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Guideline

Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022)

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Abstract

To facilitate the achieving of the goal of "eliminating viral hepatitis as a major public health threat by 2030" set by the World Health Organization, the Chinese Society of Hepatology together with the Chinese Society of Infectious Diseases (both are branches of the Chinese Medical Association) organized a panel of experts and updated the guidelines for prevention and treatment of chronic hepatitis B in China (version 2022). With the support of available evidence, this revision of the guidelines focuses on active prevention, large scale testing, and expansion of therapeutic indication of chronic hepatitis B with the aim of reducing the hepatitis B related disease burden.

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Introduction

Chronic infection of hepatitis B virus (HBV) is still a major public health issue in the world, especially in China and other Asia-Pacific countries/territories. During the last decades, China has been committed to implementing universal infant hepatitis B vaccination, driving down the cost of medication, exploring "functional cure" with approved drugs, and promoting Chronic hepatitis B (CHB) guidelines in primary healthcare. In 2005, the Guideline of Prevention and Treatment for Chronic Hepatitis B was first published by the Chinese Society of Hepatology and the Society of Infectious Diseases (both are branches of the Chinese Medical Association) and updated in 2010, 2015, and 2019,[1] respectively. To facilitate the achievement of the goal proposed World Health Organization (WHO) of eliminating viral hepatitis as a public health threat by 2030[2] , we updated the guidelines with the aim of greatly improving the diagnosis and treatment rates of CHB in China, which are currently only 22% and 15%, respectively.[3]

The revision process for the guidelines adhered to the standard procedures used to create clinical recommendations worldwide. It is primarily based on the best available clinical evidence (most recent studies and phase III trials of the newly approved medications), public health needs (disease burden and health threat), and health economics considerations (price and cost-effectiveness of diagnosis and treatment methods).

The quality of evidence for recommendations in the guidelines was assigned using the A, B, and C levels. The strength of recommendation was indicated using grades 1 and 2, as shown in Table 1 (revised according to the GRADE classification).

Epidemiology and prevention

Epidemiology

Hepatitis B virus (HBV) is prevalent globally. According to the WHO, the prevalence of HBsAg in the population was 3.8% worldwide, with about 1.5 million new infections, 296 million chronic HBV infections, and 820,000 deaths due to HBV-related liver failure, cirrhosis, or primary hepatocellular carcinoma (HCC) in 2019.[4] In the Western Pacific region, the

Keywords: Chronic hepatitis B; Treatment; Prevention; Guideline.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; DAA, direct-acting agents; ETV, Entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; NAs, nucleoside (acid) analogs; PCR, polymerase chain reaction; TAF, Tenofovir alafenamide fumarate; TDF, Tenofovir disoproxil fumarate; TMF, Tenofovir amibufenamide; ULN, upper limit of normal; WHO, World Health Organization.
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Table 1. Quality of evidence and strength of recommendation

Grade	Detailed Descriptions
Quality of evidence	
A: High	Further research is unlikely to change our confidence in the estimate of the effect
B: Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect
C: Low	Further research is likely to affect our confidence in the estimate of effect and may change the estimate
Strength of recommendation	
1: Strong	Factors influencing the strength of the recommendation are quality of evidence, the possible prognosis, prevention, diagnosis, and therapeutic effect of the patient, with a higher cost-benefit ratio
2: Weak	The evidence quality is variable with uncertainty in the recommendation or a poor cost-benefit ratio: a weak recommendation is more likely warranted.

prevalence of HBV is moderate, with HBsAg positivity observed in 5.9% of the general population. This translates to approximately 140,000 new infections, 116 million chronic HBV infections, and 470,000 deaths due to HBV-related complications in 2019.[4]

In 2014, the Chinese Center for Disease Control and Prevention (CCDC) reported HBsAg positive rate of 2.94% in the population aged 1–29 years and 0.32% in children aged <5 years.[5] The Polaris Observatory Collaborators estimated that HBsAg was positive in 6.1% of the general population in China in 2016, with 86 million chronic HBV infections.[6]

Routes of transmission

HBV is transmitted through mother-to-child transmission (MTCT), blood transmission, and sexual exposure. In China, MTCT is the main route of chronic HBV infection, accounting for 40–50% of new infections,[7] which mostly occur in the perinatal period through the blood or body fluids of HBV-positive mothers. The HBV DNA level of the mother is closely related to the risk of HBV infection in the newborn, and the newborns of HBeAg-positive mothers with high DNA levels are more likely to be infected with HBV.[8]

HBV is mainly transmitted through blood and sexual activities in adults, including transfusion of unqualified blood or blood products, unsafe blood purification, unsafe invasive procedures (such as unsafe injections, surgeries, and dental procedures), and unprotected sexual activities. HBV can also be transmitted through open cuts and sores, such as occupational exposure, pedicures, tattoos, piercing earring holes, and sharing of shavers or dental tools.[9,10]

Prevention

Protecting susceptible populations: Hepatitis B vaccination is the most effective approach for preventing HBV infection. Hepatitis B vaccination mainly targets newborns, followed by infants, unvaccinated individuals under 15 years of age, and high-risk adult populations.[11] The dosage of hepatitis B vaccine recommended for newborns is 10 μg of recombinant hepatitis B vaccine per dose, regardless of whether the mother is HBsAg positive or not.[12]

Newborns to HBsAg-positive mothers should receive the hepatitis B vaccine as soon as possible (preferably within 12 h after birth) and be injected with hepatitis B immunoglobulin (HBIG) at different body sites simultaneously.[13] However, there is still a small risk of failure in preventing MTCT of HBV. Even with active and passive immunization, approximately 5–10% of infants born to HBeAg-positive mothers with high DNA levels will be infected with HBV. Risk factors for this failure include HBeAg-positive mothers, high HBV DNA load, quasispecies characteristics, and HBx characteristics.[14,15] Infants born to HBeAg-positive mothers or infants with low anti-HBs levels at seven months of age should receive timely booster doses before two years of age, rather than waiting until their anti-HBs levels become negative.[16]

The dosage of hepatitis B vaccine recommended for adults is three doses of 20 μg recombinant hepatitis B vaccine. For immunocompromised or non-responders to the initial vaccine series, the dosage (e.g., 60 μg) or doses should be increased; for those who do not respond to the 0-, 1-, and 6-month schedule, one additional dose of 60 μg or three additional doses of 20 μg hepatitis B vaccine should be applied. Serum anti-HBs should be detected 1–2 months after the second vaccination. If there is still no response, an additional dose of 60 μg recombinant hepatitis B vaccine can be administered. Hepatitis B vaccination is safe for HBV-naïve women during pregnancy.[17] An accelerated vaccination schedule (0, 1, and 2 months) is feasible and effective in addition to a routine vaccination schedule.[9]

Management of the infection source: Newly identified HBsAg-positive individuals should be reported to the local CDC if they meet the reporting standards for infectious diseases. It is recommended that their family members be tested for serum HBsAg, anti-HBs, and anti-HBc levels. Moreover, hepatitis B vaccines should be administered to susceptible individuals.

The infectivity of HBV-infected patients depends mainly on serum HBV DNA levels. HBV markers should be routinely tested during health checks or medical encounters unrelated to nursery admission, school and employment enrollment.

Interrupting the transmission route: It is critical to extensively promote safe injections (including blood collection and acupuncture needles) and strictly follow standard precaution principles in nosocomial infection management. Tools used in service industries, including haircuts, shavings, pedicuring, puncturing, and tattooing, should be strictly sterilized. Individuals whose sexual partner is HBsAg-positive should receive a hepatitis B vaccine or condoms; condoms must be used to prevent HBV and other blood-borne or sexually transmitted diseases when the health status of the sexual partner is unknown. For HBsAg-positive pregnant women, amniocentesis should be avoided to maintain the completeness of the placenta and reduce the chance of newborns being exposed to maternal blood.

Recommendation 1: Newborns of HBsAg-negative mothers should receive 10 μg of hepatitis B vaccine as early as possible, within 12 h of birth, followed by the second and third doses at 1 and 6 months of age, respectively (A1).

Critically ill infants, such as those with extremely low birth weight (<1,000 g), severe birth defects, severe asphyxia, and respiratory distress syndrome, should receive the first dose of vaccine immediately after the stabilization of vital signs (A1).

