinations, chronic HBV infection can be classified into:

Table 3. Comparisons of major grading standards for liver inflammation

Score	Knodell's scoring system			Score	Scheuer's scoring system	
	Periportal inflammation with or without bridging necrosis	Intralobular degeneration and focal necrosis	Portal inflammation		Portal/periportal activity	Intralobular activity
0	None	None	None	0	None or minimal	None
1	Mild piecemeal necrosis	Mild (acidophilic bodies, ballooning degeneration or scattered foci, or both of hepatocellular necrosis in <⅓ of lobules or nodules)	Mild (a few inflammatory cells in <⅓ of portal tracts)	1	Portal inflammation alone	Inflammation but no necrosis
3	Moderate piecemeal necrosis (involving <50% of the circumference of most portal tracts)	Moderate (involving ⅓–⅔ of lobules or nodules)	Moderate (increased inflammatory cells in ⅓–⅔ of portal tracts)	2	Mild piecemeal necrosis	Focal necrosis or acidophilic bodies
4	Marked piecemeal necrosis (involving >50% of the circumference of most portal tracts)	Marked (involving >⅔ of lobules or nodules)	Marked (dense inflammatory cells in >⅔ of portal tracts)	3	Moderate piecemeal necrosis	Marked focal cell damage
5	Moderate piecemeal necrosis plus bridging necrosis	–	–	4	Marked piecemeal necrosis	Damage includes bridging necrosis
6	Marked piecemeal necrosis plus bridging necrosis	–	–			
10	Multilobular necrosis	–	–			

Score	Wang Tailing's scoring system		Score	Ishak's scoring system			
	Portal/periportal area	Intralobular area		Portal inflammation	Periportal or periseptal interface inflammation	Focal necrosis, apoptosis, or focal inflammation	Confluent necrosis
0	No inflammation	No inflammation	0	None	None	None	None
1	Portal inflammation	Degeneration and a few necrotic foci	1	Mild, involving some or all portal areas	Mild (focal, involving few portal areas)	≤1 foci per 10× objective	Focal confluent necrosis
2	Mild piecemeal necrosis	Degeneration, spotted or focal necrosis or acidophilic bodies	2	Marked, involving some or all portal areas	Mild/moderate (focal, involving most portal areas)	2–4 foci per 10× objective	Zone 3 necrosis in some areas
3	Moderate piecemeal necrosis	Degeneration, severe necrosis, or bridging necrosis	3	Moderate to severe, involving all portal areas	Moderate (continuous around <50% of tracts or septa)	5–10 foci per 10× objective	Zone 3 necrosis in most areas
4	Marked piecemeal necrosis	Bridging necrosis involving multiple lobules	4	Severe, involving all portal areas	Severe (continuous around >50% of tracts or septa)	>10 foci per 10× objective	Zone 3 necrosis and occasional portal-central bridging necrosis
			5	–	–	–	Zone 3 necrosis and multiple portal-central bridging necrosis
			6	–	–	–	Panacinar or multiacinar necrosis

–, not applicable.

Table 4. Comparisons of major staging standards for liver fibrosis

Knodell's scoring system		Scheuer's scoring system		Metavir's scoring system		Wang Tailing's scoring system		Ishak's scoring system	
0	No fibrosis	0	No fibrosis	0	No fibrosis	0	No fibrosis	0	No fibrosis
1	Fibrous expansion of portal areas	1	Fibrous expansion of portal areas	1	Fibrous expansion of portal areas, without fibrous septa	1	Fibrous expansion of portal areas	1	Fibrous expansion of some portal areas, with or without short fibrous septa
2	–	2	Periportal fibrosis or portal-portal fibrous septa but intact architecture	2	Fibrous expansion of portal areas, with few fibrous septa	2	Periportal fibrosis, with fibrous septa but intact architecture	2	Fibrous expansion of most portal areas, with or without short fibrous septa
3	Marked bridging (portal-portal as well as portal-central)	3	Fibrosis with architectural distortion but no obvious cirrhosis	3	Numerous septa, with architectural distortion, but no cirrhosis	3	Fibrous septa with architectural distortion but no obvious cirrhosis	3	Fibrous expansion of most portal areas with occasional portal-portal bridging
4	Cirrhosis	4	Probable or definite cirrhosis	4	Cirrhosis	4	Early or definite cirrhosis	4	Fibrous expansion of most portal areas with marked bridging (portal-portal as well as portal-central)
								5	Marked bridging (portal-portal, or portal-central, or both) with occasional nodules (incomplete cirrhosis)
								6	Probable or definite cirrhosis

–, not applicable.

Chronic HBV carrier state

This is also known as HBeAg-positive chronic HBV infection.[103,104] Patients are in the immune tolerance phase and are generally younger. They are positive for HBeAg, with high levels of HBV DNA (usually >2×10^7 IU/mL) and serum HBsAg (usually >1×10^4 IU/mL). However, serum ALT and AST levels are persistently normal (three follow-ups within 1 year, ≥3 months apart), and liver biopsy shows no obvious necroinflammation or fibrosis. In the absence of liver biopsy, factors such as age, HBV DNA level, HBsAg level, noninvasive liver fibrosis tests, and imaging examination should be considered to help make a diagnosis.

HBeAg-positive CHB

Patients are in the immune clearance phase and are seropositive for HBsAg and HBeAg. HBV DNA levels are high (usually >2×10^4 IU/mL). ALT levels are persistently or intermittently abnormal, or liver biopsy reveals obvious necroinflammation, or fibrosis, or both (≥G2/S2).

Inactive HBsAg carrier state[105,106]

This is also known as HBeAg-negative chronic HBV infection. Patients are in the immune control phase. They are positive for HBsAg and anti-HBe and negative for HBeAg. HBV DNA levels are <2,000 IU/mL, and HBsAg levels are <1,000 IU/mL. ALT and AST levels are persistently normal (three follow-ups within 1 year, ≥3 months apart). Imaging examination shows no signs of cirrhosis. Liver biopsy shows a histological activity index score <4, or lesions are mild using other semi-quantitative scoring systems.

HBeAg-negative CHB

This is the reactivation phase. Patients are positive for HBsAg and persistently negative for HBeAg, which is often accompanied by anti-HBe positivity. HBV DNA levels are usually ≥2,000 IU/mL. ALT levels are persistently or intermittently abnormal, or liver biopsies show obvious necroinflammation, or fibrosis, or both (≥G2/S2).

Occult HBV infection (OBI)[107]

Patients are negative for HBsAg in serum but positive for HBV DNA in serum or liver tissue, or both. A total of 80% of OBI patients might be seropositive for anti-HBs, and anti-HBe or anti-HBc, or both, which is designated as seropositive OBI; however, 1–20% of OBI patients are seronegative for all serological indicators, which is designated as seronegative OBI. Its mechanism has not been determined. One possible explanation is that HBsAg disappears after apparent (acute or chronic) HBV infection, and HBV DNA levels are usually very low in the serum or liver tissue, without obvious liver tissue damage. Another possibility is mutations in the S gene region of HBV, which makes HBsAg undetectable by currently available commercial kits. Serum HBV DNA levels are usually high, which might be accompanied by significant liver histopathological changes. These patients can transmit HBV to recipients through blood transfusion or organ transplantation and might experience reactivation of

HBV if they are immunosuppressed.

Hepatitis B cirrhosis[108,109]

The diagnosis of hepatitis B cirrhosis should meet the first and the second criteria of the following pathological diagnosis or the first and the third criteria of the following clinical diagnosis.

1. Patients are HBsAg-positive, or HBsAg-negative, anti-HBc positive and have a clear history of chronic HBV infection (presence of HBsAg >6 months), and other causes have been excluded.
2. Liver biopsy suggests cirrhosis.
3. Patients meet ≥2 of the following five criteria, and noncirrhotic portal hypertension has been excluded: (1) imaging examination shows signs of cirrhosis, or portal hypertension, or both; (2) endoscopy shows esophagogastric varices; (3) liver stiffness measurements suggest cirrhosis; (4) blood biochemical tests show reduced albumin levels (<35 g/L), or prolonged PT, or both (>3 s longer than controls); and (5) routine blood tests show platelet count $<100\times10^9$/L.

Clinically, cirrhosis is divided into the compensated stage and decompensated stage based on the presence or absence of serious complications, such as ascites, esophagogastric variceal bleeding, and hepatic encephalopathy: (1) compensated cirrhosis; patients who are pathologically or clinically diagnosed with cirrhosis but have never had serious complications, such as ascites, esophagogastric variceal bleeding, or hepatic encephalopathy, could be diagnosed as having compensated cirrhosis and most of them have Child-Pugh A liver function; and (2) decompensated cirrhosis; if patients with cirrhosis develop serious complications, such as ascites, esophagogastric variceal bleeding, or hepatic encephalopathy, they are diagnosed as decompensated cirrhosis.[110] Most of them have Child-Pugh B or C liver function.

Recently, to more accurately predict the progression, death risk, or treatment effect of patients with cirrhosis, some researchers have suggested dividing cirrhosis into five stages,[111] between which stages 1 and 2 are compensated cirrhosis, and stages 3–5 are decompensated cirrhosis: stage 1, no varicose veins or ascites; stage 2, varicose veins, no bleeding or ascites; stage 3, ascites, no bleeding, with or without varicose veins; Stage 4, bleeding, with or without ascites; and stage 5, sepsis.

Due to the advances in antiviral therapy, many patients with decompensated cirrhosis could be reversed to compensated cirrhosis following treatment. The reversal is characterized by improved liver cell function, such as higher albumin levels, shorter PT than before, the disappearance of serious complications, such as ascites and hepatic encephalopathy, and long-term survival without liver transplantation. This phenomenon is called recompensation of cirrhosis; however, there is no accurate definition and uniform diagnostic criteria for this concept.

Treatment goals

Treatment goals are to maximize long-term inhibition of HBV replication,[6,112,113] alleviate the degree of hepatocyte inflammation, necrosis, and hyperplasia of liver fibrous tissue, delay and reduce the occurrence of liver failure, decompensation of liver cirrhosis, HCC and other complications, and to improve the quality of patients' life as well as prolong their survival time. For eligible patients, the therapy aims are "clinical cure".

Clinical cure (or functional cure):[6,112,114–116] HBsAg remains negative (with or without the presence of anti-HBs), HBV DNA is undetectable, and liver biochemical indicators are normal following withdrawal of the treatment. However, because cccDNA remains in the nuclei of liver cells, patients are still at risk of HBV reactivation and HCC development.

Indications for antiviral therapy

Patients should be assessed for the risk of disease progression to determine whether to start antiviral therapy based on a comprehensive analysis of serum HBV DNA levels, ALT levels, the severity of liver disease, as well as their age, family history, and concomitant diseases.[6,112,113] Dynamic assessment is more meaningful than a single test (Fig. 1).

For patients with chronic HBV infection with positivity for serum HBV DNA, antiviral therapy is indicated if their ALT levels are persistently abnormal (>ULN) and other causes of ALT elevation have been excluded.

Other causes of ALT elevation include infection by other pathogens, drug-induced liver injury, alcoholic hepatitis, nonalcoholic steatohepatitis, autoimmune liver disease, and systemic diseases that involve the liver. In addition, the possibility of drug-induced temporarily normal ALT levels should be ruled out.

For patients with clear evidence of cirrhosis, antiviral treatment should be initiated if HBV DNA can be detected, regardless of ALT levels and HBeAg status. For patients with decompensated cirrhosis, antiviral therapy is indicated if HBV DNA is undetectable but HBsAg is positive.

Patients with seropositive HBV DNA and normal ALT levels are at a high risk of disease progression and antiviral therapy is indicated if they meet any of the following criteria: (1) obvious liver inflammation on liver biopsy (≥G2) or fibrosis (≥S2); (2) persistently normal ALT levels (tested every 3 months for 12 months) but with a family history of cirrhosis or liver cancer, and >30 years of age; (3) persistently normal ALT levels (tested every 3 months for 12 months), no family history of cirrhosis or liver cancer, but >30 years of age with noninvasive tests for liver fibrosis or liver biopsy revealing obvious liver inflammation or fibrosis; a (4) HBV-related extrahepatic manifestations (e.g., glomerulonephritis, vasculitis, polyarteritis nodosa, and peripheral neuropathy).

Recommendation 6: If serum HBV DNA is positive, ALT levels are persistently abnormal (>ULN), and other causes have been excluded, antiviral therapy is indicated (B1).

Recommendation 7: Antiviral therapy is indicated for HBV-related compensated cirrhosis patients with positive serum HBV DNA and HBV-related decompensated cirrhosis patients with positive HBsAg (A1).

Recommendation 8: If patients are seropositive for HBV DNA with normal ALT levels, antiviral therapy is indicated when they meet any one of the following criteria: (1) liver biopsy suggests obvious inflammation, or fibrosis, or both (G ≥2, or S ≥2, or both) (A1); (2) a family history of HBV-related cirrhosis or liver cancer and age >30 years-old (B1); (3) noninvasive tests or liver biopsy revealing obvious liver inflammation or fibrosis in those with persistently normal ALT levels and age >30 years-old (A1); and (4) HBV-related extrahepatic manifestations (e.g., HBV-related glomerulonephritis) (B1).