Recommendation 2: Newborns of mothers with HBsAg-positivity or unknown HBsAg status should receive 100 IU HBIG as early as possible within 12 h of birth and receive 10 μg of hepatitis B vaccine at a different injection site. The second and third vaccine doses should be administered at 1 and 6 months of age, respectively (A1).

Infants of mothers with HBsAg-positivity or unknown HBsAg status should undergo post-vaccination testing 1–2 months after completing the recommended vaccination series. If HBsAg is negative and anti-HBs levels are <10 mIU/ml, it is recommended to administer a repeat of the 3-dose vaccination series. On the other hand, if HBsAg is positive, immunization failure is indicated, and the child should be monitored regularly (A1).

Recommendation 3: Premature and low-birth-weight infants (<2,500 g) born to mothers with HBsAg-positivity or unknown HBsAg status should receive the birth doses of the vaccine and HBIG as early as possible, within 12 h of birth. Then, they should receive a three-dose vaccination series according to a schedule of 0, 1, and 6 months, starting from 1 month of age (A1).
Recommendation 4: Infants who receive the hepatitis B vaccine and HBIG within 12 h of birth can be breast-fed by HBsAg-positive mothers (B1).
Recommendation 5: Catch-up vaccination is recommended for children without vaccination or who have not completed the 3-dose vaccination series. The interval between the first and second doses should be ≥28 days, and the interval between the second and third doses should be ≥60 days (A1).
Recommendation 6: For non-responders to the initial vaccine series, one additional dose of 60 μg or three additional doses of 20 μg of the vaccine can be administered. Anti-HBs should be tested 1–2 months after the second dose. If there was still no response, another dose of 60 μg vaccine could be administered (A1).
Recommendation 7: Individuals with incidental exposure to HBV can be managed as follows:

1. Gently squeeze around the wound to drain the blood and rinse with isotonic saline (A1);
2. HBV DNA and HBsAg should be tested immediately and re-tested after 3–6 months (A1);
3. For those who have been vaccinated with known anti-HBs (≥10 mIU/mL), no additional hepatitis B vaccine is required. In those who have not been vaccinated and who have anti-HBs levels <10 mIU/ml or unknown, HBIG 200–400 IU should be injected immediately. The first dose of the vaccine (20 μg) should be administered at a different injection site, followed by the second and third doses (20 μg) at 1 and 6 months, respectively (A1).

Recommendation 8: HBsAg screening should be performed in the general population, especially in those at high-risk and women of pregnancy or childbearing age (B1).

Etiology

HBV is a partially double-stranded circular DNA virus belonging to the *Hepadnaviridae* family. The genome encodes HBsAg, HBcAg, HBeAg, viral polymerase, and HBx. HBV is highly resistant, but it can be inactivated at 65°C for 10 h, at 100°C for 10 min, or by high-pressure vapors. HBV can also be effectively inactivated by ethylene oxide, glutaraldehyde, peroxyacetic acid, and iodophor.

Sodium taurocholate co-transporting polypeptide (NTCP) on the hepatocyte membrane is the cellular receptor required for HBV infection.[18] Covalently closed circular DNA (cccDNA) is synthesized using nucleus minus-strand DNA as a template. cccDNA is difficult to eliminate and plays an important role in chronic infection. The pregenome RNA (pgRNA) transcribed from cccDNA can be released into the peripheral blood, and serum HBV RNA is related to cccDNA transcription activity in hepatocytes. HBV can be integrated into the hepatocyte genome, which is closely related to persistent HBsAg positivity and HCC occurrence.[19,20]

There are at least nine genotypes (types A to I) and one undetermined genotype (type J) of HBV,[21] of which genotypes B and C are predominant in China. The HBV genotype is associated with disease progression and responses to interferon-α treatment.[1] Additionally, HBV has a relatively high mutation rate. Mutations in the reverse transcriptase region are mainly associated with drug resistance to nucleos(t)ide analogs (NAs), while mutations in the pre-S/S region, the basic core promoter region, and the pre-C/C region may be associated with acute liver failure and HCC.[22]

Natural history and pathogenesis

Natural history

The natural history of HBV infection depends on the interaction between the virus and host. One of the most important factors influencing chronicity is the age at HBV infection. The risk of chronicity is 90% in neonates and infants under 1 year of age[23] and <5% in adults.[24]

According to virological, biochemical, and histological characteristics, the natural history of chronic HBV infection is generally divided into four phases:[25,26] HBeAg-positive chronic HBV infection (formerly known as the immune tolerance phase, chronic HBV carrier status), HBeAg-positive CHB (formerly known as the immune clearance phase, immune active phase status), HBeAg-negative chronic HBV infection (formerly known as the immune control phase, inactive HBsAg carrier status), and HBeAg-negative CHB (formerly known as the reactivation phase) (Table 2).

The following three points should be noted: First, although immunology has been formerly used to describe the phases of the natural history of chronic HBV infection, no direct immunological evidence or markers are available. Moreover, defining the phases of all HBV infections using virological, biochemical, and histological markers is difficult. Second, not

Table 2. Phases of chronic HBV infection

Phases	HBeAg-positive chronic HBV infection (immune tolerance phase, chronic HBV carrier)	HBeAg-positive CHB (immune clearance phase, immune active phase)	HBeAg-negative chronic HBV infection (immune control phase, inactive HBsAg carrier)	HBeAg-negative CHB (reactivation phase)
HBsAg (IU/mL)	$>1\times10^4$	+	$<1\times10^3$	+
HBeAg	+	+	–	–
HBV DNA (IU/mL)	$>2\times10^7$	+	–	+
ALT	<ULN	Elevated (Persistently or repeatedly)	<ULN	Elevated (Persistently or repeatedly)
Liver histology	None/minimal necroinflammation and fibrosis	Obvious necroinflammation and/or fibrosis	Minimal/mild inflammation but different degrees of fibrosis	Obvious necroinflammation and/or fibrosis

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; CHB, chronic hepatitis B; ULN, upper limit of normal.

all patients with HBV infections experience all of the above four phases in sequence. For example, there is no "immune tolerance phase" for most adolescents and adults who are infected with HBV; instead, these patients enter the "immune clearance phase" directly. Third, the phases of chronic HBV infection are not entirely consistent with the clinical diagnosis and indication for initiation of antiviral therapy.

Spontaneous HBeAg seroconversion can occur in HBeAg-positive CHB patients, with an annual incidence of 2–15%. Patients under the age of 40 years with elevated ALT levels, genotype A, or genotype B show a higher incidence of spontaneous HBeAg seroconversion.[27] Following HBeAg seroconversion, HBsAg clearance occurs in 0.5–1.0% of patients yearly.[1] Notably, in one study, it was found that even 10 years after HBsAg clearance, approximately 17.8% of the patients still tested positive for HBV DNA in their serum.[28] Furthermore, patients over 50 years of age or complicated with liver cirrhosis, HCV, or hepatitis D virus (HDV) infection may still develop HCC, even if they have achieved HBsAg seroconversion.[29,30]

The annual incidence of cirrhosis is 2–10% in CHB patients without antiviral therapy. Risk factors for this include host factors (older age, male sex, age >40 years when the HBeAg seroconversion occurs, and persistently elevated ALT levels), viral factors (HBV DNA >2,000 IU/ml, persistently HBeAg positive, and genotype C), co-infection with HCV, HDV, or HIV, and concomitant risk factors for liver injury (e.g., alcohol or obesity).[31,32] Notably, the annual incidence of progression from compensated to decompensated cirrhosis is 3–5%, and the 5-year survival rate of decompensated cirrhosis is 14–35%.[31]

The annual incidence of HCC ranges from 0.2% to 1.0% in non-cirrhotic patients with HBV infection[31–33] and from 3% to 6% in patients with cirrhosis. The risk factors include age >40 years, male sex, liver cirrhosis, family history of HCC, high levels of HBV DNA, alcohol consumption, smoking, diabetes mellitus, obesity, and exposure to aflatoxin.[31,34,35]

For some treatment-naïve patients with a 1-year follow-up, it can be challenging to classify them into the above four phases according to their HBV DNA levels, ALT levels, and liver histology. In the literature, these patients are considered to be in the "indeterminate phase." According to the four phases defined previously, the proportion of those in the "indeterminate phase" is as high as 28–55%.[36–38] In the so-called "indeterminate phase," patients are not in an independent stage, but rather the stage itself is difficult to determine. Generally, it is difficult to distinguish HBeAg-positive chronic HBV infection from HBeAg-positive CHB and HBeAg-negative chronic HBV infection from HBeAg-negative CHB. It is noted that "indeterminate phase" patients have a higher risk of disease progression compared to true HBeAg-positive chronic HBV (formerly known as the immune tolerance phase) or HBeAg-negative chronic HBV (formerly known as inactive HBsAg carrier status) patients, and antiviral therapy might be required.[36] With the introduction of the updated guideline in 2022, which provides a clearer classification of the natural history, the proportion of individuals in the "indeterminate phase" is expected to significantly decrease. This development is favorable for expanding the population eligible for antiviral therapy.