NAs treatment

Efficacy and safety of NAs

Entecavir (ETV): Numerous studies have shown that the

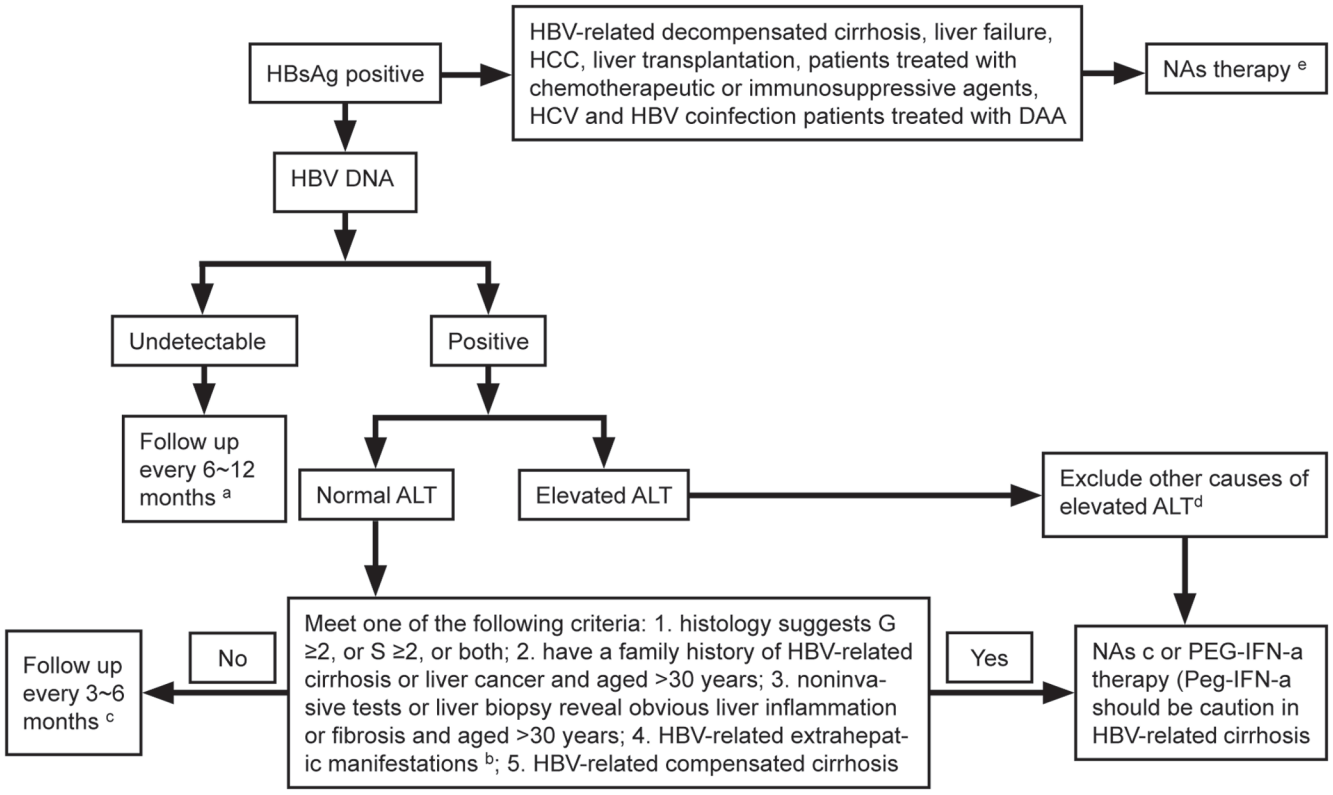

Fig. 1. Flow chart of antiviral therapy for patients with chronic HBV infection. (a) Follow-up tests: virological test, liver biochemical test, AFP test, PIVKA-II test, abdominal ultrasound, and liver stiffness measurement. (b) HBV-related extrahepatic manifestations: glomerulonephritis and vasculitis. (c) Follow-up criteria for patients with HBV-related decompensated cirrhosis during NA treatment: perform a routine blood test, liver biochemical test, renal function test, virological test, and test for blood ammonia, AFP, and PIVKA-II, and abdominal ultrasound every 3 months. If necessary, perform enhanced CT or MRI. (d) Other causes of ALT elevation: infection by other pathogens, history of drug or poison use, history of alcohol use, lipid metabolism disorders, autoimmune disorders, liver congestion or vascular diseases, inherited metabolic liver disease, systemic diseases. (e) NAs-ETV, TDF, TAF. HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; NAs, nucleos(t)ide analogs; peg-IFN-α, pegylated interferon-α.

use of ETV is safe and highly effective to suppress virus replication and reduce liver inflammation.[117–119] Long-term treatment with ETV can improve histological changes in patients with cirrhosis,[120,121] significantly reduce the incidence of cirrhosis-related complications and HCC, and reduce liver-related and all-cause mortality.[53,122] The 5-year cumulative probability of ETV resistance was 1.2% in treatment-naïve patients with CHB but increased to 51% in CHB patients who were resistant to lamivudine (LAM).[123]

Tenofovir disoproxil fumarate (TDF): Multicenter clinical studies of TDF treatment for CHB patients have shown that it can strongly inhibit virus replication and has low rates of resistance.[124,125] A study of TDF usage for 8 years showed that there were 41 cases of virological breakthroughs, 29 cases (70%) of which were due to poor compliance. In total, 59% of patients with virological breakthroughs continued to receive TDF treatment and achieved virological responses. Further nucleic acid sequencing did not identify TDF-related resistance.[126] Long-term treatment with TDF can significantly improve liver histology and reduce the incidence of HCC.[127,128]

In total, 90 CHB patients who were ETV resistant and serum HBV DNA levels >60 IU/mL were equally randomized to receive TDF alone or in combination with ETV for 48 weeks. Clearance of HBV DNA (<15 IU/mL) was achieved in 73% and 71%, respectively. HBV DNA levels decreased by 3.66 lg IU/mL and 3.74 lg IU/mL from baseline, respectively. Overall, six and three patients retained their baseline resistance mutations in TDF alone and in combination with ETV, respectively. Both regimens demonstrated a favorable safety profile.[129] Several studies into TDF therapy for patients previously treated with NAs for 48–168 weeks showed that TDF resulted in virological responses in 70–98% of LAM-resistant, adefovir dipivoxil (ADV)-resistant, ETV-resistant, or multidrug-resistant patients. In addition, virological response rates increased during treatment.[129–139]

Tenofovir alafenamide fumarate tablets (TAF): In a global phase III clinical trial, 581 HBeAg-positive CHB patients (which excluded patients with decompensated cirrhosis) received TAF treatment for 48 weeks. HBV DNA levels were <29 IU/mL in 64% of patients and ALT levels returned to normal in 72% of patients. HBeAg seroconversion occurred in 10% of patients, and HBsAg disappeared in 1% of patients. After treatment for 96 weeks, HBV DNA levels were <29 IU/mL in 73% of patients, and ALT levels returned to normal in 75% of patients. HBeAg seroconversion occurred in 18% of patients and HBsAg disappeared in 1% of patients. In 285 HBeAg-negative CHB patients (which excluded patients with decompensated cirrhosis) that received TAF treatment for 48 weeks, HBV DNA levels were <29 IU/mL in 94% of patients and ALT levels returned to normal in 83% of patients. No patients experienced HBsAg loss. Following treatment for 96 weeks, HBV DNA levels were <29 IU/mL in 90% of patients and ALT levels returned to normal in 81% of patients. HBsAg loss occurred in <1% of patients.[140–142]

During the 96-week treatment, headache (12%), nausea (6%), and fatigue (6%) were the most common ad-

Table 5. Recommendations for salvage therapy for resistance to NAs

Types of resistance	Recommended drugs
LAM- or LdT-resistant	Switch to TDF or TAF
ADV-resistant, never used LAM or LdT before	Switch to ETV, TDF, or TAF
ADV-resistant and LAM/LdT-resistant	Switch to TDF or TAF
ETV-resistant	Switch to TDF or TAF
ETV-resistant and ADV-resistant	ETV combined with TDF, or ETV combined with TAF

LAM, lamivudine; LdT, telbivudine; ADV, adefovir dipivoxil; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide fumarate.

verse events.[142] Following 96 weeks of treatment, patients that received TAF had significantly smaller decreases in bone mineral density than those that received TDF in the hip (−0.33% vs. −2.51%; $p<0.001$) and lumbar spine (−0.75% vs. −2.57%; $p<0.001$), as well as a significantly smaller median change in estimated glomerular filtration rate (eGFR) (−1.2 vs. −4.8 mg/dL; $p<0.001$).

Other drugs: Telbivudine (LdT) can improve eGFR but it is associated with high rates of resistance.[113] LdT exhibits favorable efficacy and safety in blocking mother-to-child transmission (refer to the section "Recommendations on antiviral therapy for special populations").