Pathogenesis

The pathogenesis of chronic HBV infection is complex and has not yet been fully elucidated. Evidence suggests that HBV cannot directly kill hepatocytes, and the immune response to the virus is the main pathogenesis for hepatocyte injury and necroinflammation. Persistent or repeated necroinflammation is an important factor in the progression of chronic HBV infection to liver cirrhosis and HCC.

The non-specific (innate) immune response plays an important role in the early stages of HBV infection and induces the subsequent specific (adaptive) immune response.[39,40] HBV can suppress the intensity of non-specific immune responses through HBeAg- and HBx-mediated interference with various signal transduction pathways. Patients with CHB often show a low frequency of myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC) in the peripheral blood, with impaired mDC maturation and reduced interferon α produced by pDC. Consequently, patients show a reduced capacity to directly clear viruses and induce HBV-specific T lymphocytes, negatively affecting virus clearance.[41]

HBV-specific immune responses play an important role in HBV clearance.[42] $CD8^+$ cytotoxic T lymphocytes can induce apoptosis of virus-infected hepatocytes and secrete interferon-γ to suppress the expression and replication of HBV genes in hepatocytes.[43] During chronic infection, HBV-specific T lymphocytes are prone to apoptosis, with significantly reduced ability to secrete cytokines and proliferate, resulting in exhausted function, which may be one of the mechanisms leading to persistent HBV infection.[44] Currently, the lack and/or functional insufficiency of HBsAg-specific cytotoxic T lymphocytes is considered a significant contributing factor to immune tolerance in patients with chronic HBV infection.[45]

Laboratory examination

HBV serological markers

HBV serological markers include HBsAg, anti-HBs, HBeAg,

anti-HBe, anti-HBc, and anti-HBc immunoglobulin M (IgM). Serum HBsAg can be translated not only from cccDNA-transcribed mRNA but also from HBV DNA integrated into host genome-transcribed mRNA. This implies that the presence of HBsAg indicates HBV infection. In clinical practice, the quantitative detection of HBsAg has been widely employed. Anti-HBs are protective antibodies, and positive anti-HBs suggest an immune response to HBV infection, which is always observed in hepatitis B convalescence and hepatitis B vaccine recipients. Furthermore, anti-HBc IgM positivity is typically associated with acute hepatitis B, while a low level of positive anti-HBc IgM may be seen during acute exacerbation of chronic HBV infection. Additionally, it is important to note that most anti-HBc antibodies are of the immunoglobulin G (IgG) type and remain positive even if the individual has been infected with HBV, regardless of viral clearance.

HBV virological markers

HBV DNA quantification: This method is mainly used to assess virus replication, initiate antiviral therapy, and evaluate efficacy. HBV DNA is typically quantified using real-time quantitative polymerase chain reaction (PCR) procedures. With the improvement in reagent sensitivity, the lower limit of quantification should be low (10–20 IU/mL or lower). For newly identified HBsAg-positive and CHB patients who have received antiviral therapy, HBV DNA should be detected using highly sensitive real-time quantitative PCR to identify patients with a low viral load, enabling the initiation of antiviral therapy as soon as possible or the timely adjustment of the treatment regimen.

HBV genotyping: At present, at least nine confirmed and one undetermined genotype of HBV can be identified. Some genotypes can be further divided into several sub-genotypes. In addition, HBV genotyping assists in predicting the effectiveness of interferon therapy and prognosis.[46]

Detection of drug-resistant mutations: HBV mutations may occur naturally in chronically infected subjects and may also be induced by antiviral therapy. Both lead to decreased sensitivity to antiviral drugs.[47]

Recommendation 9: For HBsAg-positive patients, HBV DNA measurement with a lower limit (10–20 IU/mL) and a wider range of quantification is recommended (A1).

Detection of HBV novel biomarkers

Quantification of HBV RNA: HBV RNA is considered to be associated with the transcriptional activity of cccDNA in hepatocytes. Currently, studies have investigated its combination with HBV DNA or hepatitis B core-related antigen (HBcrAg) in predicting the risk of recurrence after NAs withdrawal. However, whether this method can be used as an alternative to reflect viral transcriptional activity in the liver during NAs treatment (virological suppression) or after HBsAg clearance remains to be explored.[48–54]

HBcrAg: This is a novel compound marker that comprises HBcAg, HBeAg, and p22 protein, correlated with the transcription activity of hepatic cccDNA. Some studies have investigated its application in differentiating disease phases and predicting the antiviral efficacy of Peg-IFN-α, recurrence after NAs withdrawal, disappearance of HBsAg, and risk of HCC.[49,55–59]

Quantification of anti-HBc antibody: The quantitative level of anti-HBc is positively correlated with the degree of liver inflammation in treatment-naïve patients with chronic HBV infection and ALT <80 IU/L. In addition, this level decreases with liver inflammation during antiviral therapy[60,61] and is positively correlated with the degree of liver fibrosis.[62] Moreover, some studies have investigated its application in differentiating disease phases, predicting the antiviral efficacy of Peg-IFN-α and NAs, anticipating recurrence after drug withdrawal, and predicting the clinical prognosis of acute-on-chronic liver failure (ACLF).[63–69]

Serum biochemical examination

Serum ALT and AST levels partly reflect the degree of hepatocyte injury. Total bilirubin elevation can be attributed to hepatocyte injury, intrahepatic and extrahepatic bile duct obstruction, abnormal bilirubin metabolism, and hemolysis. The serum albumin level, prothrombin activity time (PT), prothrombin activity (PTA), and international normalized ratio (INR) reflect the synthetic functions of the liver. Serum γ-glutamyl transferase (GGT) in healthy individuals is mainly derived from the liver and is significantly elevated in alcoholic liver disease, drug-induced liver disease, and cholangitis with intra- and extra-hepatic cholestasis. Conversely, serum alkaline phosphatase (ALP) lacks liver specificity, and cholestasis stimulates its synthesis. Furthermore, alpha-fetoprotein (AFP) and its heterogeneous L3 protein induced by vitamin K absence or antagonist-II (PIVKA-II) serve as important diagnostic markers for HCC.[70–72]

Non-invasive diagnosis of liver fibrosis

Serological markers

Serological markers of liver fibrosis (e.g., AST to platelet ratio index [APRI] and the Fibrosis 4 score [FIB-4]) have been developed to assess significant/advanced fibrosis and cirrhosis. They have the advantages of simplicity and practicality; however, their dynamic changes cannot accurately reflect the reversal of liver fibrosis and clinical outcomes in patients with CHB receiving antiviral therapy.[73–75]

Liver stiffness measurements (LSMs)

LSMs include transient elastography (TE), ultrasound-based point shear wave elastography (p-SWE), 2D shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE). TE is widely used to accurately diagnose advanced liver fibrosis and early liver cirrhosis.[76] However, more clinical studies are warranted to determine whether the dynamic changes in TE reflect fibrosis reversal and clinical outcomes.[77–79] In addition, the diagnostic cutoff value of TE following antiviral therapy differs from that before treatment, and no unified standards are available yet.

Imaging diagnosis

Imaging examinations include abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). The main purposes of imaging examinations are to monitor the clinical progression of chronic HBV infection, to determine whether liver cirrhosis and portal hypertension exist,[80,81] to locate space-occupying lesions and identify their characteristics, and to monitor and diagnose HCC in a timely manner.[82,83]

Pathological diagnosis

Liver biopsy is typically used to assess the degree of liver

necroinflammation and fibrosis in patients with chronic HBV infection and to rule out other liver diseases, providing evidence for diagnosis, predicting prognosis, initiating antiviral therapy, and monitoring antiviral therapy efficacy.

The refined METAVIR and Ishak scoring systems, which are based on the Knodell and Scheuer scoring systems, are internationally recommended for grading hepatic necroinflammation and the staging of liver fibrosis in patients with CHB.[84–87] METAVIR ≥F2 indicates significant liver fibrosis, and ≥F3 indicates advanced liver fibrosis. On the other hand, chronic hepatitis grading (G 0–4) and staging (S 0–4) scoring systems are often used in China.[88] Additionally, the Laennec staging system subdivides liver cirrhosis (METAVIR F4) into three groups (4A, 4B, and 4C).[89] Collagen area and its morphological characteristics can be quantified.[90] The P-I-R classification of liver fibrosis proposed by Chinese scholars divides liver fibrosis above Ishak F3 into three types: progressive (P), intermediate (I), and reversal (R), which help evaluate the trends in histological changes of liver fibrosis.[91]

Clinical diagnosis

Chronic HBV carrier

Patients in this phase are young patients with high HBV DNA levels (usually >2×10^7 IU/mL), high serum HBsAg levels (usually >1×10^4 IU/mL), and positive HBeAg. Additionally, serum ALT and AST levels are persistently normal (as determined through three consecutive follow-up visits within one year, each with an interval of at least three months) in these carriers. Furthermore, liver histopathological examinations reveal no obvious necroinflammation or fibrosis in these patients.

HBeAg-positive CHB

Patients in this phase include those that are serum HBsAg-positive, HBeAg-positive, and HBV DNA-positive. Additionally, they can be accompanied by persistent or repeated abnormal ALT levels, can present with obvious necroinflammation by liver histopathology, or present with significant fibrosis (≥F2), as indicated by liver histopathology or non-invasive markers.

Inactive HBsAg carriers

Patients in this phase include those that are serum HBsAg positive, HBeAg negative, anti-HBe positive, and HBV DNA negative (undetectable). Additionally, they typically have HBsAg levels <1,000 IU/ml and persistently normal ALT and AST levels (as determined through three consecutive follow-up visits within one year, each with an interval of at least three months). Furthermore, in these carriers, liver cirrhosis tends to be absent, and inflammation tends to be mild.

HBeAg-negative CHB

Patients in this phase include those that are serum HBsAg positive, persistently HBeAg negative, often anti-HBe positive, and HBV DNA positive. Additionally, these patients are accompanied by persistent or repeatedly abnormal ALT levels or obvious necroinflammation when analyzed using liver histopathology or demonstrate significant fibrosis (≥F2) as indicated by liver histopathology or non-invasive markers.

Occult HBV infection (OBI)

OBI patients exhibit specific characteristics. They test negative for serum HBsAg, indicating the absence of detectable surface antigens. However, they may still have detectable HBV DNA in their serum and/or liver tissue. Among individuals with OBI, approximately 80% show positive results for serum antibodies such as anti-HBs, anti-HBe, and/or anti-HBc, which is referred to as seropositive OBI. On the other hand, approximately 1–20% of OBI cases show negative results for all serological markers, known as seronegative OBI.

HBV-related liver cirrhosis

The diagnosis of HBV-related liver cirrhosis should meet the following criteria: (1) and (2) (pathological diagnosis), or (1) and (3) (clinical diagnosis).

1. The patient is currently HBsAg positive, or HBsAg negative and anti-HBc positive with a clear history of chronic HBV infection (with a history of being HBsAg positive for >6 months), with other etiologies being ruled out.
2. Liver pathology reveals cirrhosis.
3. Two or more of the following five items are met, excluding those with non-cirrhotic portal hypertension:
   a. Imaging studies show signs of cirrhosis and/or portal hypertension;
   b. Endoscopy reveals gastroesophageal varices;
   c. LSMs indicate cirrhosis (ALT<ULN, LSM ≥12.0 kPa, ULN<ALT<5× ULN, and LSM ≥17.0 kPa);[76]
   d. Blood biochemistry reveals decreased albumin levels (<35 g/L) and/or prolonged PT (>3 seconds longer than controls).
   e. Complete blood count reveals platelet counts <100×10^9/L, after excluding other etiologies.

Clinically, cirrhosis is classified into compensated and decompensated stages according to the presence of severe complications such as ascites, gastroesophageal variceal hemorrhage, and hepatic encephalopathy. Patients with compensated cirrhosis have liver function reserve Child-Pugh class A. Decompensated cirrhosis is defined as the development of severe complications such as ascites, gastroesophageal variceal hemorrhage, or hepatic encephalopathy in patients with cirrhosis;[92] these patients have liver function classified as Child-Pugh class B or C.

Re-compensation

Some patients with decompensated HBV-related cirrhosis have the potential to revert to compensated cirrhosis following antiviral therapy, a phenomenon referred to as "re-compensation" of cirrhosis. This is defined as the absence of severe complications such as ascites, hepatic encephalopathy, and gastroesophageal variceal hemorrhage for at least one year and improved liver function after removing or controlling the underlying etiologies.[1,93] Chinese scholars recently conducted a 120-week follow-up of HBV-related decompensated cirrhosis and proposed that MELD scores <10 and/or Child-Pugh class A status (albumin >35 g/L, INR <1.5 and total bilirubin <34 μmol/L) can be used as the criteria for stable improvement of liver function in patients with re-compensation.[94]

Goal of therapy

The goal of therapy is to maximally and sustainably suppress HBV replication, alleviate liver necroinflammation and fibrosis, delay and reduce the occurrence of liver failure, decompensation cirrhosis, HCC, and other complications, thereby improving the quality of life of patients, and prolonging the life expectancy of patients.[1] For some eligible patients, a clinical cure should be pursued.[1,9,95]

Indications of antiviral therapy

The indications for antiviral therapy are generally based on serum HBV DNA (a high-sensitivity assay is recommended), ALT levels, and the severity of the liver disease in combina-