Selection of NAs

Antivirals with high potency and low risk of resistance (ETV, TDF, and TAF) should be the preferred NAs for treatment-naïve patients. ADV and LAM are not recommended for antiviral therapy for HBV-infected patients.

For patients who are being treated with nonpreferred drugs, it is recommended that they switch to antivirals with high potency and low risk of resistance to further reduce the risk of resistance. For patients that receive ADV, it is recommended that they switch to ETV, TDF, or TAF. For patients that receive LAM or LdT, it is recommended that they switch to TDF, TAF, or ETV. For patients that are resistant to LAM or LdT, it is recommended that they switch to TDF or TAF. For patients that are resistant to ADV, it is recommended that they switch to ETV, TDF, or TAF.[143] For patients that are being treated with ADV in combination with LAM/LdT, it is recommended that they switch to TDF or TAF.

Prevention and management of NA resistance

Treatment-naïve patients: Potent antivirals with minimal resistance, such as ETV, TDF, and TAF are recommended.

During treatment: HBV DNA levels should be quantified regularly to detect virological breakthroughs and initiate save therapy as soon as possible (Table 5). For patients who develop resistance to NAs, IFN-α is associated with low response rates.

Monitoring of NA treatment

Detection of the following relevant indicators at baseline before treatment: (1) major biochemical markers, such as ALT, AST, bilirubin, and albumin; (2) major virological and serological markers, such as HBV DNA quantification, HBsAg, HBeAg, and anti-HBe; (3) blood routine serum creatinine levels, blood phosphorus levels, and renal tubular function should be tested if required; (4) noninvasive tests for liver fibrosis, such as liver stiffness measurement; and (5) when ETV and TDF are used in patients with creatinine clearance <50 mL/min, the doses of both drugs should be adjusted. There is no recommended dose for TAF when it is used in patients with creatinine clearance <15 mL/min who are not receiving hemodialysis. In other cases, no dose adjustment is required.

Patient compliance: It should be closely monitored, which includes dosage, method of use, missed medication or self-discontinuation, to ensure that patients understand the risks that might result from unwarranted discontinuation and improve their compliance.

Prevention and management of rare adverse events: Although NAs are generally safe and well-tolerated, serious adverse events such as renal insufficiency (TDF, ADV), hypophosphatemic bone disease (TDF, ADV), myositis/rhabdomyolysis (LdT), and lactic acidosis (ETV, LdT) can occur in rare cases, and require attention. It is recommended that physicians make detailed inquiries into the medical history before treatment to reduce the risk. Patients should be closely monitored if they present with significant increases in serum levels of creatinine, creatine kinase, or lactate dehydrogenase during treatment, which could be accompanied by clinical manifestations, such as general deterioration, myalgia, muscle weakness, and bone pain. If they are diagnosed with renal insufficiency, myositis, rhabdomyolysis, or lactic acidosis, the existing regimen should be withdrawn and changed to other treatment interventions.

Monitoring and management of drug resistance: The use of potent antiviral drugs with minimal resistance has resulted in significantly reduced rates of resistance that could arise from long-term treatment of NAs. If HBV DNA levels increased >2 lg IU/mL from nadir during treatment and the potential of poor compliance has been ruled out, salvage therapy should be initiated promptly, and drug resistance should be tested for.

IFN-α treatment

Peg-IFN-α and IFN-α have been approved for CHB treatment in China.

Regimens and efficacy of peg-IFN-α therapy

Initial monotherapy with peg-IFN-α: In several multicenter, randomized, controlled clinical trials, HBeAg-positive CHB patients were treated with peg-IFN-α-2a or peg-IFN-α-2b for 48 weeks (180 g/week). HBV DNA levels were <2,000 IU/mL in 30% of the patients and HBeAg seroconversion occurred in 30.75–36.3% of patients at week 24 after drug discontinuation (or 68.4% of patients with HBsAg <1,500 IU/mL at week 12 of treatment and baseline ALT >2×ULN). In addition, HBsAg seroconversion occurred in 2.3–3% of patients at week 24 after drug discontinuation; HBsAg clearance was achieved in 11% of patients after 3 years of drug withdrawal.[113,144–146] In HBeAg-negative patients with chronic HBV infections (60% Asians) treated with peg-IFN-

α-2a for 48 weeks, HBV DNA levels were <2,000 IU/mL in 43% and 42% of patients at 24 and 48 weeks after drug withdrawal, respectively. HBsAg clearance was achieved in 3%, 8.7%, and 12% of patients 24 weeks, 3 years, and 5 years after drug withdrawal.[113,146]

At week 24 of peg-IFN-α therapy, if HBV DNA levels decreased by ≤2 lg IU/mL and HBsAg levels were >20,000 IU/mL in HBeAg-positive patients or decreased by <1 lg IU/mL in HBeAg-negative patients, it is recommended to stop peg-IFN-α treatment and switch to NAs therapy.[112,116,146]

Combined treatment of peg-IFN-α and NAs: The combined use of peg-IFN-α in eligible CHB patients treated with NAs could achieve clinical cure in some patients.[116,146] HBsAg clearance was high after combined treatment in patients with low levels of HBsAg (<1,500 IU/mL) before treatment and who experienced a rapid decline of HBsAg levels during treatment (HBsAg <200 IU/mL or a decrease of >1 lg IU/mL at week 12 or 24).[147–151] However, further research is required to determine baseline conditions, the optimal course of treatment, and sustained virological responses of combination therapy.

Peg-IFN-α further reduces the incidence of HBV-related liver cancer: In a study of CHB patients that were treated with peg-IFN-α or ETV, a 5-year follow-up showed that none of the patients treated with peg-IFN-α developed HCC within 5 years; however, two and one patients treated with ETV developed HCC at years 4 and 5, respectively. There was no significant difference in the cumulative HCC incidence between the observed and the predicted cases for patients treated with ETV (p=0.36).[152] In another retrospective study that included 682 patients treated with NAs and 430 patients treated with IFN-α alone or in combination with NAs, a total of 31 patients developed HCC at a median follow-up of 5.41 years and the 10-year cumulative incidence of HCC was significantly lower in patients treated with IFN-α than those treated with NAs (2.7% vs. 8.0%, p<0.001).[146,153] The role of peg-IFN-α in reducing the incidence of HBV-related liver cancer requires further research.

Predictive factors for the efficacy of peg-IFN-α-based antiviral therapy

Pretreatment predictors: HBV DNA levels <2×10^8 IU/mL, high ALT levels (2–10×ULN) or liver tissue necroinflammation ≥G2, genotype A or B, low baseline HBsAg (<25,000 IU/mL),[6,112,113,146,154,155] high levels of anti-HBc at baseline (qAnti-HBc),[62,63] signal transducer and activator of transcription 4 (commonly known as STAT4) rs7574865 polymorphism at baseline[156] are predictors for favorable outcomes of IFN-based therapy. HBV DNA levels and HBsAg levels at 12 weeks of peg-IFN-α therapy and their dynamic changes could be used to predict the efficacy of peg-IFN-α.[146]

Management of adverse events of peg-IFN-α therapy[6,112,113]

Influenza-like syndrome: If patients complain of fever, headache, myalgia, or fatigue, peg-IFN-α could be injected before sleep or taking nonsteroidal anti-inflammatory agents along with the IFN-α.

Myelosuppression: If neutrophil count ≤0.75×10^9/L and/or platelet count <50×10^9/L develops, peg-IFN-α dosage should be reduced and cell counts retested after 1–2 weeks. If cell counts return to normal, the initial dosage should be restored. If neutrophil count ≤0.5×10^9/L or platelet count <25×10^9/L, or both, the peg-IFN-α should be discontinued. Granulocyte colony-stimulating factor (commonly known as G-CSF) or granulocyte-macrophage colony-stimulating factor (commonly known as GM-CSF) could be used for those with significantly decreased neutrophil counts.

Mental disorders: If patients experience depression, delusions, severe anxiety, or other mental disorders, peg-IFN-α should be immediately withdrawn, and patients could seek consultations with psychiatrists and psychologists if required.

Autoimmune diseases: Some patients might develop autoantibodies, and few patients develop thyroid disease, diabetes, decreased platelet count, psoriasis, vitiligo, rheumatoid arthritis, and systemic lupus erythematosus-like syndrome. In such cases, patients should have consultations with physicians with related expertise, and treatment should be discontinued for patients with severe symptoms.

Other rare adverse events: For other rare adverse events, which include retinopathy, interstitial pneumonia, hearing loss, kidney damage, and cardiovascular complications, peg-IFN-α therapy should be discontinued.

Contraindications for peg-IFN-α therapy[6,112,113]

Absolute contraindications: Pregnancy or intention to be pregnant in the short-term, history of mental illness (e.g., history of schizophrenia or severe depression), uncontrolled epilepsy, decompensated cirrhosis, uncontrolled autoimmune diseases, severe infection, retinal disease, heart failure, chronic obstructive pulmonary diseases, and other underlying diseases.

Relative contraindications: These include thyroid disease, a history of depression, uncontrolled diabetes, hypertension, and heart disease.

Recommendation 9: HBeAg-positive CHB patients should be treated with ETV, TDF, or TAF. If HBV DNA levels are below the detection limit, ALT levels return to normal, and HBeAg seroconversion occurs after 1 year of treatment, patients should receive consolidation treatment for at least 3 years (followed up every 6 months). Treatment could be discontinued if HBV DNA remains undetectable, and ALT normalization and HBsAg loss are maintained. A longer duration of treatment might reduce recurrence (A1).

Recommendation 10: HBeAg-positive CHB patients could be treated with peg-IFN-α. At week 24 of treatment, if HBV DNA decrease <2 lg IU/mL and HBsAg levels >20,000 IU/mL, it is recommended that peg-IFN-α therapy should be discontinued and changed to NA treatment (A1). For patients who responded effectively, the course of treatment is 48 weeks, and it might be extended according to the patient's condition but it should not exceed 96 weeks (B1).

Recommendation 11: HBeAg-negative CHB patients should be treated with ETV, TDF, or TAF. Discontinuation and subsequent follow-up are advised if HBsAg loss and undetectable HBV DNA are achieved (A1).

Recommendation 12: HBeAg-negative CHB patients could be treated with peg-IFN-α. At week 12 of treatment, if HBV DNA decreased <2 lg IU/mL or HBsAg decreased <1 lg IU/mL, it is recommended that peg-IFN-α treatment should be discontinued and changed to NA treatment (B1). For patients who responded effectively, the course of treatment is 48 weeks, and it might be extended according to the patient's condition, but it should not exceed 96 weeks (B1).

Recommendation 13: For HBV-related compensated cirrhosis patients, long-term treatment with ETV, TDF, or TAF, or peg-IFN-α therapy is recommended. The adverse events of peg-IFN-α must be closely monitored (A1).

Recommendation 14: For HBV-related decompensated cirrhosis patients, long-term treatment with ETV or TDF is recommended (A1). TAF therapy could be used if necessary (C1).

Other treatments

Anti-HBV therapy can reduce the incidence of HBV-related complications, HBV-related liver cancer, and improve the survival rate of patients, which is the most important treatment for chronic HBV infection. In addition, other treatment options include anti-inflammatory, antioxidant, hepatoprotective, anti-fibrosis, and immunomodulatory interventions.

Anti-inflammatory, antioxidant, and hepatoprotective treatment

The necroinflammation of liver cells caused by HBV infection is an important pathological and physiological process of disease progression. Glycyrrhizic acid, silymarin, polyunsaturated lecithin, and bicyclol have anti-inflammatory, antioxidant, and hepatoprotective effects, and might reduce inflammatory damage of the liver. For patients with obvious liver inflammation or significantly elevated ALT levels, these agents could be used where appropriate, but it is not advised to use more than two of them in combination.

Antifibrosis treatment

Several antifibrosis Chinese medicine prescriptions, such as Anluohuaxian wan, Fufang Biejiaruangan tablets, Fuzhenghuayu capsules, have shown protective effects against fibrosis in animal experiments and clinical studies.[157–161] They could be used where appropriate for patients with obvious fibrosis or cirrhosis. However, multicenter randomized controlled studies are required to further define their treatment course of and long-term efficacy.

Monitoring and follow-up management of people with chronic HBV infection[6,112,113]

Management of chronic HBV carriers and inactive HBsAg carriers

Because chronic HBV carriers are in the immune tolerance phase, they do not have or only have mild inflammatory activity in the liver, patients in this phase respond poorly to antiviral treatment. Therefore, antiviral therapy is not recommended. However, it is emphasized that some patients in the immune tolerance phase might enter the immune clearance phase and develop hepatitis flares. Inactive HBsAg carriers are in the immune control phase, but they might progress to HBeAg-negative CHB and are at risk of developing HCC in long-term follow-up.

Therefore, for chronic HBV carriers and inactive HBsAg carriers, it is recommended that they should undergo routine blood tests, biochemical tests, virological tests, AFP tests, abdominal ultrasound, and noninvasive tests for liver fibrosis every 6–12 months. A liver biopsy is recommended if necessary. Antiviral therapy should start if they meet the indications for such treatment.

Monitoring during antiviral therapy

Regular monitoring during antiviral therapy aims to monitor the efficacy of antiviral therapy, compliance of patient, drug resistance, and adverse events.

Patients treated with peg-IFN-α: Routine blood tests (every 1–2 weeks in the 1st month of treatment, then once a month after measurements become stable), liver biochemical tests (once a month), thyroid function and blood glucose tests (once every 3 months), quantitative tests of HBV DNA, HBsAg, HBeAg and anti-HBe (every 3 months), liver stiffness measurement (every 6 months), abdominal ultrasound and AFP tests (every 6 months for patients without cirrhosis, and every 3 months for patients with cirrhosis). Enhanced CT or enhanced MRI for early detection of HCC may be performed if necessary.

NAs: Routine blood tests, liver biochemical tests, HBV DNA quantification, serological markers, and liver stiffness measurement should be performed every 3 to 6 months; abdominal ultrasound and AFP test should be performed every 6 months for patients without cirrhosis, and every 3 months for patients with cirrhosis. Enhanced CT or enhanced MRI for early detection of HCC may be performed if necessary. For patients treated with TDF, blood phosphorus levels and renal function should be tested every 6 to 12 months. Early renal tubular injury may be monitored if feasible.

Follow-up after the end of antiviral therapy

The purpose of follow-up of patients after the end of treatment is to evaluate the long-term efficacy of antiviral therapy, monitor disease progression and the development of HCC. Therefore, regardless of patient's response to antiviral treatment, biochemical tests of the liver, and HBV DNA quantification should be performed once a month within the first 3 months after drug withdrawal, every 3 months thereafter, and every 6 months one year after drug withdrawal. Patients without cirrhosis need to undergo abdominal ultrasound and AFP test every 6 months, and patients with cirrhosis need to be tested every 3 months, and if necessary, enhanced CT or enhanced MRI may be performed for early detection of HCC.