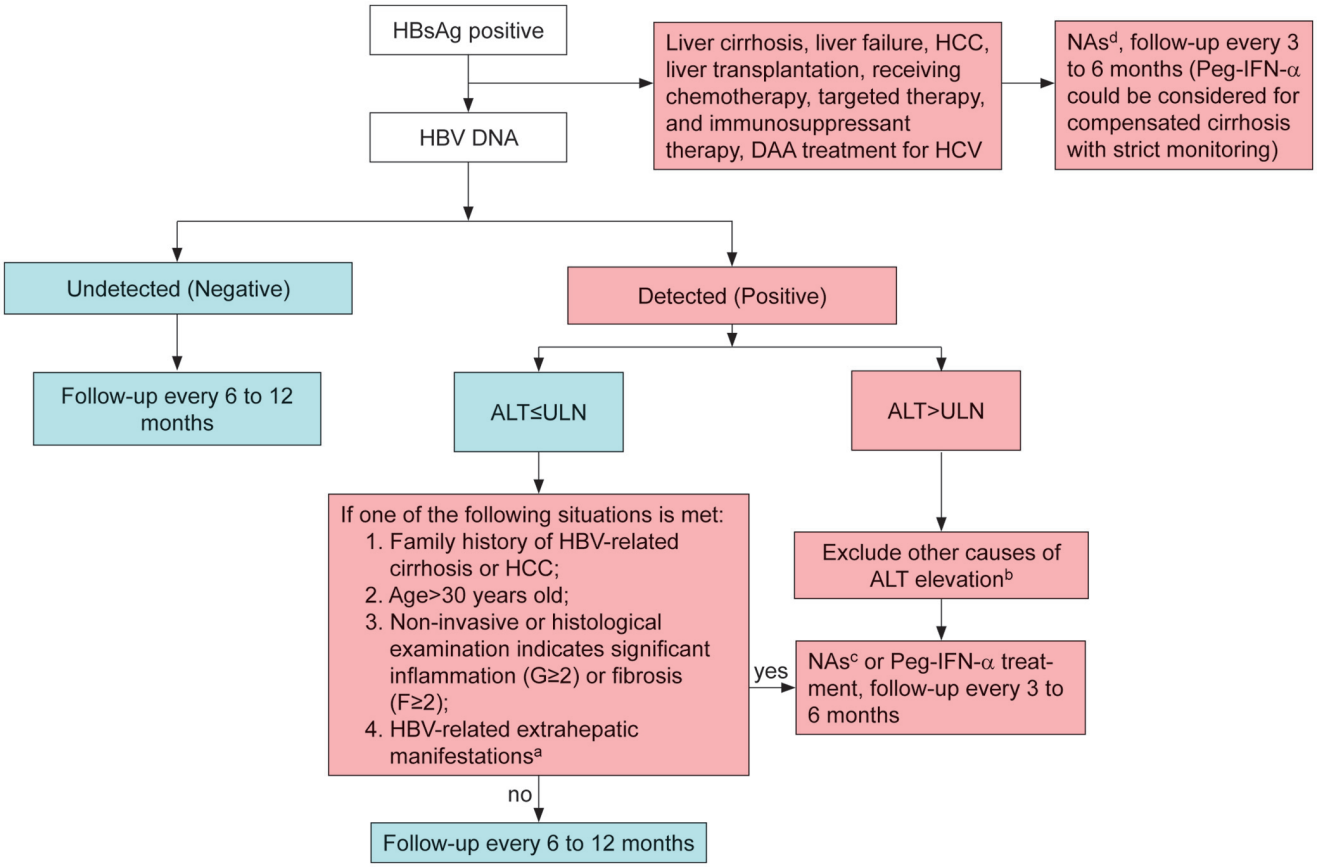

Fig. 1. Indications for antiviral therapy of chronic HBV infection. (a) HBV-related extrahepatic manifestations: glomerulonephritis, vasculitis, etc.; (b) Exclude other causes of ALT elevation: infection with other pathogens, history of taking drugs or poisons, history of alcohol consumption, lipid metabolism disorder, autoimmune disorder, liver congestion or vascular disease, genetic and metabolic liver injury, systemic disease, etc.; (c) NAs: ETV, TDF, TAF or TMF; (d) NAs: ETV, TDF or TAF. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; DAA, direct-acting agents; Nas, nucleoside (acid) analogs; ALT, alanine aminotransferase; ULN, upper limit of normal; Peg-IFN-α, pegylated interferon alpha.

tion with factors such as age, family history, and concomitant diseases. These factors are assessed comprehensively to determine the risk of disease progression (Fig. 1).[96]

The ALT threshold for initiating antiviral therapy has traditionally been based on the folds of the ULN. However, several studies have demonstrated that even in patients with ALT levels below the ULN, there is a correlation between ALT levels and significant necroinflammation (≥G2) or fibrosis (≥F2) on liver pathology.[97,98] Moreover, elevated ALT levels have been associated with the development of decompensated cirrhosis and HCC.[99,100] It is important to note that the recommended ALT cutoff values for initiating treatment vary among international guidelines, and consensus has been difficult to achieve due to differences in factors such as race, research population characteristics, control methods of factors that can affect ALT levels (such as alcohol consumption, body weight, and diabetes), study designs (cross-sectional studies or cohort studies), and ALT measurement methods. In the interest of expanding antiviral therapy and improving treatment coverage, this updated guideline recommends lowering the ALT cutoff value for initiating treatment in order to reduce the incidence of liver inflammation, fibrosis, cirrhosis, HCC, and liver disease-related deaths. Notably, many international guidelines have set the ALT cut-off value for treatment as 30 U/L for men and 19 U/L for women.[100–102] However, whether this ALT cutoff value applies to Chinese CHB patients requires further investigation.

To mitigate the risk of disease progression, it is essential to strengthen antiviral therapy in patients who are at risk. Notably, a family history of HBV-related cirrhosis or HCC and age >30 years are two independent risk factors for disease progression.[9,103–108] Therefore, in patients diagnosed with liver cirrhosis, it is imperative to prioritize and intensify antiviral therapy.

Studies have suggested that even in patients with HBV DNA-negative compensated cirrhosis, the cumulative incidence of HCC in patients not receiving antiviral treatment is significantly higher compared to those receiving antiviral treatment.[109] Thus, many international guidelines and consensus statements recommend active antiviral treatment due to the high risk of disease progression in these patients.[103,110,111] Furthermore, antiviral therapy could be considered when evidence of compensated or decompensated cirrhosis is present, regardless of ALT levels, HBV DNA levels, or HBeAg status.

Recommendation 10: Antiviral therapy is recommended for patients with detectable HBV DNA and persistently elevated ALT levels (>ULN) after excluding other causes (B1).

Recommendation 11: Antiviral therapy is recommended for patients with detectable HBV DNA, regardless of ALT levels, if one of the following criteria are fulfilled:

1. Family history of HBV-related cirrhosis or HCC (B1) ;
2. Age >30 years (B1);
3. Non-invasive or histological examinations indicate significant inflammation (G≥2) or fibrosis (F≥2) (B1);
4. HBV-related extrahepatic manifestations (B1).

Recommendation 12: Antiviral therapy is recommended for HBV-related compensated or decompensated cirrhosis, regardless of ALT levels, HBV DNA levels, or HBeAg status. Other causes of cirrhosis (such as alcohol-associated fatty liver disease, metabolic dysfunction-associated fatty liver disease, diabetes, and autoimmune or genetic metabolic liver disease) should be identified and treated (B1).

NAs treatment

Efficacy and safety of NAs

Entecavir (ETV): ETV is highly effective in suppressing viral replication and reducing liver inflammation. Long-term ETV treatment can improve the histology in patients with cirrhosis, significantly reduce the incidence of decompensation and HCC, and reduce liver-related and all-cause mortality.[108,112–114]

Tenofovir disoproxil fumarate (TDF): TDF is highly effective in suppressing virus replication. Long-term TDF treatment can significantly improve liver histology and reduce the incidence of HCC.[115–117] The prevalence of TDF resistance is extremely low. TDF is relatively safe, with few adverse events reported in clinical trials. However, risks of renal impairment and osteoporosis have been observed with long-term treatment.[116] Furthermore, the virological response rate of TDF remains high in patients with resistance against other NAs.[118,119]

Two cohort studies from South Korea and Hong Kong reported that the long-term use of TDF in the treatment of CHB is superior to ETV in reducing the risk of HCC.[120,121] However, other large cohort studies worldwide reported that TDF and ETV were comparable in reducing the risk of HCC.[122–125] A meta-analysis based on the above studies also failed to reach consistent and clear conclusions. This lack of consensus can be attributed to several factors, including regional variations, variations in the duration of NAs usage, differences in disease stages at the start of the study, as well as variations in the establishment of cohorts and follow-up durations across different research groups.[126,127]

Tenofovir alafenamide fumarate (TAF): TAF is highly effective in suppressing virus replication. Long-term TAF treatment shows a comparable virological response to TDF and provides a better biochemical response rate.[128–130] Moreover, TAF is safer than TDF in terms of bone metabolism and renal safety profiles, but it may affect lipid metabolism.[129] TAF can be used in patients with a partial virological response to ETV.[131,132] Notably, a prospective study in China showed that the complete virological response rate and ALT normalization rate were significantly higher after 24 weeks of TAF treatment in patients who switched from ETV compared to those who continued ETV treatment.[131]

Tenofovir amibufenamide (TMF): TMF, known for its higher hepatocyte targeting, has shown promising results in phase III clinical trials. After 96 weeks of treatment, TMF had a comparable virological response to TDF and provided a better ALT normalization rate. Moreover, TMF exhibits better bone metabolism and renal safety profiles compared to TDF. However, it should be noted that TMF therapy showed a higher rate of dyslipidemia than TDF therapy at week 48, although lipid parameters remained stable in both groups from week 48 to week 96.[133,134]

Prevention and treatment of NAs drug resistance

In treatment-naïve patients: Highly potent drugs with low drug resistance are preferred.

During treatment: HBV DNA should be regularly tested to detect virological breakthroughs, low viremia, and poor response to provide rescue treatment as soon as possible. NAs-resistant patients who switched to Peg-IFN-α combination therapy tend to exhibit poor response rates.