Recommendations on antiviral therapy for special populations

Patients with poor response

CHB patients: After treatment with ETV, TDF, or TAF for 48 weeks, if HBV DNA is $>2\times10^3$ IU/mL, and excluding compliance and detection errors, NA-based treatment regimens should be adjusted (those using ETV could be switched to TDF or TAF,[162,163] and those using TDF or TAF could be switched to ETV), or combination therapy could be used (ETV combined with TDF or TAF). Peg-IFN-α therapy can also be used in combination.

Patients with HBV-related cirrhosis: After treatment with ETV, TDF, or TAF for 24 weeks, if HBV DNA is $>2\times10^3$ IU/mL, and excluding compliance and detection errors, NA-based treatment regimens could be adjusted (those using ETV could be switched to TDF or TAF, and those using TDF or TAF could be switched to ETV), or combination therapy might be used (ETV combined with TDF or TAF).

Patients treated with chemotherapeutic or immunosuppressive agents

Chemotherapy or immunosuppressive therapy in CHB patients might cause HBV reactivation and might lead to liver failure or even death in severe cases. HBV reactivation occurs after antitumor therapy in approximately 20–50% of HBsAg-positive, anti-HBc-positive tumor patients, and in 8–18% of HBsAg-negative, anti-HBc-positive tumor pa-

tients.[164,165] Prophylactic antiviral therapy can significantly reduce the incidence of hepatitis B reactivation.[166,167] ETV, TDF, or TAF, which are potent antivirals with minimal resistance, are recommended.[168–170]

All patients that receive chemotherapy or immunosuppressive therapy should be routinely screened for HBsAg and anti-HBc before starting treatment.

HBsAg-positive patients should be given NA therapy (usually 1 week) before or when they start receiving immunosuppressive or chemotherapeutic agents.[6,171,172]

In addition, HBsAg-negative, anti-HBc-positive patients need prophylactic antiviral therapy if they are positive for HBV DNA;[112] if HBV DNA is negative, ALT levels, HBV DNA, and HBsAg should be monitored every 1–3 months. Antiviral therapy should be initiated immediately when HBV DNA or HBsAg becomes positive.[112,173]

For HBsAg-negative and anti-HBc-positive patients, the use of B-cell monoclonal antibodies or hematopoietic stem cell transplantation is associated with a high-risk of HBV reactivation.[174,175] The prophylactic use of antiviral drugs is recommended.[112,165,168,176,177]

For patients with CHB or cirrhosis that are treated with chemotherapy and immunosuppressants, the course of NA treatment, follow-up monitoring, and drug withdrawal are the same as those for patients with CHB or cirrhosis that receive no chemotherapy or immunosuppressants. For patients with chronic HBV infection in the immune tolerance or immune control phases, or HBsAg-negative, anti-HBc-positive patients that require the prophylactic use of NAs, treatment with ETV, TDF, or TAF should be continued for 6–12 months after the end of chemotherapy and immunosuppressive therapy.[6,168,178]

For patients that receive B-cell monoclonal antibodies or undergo hematopoietic stem cell transplantation, NAs could be discontinued at least 18 months after the end of immunosuppressive therapy.[179,180] HBV could recur or even worsen after NAs are withdrawn. Patients should be followed up for 12 months, during which HBV DNA should be monitored every 1–3 months.

Pregnancy

Women of childbearing age or women that are preparing to become pregnant should be screened for HBsAg, and HBV DNA should be tested for HBsAg-positive patients.[181] Peg-IFN-α treatment should be initiated before pregnancy if antiviral therapy is indicated, and antiviral therapy should be completed 6 months before pregnancy. Reliable contraceptive measures should be taken during treatment. If peg-IFN-α is not indicated or fails, TDF could be used for antiviral therapy. For patients diagnosed with CHB for the first time during pregnancy, treatment indications are the same as those for other CHB patients, and TDF could be used for antiviral therapy. Pregnant women with CHB who started taking antiviral drugs before or during pregnancy should continue antiviral therapy after delivery, and based on virological responses, decide whether to continue the original treatment regimen or change to other NAs or peg-IFN-α.

For patients with unexpected pregnancy during antiviral therapy, it is recommended that they continue their pregnancy if they are taking TDF. Patients do not have to terminate the pregnancy if they are taking ETV, and it is suggested that they switch to TDF instead. If pregnant patients are receiving IFN-α treatment, they should be informed (and their family members) of the associated risks, and whether or not to continue the pregnancy should be decided by patients themselves; if the pregnancy choice is to continue, patients should change to TDF treatment.

High levels of serum HBV DNA is a high-risk factor for mother-to-child transmission. If HBV DNA levels are $>2\times10^5$ IU/mL in the second and third trimesters of pregnancy,[182] the patients should be informed of the associated risks and their consent should be obtained to start antiviral therapy at 24–28 weeks of the pregnancy using TDF or LdT.[183,184] Breastfeeding is not a contraindication for TDF therapy.[185,186] Pregnant women taking NAs at the immune tolerance phase could discontinue NAs immediately after delivery or continue for another 1–3 months. Approximately 17.2–62% of patients might develop hepatitis flares after discontinuation, which usually occurs within 24 weeks.[187–189] Postpartum monitoring is needed. Blood biochemical indexes for the liver and HBV DNA should be rechecked 4–6 weeks after delivery. If the biochemical markers for the liver are normal, they should be followed up every 3 months until 6 months after delivery. If patients develop hepatitis flares, antiviral therapy is indicated.

Fertility issues for male patients that receive antiviral therapy: Male patients treated with IFN-α might consider having children 6 months after drug withdrawal. No evidence is currently available that indicates NA therapy harms sperm in male patients that receive NA therapy. Male patients should be informed of the potential risks when they consider having children.

Pediatric patients

If children with HBV infection are in the immune tolerance phase, antiviral therapy is not considered. Antiviral therapy should be initiated as soon as possible for children with chronic hepatitis or cirrhosis. Antiviral therapy for children with CHB can significantly inhibit HBV DNA replication and increase the chance of ALT normalization and HBeAg seroconversion.[190] However, the safety and resistance issues associated with long-term treatment should be concerned.[112,191,192]

The drugs approved by the USA's Food and Drug Administration (FDA) for the treatment of pediatric patients include IFN-α (aged ≥1 year), ETV (aged ≥2 years), and TDF (aged ≥2 years and body weight ≥10 kg).[6,190] China has approved TAF for adolescents (aged ≥12 years and body weight ≥35 kg). Peg-IFN-α-2a could be used in CHB children aged ≥5 years.[6]

HBeAg-positive CHB patients with elevated ALT levels should be treated with a finite course of IFN-α or peg-IFN-α-2a therapy to achieve HBeAg conversion.[178,193] Alternatively, they could be treated with ETV, TDF, or TAF. The recommended dose of IFN-α for pediatric patients is 3–6 million U/m^2, three times a week. The maximum dose should not exceed 10 million U/m^2, and the recommended duration of treatment is 24–48 weeks. Peg-IFN-α-2a should be dosed at 180 μg/1.73 m^2, with a treatment course of 48 weeks.[194] The doses of ETV, TDF, or TAF refer to the recommendations of the USA's FDA and WHO, and drug labels (Table 6).[8,190,193]

For children with CHB or cirrhosis that receive therapy with IFN-α or peg-IFN-α-2a but fail to achieve HBeAg seroconversion or HBeAg-negative status, NAs should be used for treatment.[178]

Patients with renal injury

High-risk factors for renal injury include ≥1 of the following: decompensated cirrhosis; eGFR <60 mL/min; poorly controlled hypertension; proteinuria; uncontrolled diabetes; active glomerulonephritis; concomitant use of nephrotoxic drugs; or history of solid organ transplantation.[112] When there are high-risk factors for renal injury, the changes in

Table 6. Recommended doses of NAs for children

Drug	Body weight (kg)	Dose (mg/d)
ETV (aged ≥2 years, and body weight ≥10 kg; use adult dose if body weight >30 kg)	10–11	0.15
	>11–14	0.20
	>14–17	0.25
	>17–20	0.30
	>20–23	0.35
	>23–26	0.40
	>26–30	0.45
	> 30	0.50
TDF		
Aged ≥2 years and body weight ≥17 kg, who can take tablets orally	17–22	150
	22–28	200
	28–35	250
	≥35	300
Aged ≥2 years and body weight ≥10 kg; those who cannot take tablets orally can be given powder using a special spoon (40 mg/spoon)	10–12	80 (2 spoons)
	12–14	100 (2.5 spoons)
	14–17	120 (3 spoons)
	17–19	140 (3.5 spoons)
	19–22	160 (4 spoons)
	22–24	180 (4.5 spoons)
	24–27	200 (5 spoons)
	27–29	220 (5.5 spoons)
	29–32	240 (6 spoons)
	32–34	260 (6.5 spoons)
	34–35	280 (7 spoons)
	≥35	300 (7.5 spoons)
TAF (aged ≥12 years)	≥35	25

ETV, entecavir; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

renal function should be monitored during the use of any NA. If ADV or TDF is used for treatment, serum creatinine and blood phosphorus levels should be monitored regularly, regardless of the presence or absence of high-risk factors for renal injury.[195,196]

For patients with chronic kidney disease, renal insufficiency, or who receive renal replacement therapy, ETV or TAF is recommended as the first-line anti-HBV therapy; LdT could also be chosen for antiviral therapy, where appropriate. ADV or TDF is not recommended.[142,197] When TAF is used in patients without HIV coinfection, no dose adjustment is necessary when eGFR is ≥15 mL/min; however, the doses of other NAs currently on the market need to be adjusted when eGFR is <50 mL/min. Dosing adjustments should refer to drug labels.

ETV or TAF could be used as prophylactic or therapeutic drugs for HBsAg-positive patients that receive kidney transplantation. Because of the increased risk of rejection, kidney transplant patients should avoid IFN-α or peg-IFN-α therapy.

HBV-related glomerulonephritis could be treated with NA therapy, and ETV or TAF is recommended.[198]

For patients that have been treated with ADV or TDF, it is recommended that they should change to ETV or TAF if kidney or bone disease occurs, or if other high-risk factors are involved.[197]

Recommendation 15: For CHB patients, after 48 weeks of treatment with ETV, TDF, or TAF, of HBV DNA is $>2\times10^3$ IU/mL, NAs treatment regimens should be adjusted when excluding compliance and detection errors. Those using ETV could change to TDF or TAF, and those using TDF or TAF could change to ETV, or combination therapy might be used (ETV combined with TDF or TAF) (C2). Peg-IFN-α therapy could be used in combination (B1).

For patients with HBV-related cirrhosis, after treatment with ETV, TDF, or TAF for 24 weeks, of their HBV DNA is $>2\times10^3$ IU/mL, and excluding compliance and detection errors, NAs treatment regimens could be adjusted. Those using ETV could change to TDF or TAF, and those using TDF or TAF could change to ETV, or combination therapy might be

used (ETV combined with TDF or TAF) (C2).

Recommendation 16: All patients that receive chemotherapy or immunosuppressive therapy should be routinely screened for HBsAg and anti-HBc before starting treatment (A1). For HBsAg-positive patients, antiviral therapy should be given 1 week before or when they start to receive immunosuppressive therapy or chemotherapy (A1), and ETV, TDF, or TAF should be used (B1). For HBsAg-negative and anti-HBc-positive patients, antiviral therapy with ETV, TDF, or TAF is recommended if they receive B-cell monoclonal antibodies or undergo hematopoietic stem cell transplantation (B1).

Recommendation 17: When patients with chronic HBV infection attempt pregnancy or have antiviral indications during pregnancy, TDF could be used when informed consent has been obtained (B1).

Recommendation 18: For patients with unexpected pregnancy during antiviral therapy it is recommended that they continue their pregnancy if they are taking TDF. Patients do not have to terminate the pregnancy if they are taking ETV and it is suggested that they change to TDF instead (B1). If patients are receiving IFN-α treatment, they (and their family members) should be informed of the associated risks, and whether or not to continue the pregnancy should be decided by patients themselves; if they decide to continue, they should change to TDF treatment (C2).

Recommendation 19: If HBV DNA levels are $>2\times10^5$ IU/mL during the second and third trimesters of pregnancy, patients should be informed of the associated risks and could start antiviral therapy at 24–28 weeks of pregnancy using TDF or LdT when they give informed consent (A1). Pregnant women in the immune tolerance phase should stop medication immediately after delivery or after 1–3 months of treatment. Breastfeeding is not a contraindication for TDF treatment (C2). Blood biochemical indexes for the liver function and HBV DNA levels should be tested at least every 3 months until 6 months after delivery after drug withdrawal. Patients that develop hepatitis flares should start antiviral therapy immediately (A2).

Recommendation 20: For children with advanced liver disease or cirrhosis, antiviral therapy should be given in time, but safety and resistance issues associated with long-term antiviral treatment should be considered. IFN-α treatment could be considered for children aged ≥1 year, ETV or TDF for children aged ≥2 years, peg-IFN-α-2a for children aged ≥5 years. and TAF treatment for children aged ≥12 years (A1).

Recommendation 21: For patients with chronic kidney disease, renal insufficiency, or who receive renal replacement therapy, ETV or TAF is recommended as the first-line anti-HBV therapy. Alternatively, LdT could be used for antiviral therapy, where appropriate. ADV or TDF is not recommended (B1). The changes in renal function should be monitored during the use of any NAs for CHB patients at a high-risk of kidney injury. For patients that have been treated with ADV or TDF, it is recommended that they switch to ETV or TAF if they develop kidney or bone disease or present with other high-risk factors (B1).

Patients with coinfection of HBV and HCV

All people that are HBsAg-positive should be screened for anti-HCV. If they are positive, they need further testing for HCV RNA. Those who test positive for HCV RNA should receive DAA therapy. These patients are at risk of HBV reactivation. Therefore, it is recommended that they receive antiviral therapy with ETV, TDF, or TAF during and within 3 months after the end of anti-HCV therapy and they should be closely monitored.[112]

In addition, HBsAg-negative and anti-HBc-positive patients are at risk of HBV reactivation during treatment of hepatitis C with DAAs. Serum HBV DNA levels and HBsAg should be monitored monthly. If HBsAg seroreversion occurs, antiviral therapy is recommended.[112]

Recommendation 22: When a DAA is used to treat HCV in patients with coinfection of HCV and HBV, NA treatment should be administered to prevent HBV reactivation if HBsAg is positive. NA treatment could be withdrawn 12 weeks after the end of DAA treatment (B2). HBsAg-negative, anti-HBc-positive patients should be closely monitored for HBV DNA and HBsAg levels during DAA therapy. If HBsAg seroreversion occurs, NA therapy is recommended (B2).