NAs withdrawal

Most patients require long-term NAs treatment, and the rate of virological relapse is high after discontinuation of the drug.[135] For HBeAg-positive CHB patients who achieved HBeAg seroconversion and undetectable HBV DNA, HBsAg <100 IU/ml indicates a low risk of recurrence after discontinuing the drug.[136,137] However, for HBeAg-negative CHB patients, long-term treatment is generally required. Drug withdrawal can only be considered when HBV DNA is undetectable and there is HBsAg loss with/without anti-HBs, along with at least 6 months of consolidation therapy.

Interferon alpha treatment

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

The regimen and efficacy of Peg-IFN-α treatment

Peg-IFN-α monotherapy: Peg-IFN-α treatment of treatment-naive CHB patients can achieve partial virological response (<50% in both HBeAg-positive and HBeAg-negative patients) and HBsAg clearance (HBsAg clearance rate of 8.7–11.0% after three years of treatment). HBV DNA $<2\times10^8$ IU/mL, high levels of ALT (2–10×ULN) or liver inflammation ≥G2, genotype A or B, low HBsAg levels (<25,000 IU/mL),[95] and high quantitative levels of anti-HBc antibodies at baseline[65] are good predictors of IFN efficacy.

Combination therapy of Peg-IFN-α and NAs: For select eligible CHB patients receiving NAs, the addition of Peg-IFN-α in a combination therapy regimen has been shown to promote a clinical cure.[138–142] Patients with low HBsAg levels (<1,500 IU/ml) and negative HBeAg before IFN therapy are more likely to achieve clinical cure after sequential Peg-IFN-α therapy.[139–141] Early virological response (HBsAg <200 IU/mL or a >1 $\log_{10}$ IU/mL decrease at 24 weeks of treatment) can help predict clinical cure after 48–96 weeks of combination therapy.[95,142,143] Low levels of HBcrAg and high levels of anti-HBs at the end of treatment may predict a durable clinical cure after Peg-IFN-α discontinuation.[144]

Peg-IFN-α may reduce the incidence of HBV-related HCC: Some studies have shown that Peg-IFN-α treatment reduced the incidence of HCC in CHB patients during long-term follow-up;[95,138,145] however, this requires further confirmation.

Adverse events and contraindications of Peg-IFN-α

The main adverse events of Peg-IFN-α include influenza-like syndrome (fever, headache, myalgia, fatigue), bone marrow

suppression, and others (autoimmune diseases, mental disorders).[9,95]

Contraindications to Peg-IFN-α therapy include:

1. Absolute contraindications: pregnancy or pregnancy planning, history of mental illness (with a history of schizophrenia or severe depression), uncontrolled epilepsy, decompensated cirrhosis, uncontrolled autoimmune diseases, and underlying diseases, such as severe infection, retinal disease, heart failure, and chronic obstructive pulmonary disease.
2. Relative contraindications: thyroid disease, history of depression, uncontrolled diabetes, high blood pressure, and heart disease.

Recommendation 13: For patients with HBeAg-positive CHB, NAs (ETV, TDF, TAF, or TMF) are recommended (A1). NAs can be discontinued after HBsAg loss has been confirmed. For those patients who prefer to stop the NAs, discontinuation can be attempted if ALT normalization, HBV DNA undetectable, and HBeAg seroconversion are achieved after one year of treatment and maintained during 3 years of consolidation (monitor every 6 months), along with HBsAg <100 IU/mL. Close monitoring is necessary, and a longer duration of consolidation can help reduce the virological relapse rate (B2).

Recommendation 14: Peg-IFN-α can be considered for HBeAg-positive CHB patients. For patients with a decline in HBV DNA <2 $\log_{10}$ IU/mL and an HBsAg level >2×10^4 IU/mL at treatment week 24, Peg-IFN-α should be stopped and NAs should be initiated (A1). For patients who respond well to Peg-IFN-α, a 48-week treatment duration is preferred, which can be extended but should not exceed 96 weeks (B1).

Recommendation 15: For patients with HBeAg-negative CHB, NAs (ETV, TDF, TAF, or TMF) are recommended (A1). In patients who achieve undetectable HBV DNA and HBsAg loss (with/without anti-HBs) and maintain this response during a six-month consolidation period, NAs can be discontinued. However, follow-up is warranted in these patients (B1).

Recommendation 16: Peg-IFN-α can be considered for HBeAg-negative CHB patients. In patients with a decline in HBV DNA level <2 $\log_{10}$IU/mL or a decline in HBsAg level <1 $\log_{10}$IU/mL after 12 weeks of treatment, Peg-IFN-α should be stopped and NAs should be initiated (B1). For patients who respond well to Peg-IFN-α, a 48-week treatment duration is preferred, which can be extended but should not exceed 96 weeks (B1).

Recommendation 17: Peg-IFN-α as an add-on therapy can be considered in highly selected patients that meet specific criteria, including undetectable HBV DNA, HBeAg seroconversion, and HBsAg levels <1,500 IU/mL after NAs treatment. The decision to pursue a clinical (functional) cure with Peg-IFN-α should take into account the patient's preference. If the patient's HBsAg level is <200 IU/mL or decreases to >1 $\log_{10}$ IU/mL after 24 weeks of add-on therapy, adding Peg-IFN-α for 48–96 weeks is recommended. In contrast, if their HBsAg level remains at or above 200 IU/mL after 24 weeks of add-on therapy, discontinuing Peg-IFN-α and continuing NAs treatment is recommended (B2).

Recommendation 18: Long-term antiviral therapy with ETV, TDF, or TAF is recommended for patients with HBV-related compensated cirrhosis. Close monitoring of adverse events is required if Peg-IFN-α is used (A1).

Recommendation 19: Long-term treatment with ETV or TDF is recommended for patients with HBV-related decompensated cirrhosis Peg-IFN-α is contraindicated (A1). TAF can be considered if necessary (B1).

Other treatments

Antiviral therapy is the most important treatment for patients with chronic HBV infection. In addition, there are anti-inflammatory, anti-oxidation, liver protection, anti-fibrosis, and immune regulatory treatment options.

Anti-inflammation, anti-oxidation, and liver-protecting treatments

Necroinflammation of hepatocytes due to HBV infection is an important pathophysiological process in the progression of the disease. Glycyrrhizic acid, silymarin preparations, polyunsaturated lecithin preparations, and bicyclols have shown anti-inflammatory, antioxidative, and hepatocyte-protecting effects, and these are expected to reduce the degree of liver inflammatory injury. These drugs can be used in patients with obvious liver inflammation or significantly elevated ALT levels, but multiple combinations are not recommended.

Anti-fibrosis treatment

Several anti-fibrosis traditional Chinese medicine prescriptions such as Anluo Huaxian pills, Biejia Ruangan tablets, and Fuzheng Huayu tablets have shown some anti-fibrosis effects in animal experiments and clinical studies,[146–149] and these can be considered for patients with significant fibrosis or liver cirrhosis.

Monitoring and follow-up management of patients with chronic HBV infection

Management of chronic HBV carriers and inactive HBsAg carriers

Routine blood examinations, biochemical tests, monitoring of virological markers, AFP, abdominal ultrasound, and non-invasive fibrosis tests should be performed every 6 to 12 months. Liver biopsy should be performed when necessary. Antiviral therapy should be initiated immediately if patients meet the indications for treatment.

Monitoring during antiviral therapy

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

Tests at baseline: (1) Biochemical tests: ALT, AST, bilirubin, albumin, and others; (2) Virological and serological markers: HBV DNA level, HBsAg, HBeAg, anti-HBe; (3) Blood routine tests: serum creatinine, serum phosphorus, renal tubular function markers, and other markers as necessary; (4) Non-invasive fibrosis detection such as LSM; (5) When ETV and TDF are used in patients with creatinine clearance <50 mL/min, the dose should be adjusted. TAF is not recommended for patients with creatinine clearance <15 mL/min who are not undergoing dialysis, and no dose adjustment is required in other cases.

Patient treatment compliance: Monitoring the dosage, administration method, and adherence to medication is crucial to ensure that patients understand the potential risks as-

sociated with self-discontinuation of the drug. This proactive approach helps enhance patient compliance by promoting awareness and understanding of the importance of consistent treatment.

NAs drugs: Routine blood tests, liver biochemical tests, monitoring of HBV DNA levels and HBV serum virological markers, and LSMs should be performed every 6 months in those without cirrhosis and every 3 months in those with cirrhosis. Additionally, if necessary, enhanced CT or enhanced MRI should be used to detect HCC early. Moreover, for those taking medicines that may affect renal function or bone metabolism, serum phosphorus and renal function markers should be tested every 6 to 12 months, and early renal tubular damage markers can be monitored if available.

Peg-IFN-α: Routine blood tests should be performed every 1 to 2 weeks in the first month of treatment. Additionally, routine blood tests and liver biochemical markers should be detected once every month after stabilization. Furthermore, thyroid function markers, blood glucose, and HBV serum virological markers should be detected every 3 months. Finally, LSM should be performed once every 6 months.

Prevention and treatment of rare adverse events: NAs are generally safe and well tolerated; however, rare serious adverse events may still occur, such as renal insufficiency (especially with TDF and ADV), hypophosphatemic bone disease (especially with TDF and ADV), myositis/rhabdomyolysis, lactic acidosis (especially with ETV), and so on. Thoroughly inquiring about the patient's relevant medical history before medication is crucial to mitigate potential risks. Furthermore, patients with significantly elevated serum creatinine, creatine kinase, or lactate dehydrogenase levels during treatment, along with corresponding clinical manifestations, should be closely monitored. If any of the aforementioned adverse events occur, the drug should be discontinued immediately.

HBV DNA response: If the HBV DNA level is >2 $\log_{10}$ IU/mL higher than the lowest value during the treatment, after excluding poor compliance, rescue treatment should be provided immediately, and a drug resistance test should be performed.

Follow-up after antiviral therapy discontinuation

Close follow-up after treatment discontinuation aims to evaluate the long-term efficacy of antiviral therapy and monitor the progression of liver disease and development of HCC. Regardless of the response to antiviral therapy, liver biochemical tests, monitoring of HBV serum virological markers, and detection of HBV DNA levels should be performed once a month within the first 3 months after drug withdrawal, once every 3 months after drug withdrawal, and once every 6 months after one year. In addition, abdominal ultrasonography and AFP detection should be performed once every 6 months for patients without cirrhosis and every 3 months for those with cirrhosis. Finally, enhanced CT or MRI should be performed if necessary.

Screening and monitoring of HCC

Chronic HBV infection is the main cause of hepatocellular carcinoma (HCC) in China. Regular screening and monitoring can improve the early diagnosis rate of HCC and reduce mortality.[150] Nowadays, several HCC risk assessment models have been reported to accurately identify high-risk patients for HCC. For example, the aMAP score (age-Male-ALBI-Platelets score) can conveniently and accurately divide patients with chronic HBV infection into low-, medium-, and high-risk groups for HCC, with incidences of 0–0.2%, 0.4–1.0%, and 1.6–4.0%, respectively.[151] Indeed, patients with chronic HBV infection should be screened for HCC every 6 months through abdominal ultrasonography and AFP detection. Moreover, high-risk patients should be screened for HCC at least once every 3–6 months, and enhanced CT or MRI should be performed when necessary.

Antiviral therapy recommendations for special populations

Patients with poor response and low viremia

Although potent oral antiviral therapy with low drug resistance can effectively suppress HBV replication, some patients still present with poor response or low viremia. In these cases, suboptimal responses are defined as HBV DNA >2×10^3 IU/mL, and low viremia (LLV) is defined as detectable HBV DNA <2,000 IU/mL in CHB patients receiving ETV, TDF, TAF, or TMF for at least 48 weeks with good compliance.[152] Notably, LLV after antiviral therapy is closely related to the fibrosis progression of CHB, the risk of decompensated cirrhosis and HCC, and reduced long-term survival rates.[153–155]

Recommendation 20: In CHB patients treated with ETV, TDF, TAF, or TMF for 48 weeks but who still have detectable HBV DNA (>20 IU/mL), after excluding medication non-adherence, NAs can be modified. This can involve switching to or adding on TDF or TAF in those who are already on ETV, and vice versa (B1). The addition of Peg-IFN can also be considered (B1).

Recommendation 21: In patients with HBV-related cirrhosis treated with ETV, TDF, or TAF for 24 weeks but who still have detectable HBV DNA (>20 IU/mL), after excluding medication non-adherence, NAs can be modified. This can involve switching to or adding on TDF or TAF in those who are already on ETV, and vice versa (C2).

Patients undergoing chemotherapy, targeted therapy, and immunosuppressant therapy

HBV reactivation or even liver failure may occur in patients with chronic HBV infection undergoing chemotherapy, targeted therapy, or immunosuppressant therapy. The risk of HBV reactivation in HBsAg-positive patients is 5–8 times that in HBsAg-negative patients.[156] Additionally, the risk of HBV reactivation varies among patients with different anti-HBs statuses, with anti-HBs-positive patients experiencing a 5.0% risk and anti-HBs-negative patients facing a higher risk of 14.0%.[157] To mitigate these risks, the implementation of prophylactic antiviral therapy has proven to be effective in significantly reducing the incidence of HBV reactivation.[158]

ETV, TDF, or TAF antiviral therapy is recommended in patients undergoing chemotherapy, targeted therapy, or immunosuppressant therapy.[133,159,160] In these patients, the recommendations for antiviral therapy, follow-up monitoring, and drug withdrawal are the same as those for patients with CHB or cirrhosis. For chronic HBV carriers, inactive HBsAg carriers, or patients with negative HBsAg and positive anti-HBc, if NAs are being employed as the current prophylactic antiviral therapy, discontinuation of NAs can be attempted 6–12 months after completing chemotherapy, targeted therapy, or immunosuppressant therapy. For patients receiving B lymphocyte monoclonal antibodies or undergoing hematopoietic stem cell transplantation, discontinuation of NAs can

be attempted at least 18 months after treatment. However, it should be noted that NAs discontinuation can lead to HBV relapse or exacerbation. Therefore, it is recommended to closely follow up with patients for a period of 12 months after discontinuation. During this follow-up period, regular monitoring of HBV DNA levels and liver biochemical markers should be conducted at intervals of 1–3 months.[161,162]

Recommendation 22: For patients with pending chemotherapy, targeted therapy, or immunosuppressive therapy, screening for HBV markers (HBsAg, anti-HBs, and anti-HBc) should be recommended (A1). For HBsAg-and/or HBV DNA-positive patients, NAs (ETV, TDF, or TAF) should be initiated at least one week before starting chemotherapy, targeted therapy, or immunosuppressive therapy, or at the same time if necessary (A1). For HBsAg-negative and anti-HBc-positive patients, ETV, TDF, or TAF antiviral treatment is recommended if they have advanced liver fibrosis/cirrhosis, plan to receive B lymphocyte depletion therapy with monoclonal antibody agents, or undergo hematopoietic stem cell transplantation (B1).

Management of pregnancy-related conditions

It is recommended to screen women of childbearing age and those planning pregnancy for HBsAg. Additionally, women with HBV should be tested for HBsAg-positive DNA.[163] The treatment indications for newly diagnosed CHB during pregnancy are the same as those for CHB patients, and TDF antiviral therapy can also be initiated. Pregnant women with CHB who initiate antiviral therapy before or during pregnancy should continue the antiviral therapy until delivery and decide whether to continue the original treatment regimen or switch to other NAs or Peg-IFN-α according to their virological response.

A high serum HBV DNA level is a high-risk factor for mother-to-child transmission. Approximately 85% of HBeAg-positive pregnant women without antiviral therapy present HBV DNA levels >2×10^5 IU/mL. Therefore, maternal-positive HBeAg can be used as a surrogate indicator for antiviral therapy to prevent mother-to-child transmission when HBV DNA detection is unavailable.[164,165]

Clinical studies with small samples have shown that the effect of TAF in preventing mother-to-child transmission is similar to that of TDF, and TAF is well-tolerated in pregnant women.[166,167] However, the safety profiles of TAF in neonatal birth defects and breastfeeding remain to be further confirmed. In the case of an unintended pregnancy while taking TAF, more evidence is needed to determine whether it is necessary to switch to TDF. However, there is currently no evidence regarding the safety of TMF in fetuses and newborns.