Patients with coinfection of HBV and HIV

Antiretroviral therapy (commonly referred to as ART) should be initiated as soon as possible if there is no contraindication for anti-HIV therapy, regardless of $CD4^+T$ lymphocyte count. HIV/HBV co-infected patients should be treated for both viral infections at the same time. The highly active anti-retroviral therapy (HAART) regimen should include two drugs active against HBV, preferably TDF or TAF + LAM or emtricitabine (FTC) (TDF+FTC and TAF+FTC are available as a mixture). HBV-related markers, such as HBV DNA, liver biochemical indicators, and liver imaging should be monitored during treatment. For HIV/HBV co-infected patients, a treatment regimen for hepatitis B that contains only one NA against HBV is not recommended (TDF, LAM, ETV, LdT, ADV).[199,200]

The following should be noted for patients with renal insufficiency: (1) if the creatinine clearance rate is <60 mL/min, avoid use of TDF; and (2) if the creatinine clearance rate is between 30 mL/min and 50 mL/min, TAF+ (FTC or LAM) could be considered in the regimen. However, TAF has not been approved for use yet in patients with a creatinine clearance rate <30 mL/min. Finally, (3) when TDF/TAF cannot be used, ETV should be added to the HAART regimen. For pregnant women with HIV/HBV co-infection, the recommended regimen should include LAM (FTC)+TDF.[201]

Recommendation 23: For people who are co-infected with HBV and HIV, it is recommended that a combination of antiviral drugs effective for both HIV and HBV be chosen (A1).

Patients with HBV-related liver failure

Patients with HBV-related acute, subacute, acute-on-chronic, and chronic liver failure are associated with high mortality. If HBsAg is positive, antiviral therapy is indicated.

Anti-HBV therapy can improve the long-term prognosis of HBV-related acute-on-chronic liver failure (ACLF).[202,203] Several clinical studies have confirmed that both ETV and LAM can effectively reduce the mortality of ACLF.[204,205] Meta-analyses have shown that ETV is superior to LAM for the treatment of HBV-related ACLF.[205,206] Small cohort clinical studies have found that HBV-related ACLF can benefit from the use of LdT and TDF.[207,208] Compared with TDF, TAF can reduce nephrotoxicity and maintain antiviral efficacy,[142] but no definite clinical evidence is available to support the use of TAF for liver failure. Early rapid reduction of HBV DNA levels is key to treatment.[204,207] If HBV DNA levels can be reduced by 2 lg IU/mL within 2–4 weeks, survival can be improved.[206,207] Fast-acting NAs with high potency and minimal resistance (ETV, TDF, or TAF) should be chosen for antiviral therapy.[209] Antiviral therapy should be continued for long periods after patients with liver failure recover.

Recommendation 24: For patients with HBV-related

acute, subacute, acute-on-chronic, and chronic liver failure, it is recommended that they should receive antiviral therapy with ETV, TDF, or TAF if they are positive for HBsAg (A1).

Patients with HBV-related HCC

HBV DNA-positive HCC patients that receive anti-HBV treatment could reduce the recurrence of HCC after surgery and improve the overall survival rate.[210–216] Fast-acting NAs with high potency (ETV, TDF, or TAF) should be chosen for antiviral therapy. Patients without contraindications could use IFN-α.

HCC patients that are HBsAg-positive but HBV DNA-negative might experience HBV reactivation when undergoing liver resection, transcatheter arterial chemoembolization, radiotherapy, or systemic chemotherapy.[217–221] ETV, TDF, or TAF are recommended for antiviral therapy.

Recommendation 25: Patients with HBV-related HCC are recommended to use ETV, TDF or TAF for antiviral therapy if they are positive for HBsAg (A1).

Liver transplant patients

For patients that undergo liver transplantation for HBV-related diseases (including liver failure and HCC), anti-HBV regimens should be rationally selected to reduce the risk of reinfection of HBV in the transplanted liver. The design of treatment regimens mainly depends on the major risk factor for reinfection, i.e. HBV DNA levels before transplantation.

A negative HBV DNA quantification test before transplantation suggests a low risk of reinfection. High potency NAs with minimal resistance, such as ETV, TDF, or TAF, should be used as early as possible before surgery to prevent HBV reactivation. There is no need to use HBIG after surgery.[222,223] Positive HBV DNA testing before transplantation suggests a high-risk of reinfection. NAs with high potency and minimal resistance should be used as early as possible before surgery to reduce HBV DNA levels; HBIG should be injected intravenously during the anhepatic phase. After surgery, low-dose HBIG should be used in combination with NAs for 0.5–1.0 year, followed by the use of NAs alone.[222,224,225] A recent study found that a shortened course of HBIG was effective in patients treated with ETV.[226] If patients have already used other NAs, HBV DNA should be closely monitored to detect drug resistance and adjust the regimen if necessary. In addition, hepatitis B vaccination was reported to prevent recurrence after liver transplantation, but its clinical use remains controversial.[227]

Recommendation 26: For patients that undergo liver transplantation for HBV-related infections, it is recommended that they start antiviral therapy with ETV, TDF, or TAF before transplantation if they are positive for HBsAg (A1).

Unsolved clinical issues

1. Identify and evaluate new markers that could be used to differentiate the various stages of the natural course of chronic HBV infections.
2. Define the value of new serum markers, such as anti-HBc levels during the treatment planning for patients with normal ALT levels.
3. Define the value of noninvasive tests for liver fibrosis in initiating treatment, evaluating the efficacy, and predicting long-term outcome.
4. Assess the effect of long-term treatment with different NAs on the reversal of cirrhosis and the incidence of HCC.
5. Identify clinical indicators and biological markers that could guide the safe discontinuation of NAs.
6. Develop innovative drugs aimed at a clinical cure (functional cure) and evaluate their synergy and combined use with existing drugs.
7. Use real-world data (e.g., long-term follow-up cohorts or medical insurance databases) to evaluate the safety, efficacy, and cost-effectiveness of marketed drugs and provide evidence for clinical and public health decisions.
8. Innovate the management of CHB, enhance the ability to detect, diagnose, and cure CHB, and reduce mortality related to hepatitis B.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Authors (sorted by strokes of last name)

Guiqiang Wang, Fusheng Wang, Hui Zhuang, Taisheng Li, Sujun Zheng, Hong Zhao, Zhongping Duan, Jinlin Hou, Jidong Jia, Xiaoyuan Xu, Fuqiang Cui, Lai Wei.

Guideline development group (sorted by strokes of last name)

Yan Wang, Guiqiang Wang, Fusheng Wang, Hong You, Qin Ning, Hong Ren, Hui Zhuang, Jie Li, Taisheng Li, Lanjuan Li, Wenhong Zhang, Xinxin Zhang, Lungen Lu, Yu Chen, Sujun Zheng, Qinghua Meng, Hong Zhao, Yuemin Nan, Zhongping Duan, Jinlin Hou, Huiying Rao, Jidong Jia, Xiaoyuan Xu, Xinhua Weng, Hong Tang, Fuqiang Cui, Jie Peng, Chongwen Si, Ying Han, Qing Xie, Xiaoguang Dou, Lai Wei.

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