Pregnant women in the immune tolerance period who receive NAs can discontinue the drug immediately or 1–3 months after delivery. It is important to note that hepatitis activity may occur in a significant percentage of patients (17.2–62.0%) after drug withdrawal, with most cases occurring within 24 weeks.[168,169] Therefore, postpartum monitoring should be strengthened. To ensure proper assessment, it is recommended to re-test liver biochemical markers and HBV DNA levels 4–6 weeks after delivery. Furthermore, re-detection is recommended every 3 months until 6 months after delivery if the mother's liver biochemical markers are normal, whereas antiviral treatment is recommended if HBV activity is detected.

Recommendation 23: For HBsAg-positive women that are pregnant or planning for a pregnancy who are indicated for antiviral therapy, TDF is recommended after comprehensive counseling and obtaining informed consent (B1). In addition, TAF can be considered in patients with renal insufficiency (B2).

Recommendation 24: For women with incidental pregnancy and already on antiviral therapy, TDF should be continued while ETV or other NAs should be switched to TDF, without termination of pregnancy (B1). If IFN therapy is already being used, a switch to TDF is recommended if the pregnancy is to be continued after comprehensive counseling and obtaining informed consent (C2).

Recommendation 25: For pregnant women with HBV DNA levels >2×10^5 IU/mL, TDF therapy should be initiated at week 24–28 of gestation after comprehensive counseling and obtaining informed consent (A1). For mothers with HBeAg-positive chronic HBV infection (immune tolerance phase), TDF may be withdrawn immediately or 1–3 months after delivery. Liver biochemistry and HBV DNA levels should be tested at least every 3 months until 6 months after delivery. In addition, antiviral therapy should be initiated immediately for those with active hepatitis (A2). For mothers with HBeAg-positive or-negative CHB, TDF can be continued postpartum after comprehensive counseling and obtaining informed consent. Breastfeeding is not contraindicated in women undergoing TDF treatment (C2).

Pediatric patients

Antiviral therapy should be initiated immediately in children with active CHB or liver cirrhosis. Children with HBeAg-positive CHB and elevated ALT levels can be treated with a limited course of common IFN-α or Peg-IFN-α-2a to achieve clinical cure (HBsAg clearance with or without anti-HBs).[104,170] ETV, TDF, or TAF treatment can also be used. It is important to note that the dosages of ETV, TDF, or TAF should adhere to the recommendations provided by regulatory bodies such as the US Food and Drug Administration, WHO, and relevant drug instructions.[109] Additionally, NAs can be administered to children with CHB and cirrhosis who have not achieved HBeAg seroconversion or who are HBeAg-negative after treatment with common IFN-α or Peg-IFN-α-2a.[170,171]

No consensus has been reached on the need for treatment in children in the immune-tolerance phase. A study found that children in the clinically diagnosed immune tolerance phase presented with a certain degree of inflammatory activity and/or fibrosis through histological examinations.[172] Furthermore, studies have indicated a significant increase in the HBV DNA response rate, HBeAg seroconversion rate, and HBsAg clearance rate among children aged 1–7 years in the immune tolerance phase.[173,174] However, it is crucial to systematically evaluate treatment decisions for children in the immune tolerance phase, taking into consideration long-term treatment safety and the risk of drug resistance.[175,176] This evaluation should include histological examination, non-invasive examination for liver fibrosis, and dynamic liver function evaluation.

Recommendation 26: For children with advanced liver disease or cirrhosis, antiviral therapy should be initiated immediately, regardless of age; however, long-

term treatment safety and drug resistance should also be considered. IFN-α is recommended for children aged ≥1 year, ETV or TDF for children aged ≥2 years, Peg-IFN-α-2a for children aged ≥5 years, and TAF for children aged ≥12 years (A1).

Recommendation 27: For children with positive HBV DNA and ALT<ULN, liver biopsy is recommended, and antiviral therapy could be initiated for those with histological grade G≥1 (B1). For children aged 1–7 years, even without a liver biopsy, antiviral treatment can be considered after comprehensive counseling with their guardians and obtaining informed consent (C1).

Patients with renal impairment

High-risk factors for renal impairment include decompensated cirrhosis, uncontrolled hypertension, uncontrolled diabetes, concomitant use of nephrotoxic drugs, or solid organ transplantation.[1] When there is a high risk of renal impairment, changes in renal function should be monitored when applying NAs. In addition, serum creatinine and phosphorus levels should be monitored regularly when ADV or TDF is administered.[177]

ETV or TAF is recommended as the first-line treatment for patients with chronic kidney disease, renal insufficiency, or renal replacement therapy.[128,178] In contrast, treatment with ADV or TDF is not recommended. When TAF is applied to patients without HIV infection, there is no need to adjust the dosage of TAF when the estimated glomerular filtration rate (eGFR) is ≥15 mL/min. However, the dosages of other NAs require adjustment when the eGFR is ≤50 mL/min. Please refer to the drug instructions for further details.

ETV or TAF can be used as prophylactic or therapeutic drugs in HBsAg-positive kidney transplant recipients. Kidney transplant recipients should avoid treatment with IFN-α or PEG-IFN-α.

Patients with HBV-related glomerulonephritis can be treated with NAs. As a result, the recommendation is to consider ETV or TAF as suitable treatment options. For patients treated with ADV or TDF who develop renal or bone disease or are at high risk, switching to ETV or TAF is recommended.[178]

Recommendation 28: For CHB patients with chronic kidney disease, renal insufficiency, or renal replacement therapy, ETV or TAF is recommended, and ADV or TDF treatment should be avoided (B1). For CHB patients with a high risk of renal impairment, renal function should be closely monitored during NAs treatment. Moreover, in ADV- or TDF-treated patients who develop or are at high risk of renal or bone diseases, switching to ETV or TAF is recommended (B1).

Co-infection of HBV and HCV

All HBsAg-positive patients should be tested for anti-HCV, and further detection of HCV RNA levels is required for patients with positive anti-HCV. Patients with positive HCV RNA should be treated with direct-acting agents (DAA), and it should be noted that these patients are at risk of HBV reactivation. Therefore, during anti-HCV therapy and within three months of drug discontinuation, combined antiviral therapy with ETV, TDF, or TAF is recommended with close monitoring.[179]

HBsAg-negative and anti-HBc-positive patients are also at risk of HBV reactivation during DAA treatment. Therefore, monthly monitoring of serum HBV DNA and HBsAg levels is recommended in these patients. Moreover, antiviral therapy is recommended when HBsAg is positive in these patients.[179]

Recommendation 29: For HBsAg-positive CHC patients receiving DAA therapy, adding NAs is recommended until 12 weeks after DAA cessation. For HBsAg-negative and anti-HBc-positive CHC patients on DAA therapy, HBV DNA and HBsAg levels should be closely monitored, and NAs treatment is recommended when HBsAg becomes positive (B2).

Co-infection with HBV and HIV

As long as there is no indication to suspend the anti-HIV treatment, anti-retroviral therapy should be initiated as soon as possible, regardless of the level of CD4+T lymphocytes. Patients co-infected with HIV and HBV should be treated with drugs suppressing the two viruses simultaneously, including two drugs with anti-HBV activity, to avoid the development of drug resistance to NAs. For a highly active anti-retroviral therapy (HAART) regimen, TDF, TAF + lamivudine, or emtricitabine (FTC) (mixture formulations of TDF + FTC and TAF + FTC are available) are recommended. In addition, HBV-related markers, such as HBV DNA, liver biochemical markers, and liver imaging markers, should be monitored during treatment. For HIV and HBV co-infected patients, it is not recommended to select a regimen that contains only one NAs that is effective against HBV (TDF, lamivudine, ETV, telbivudine, or ADV) to avoid the development of drug resistance to NAs.[180,181]

It should be noted that for patients with renal insufficiency:

1. If the creatinine clearance rate is <60 mL/min, TDF cannot be selected, and the dosage of TDF should be adjusted.
2. If the creatinine clearance rate falls between 30 mL/min and 50 mL/min, a regimen containing TAF+ (FTC or lamivudine) can be applied. However, it is important to note that TAF has not been approved for use in patients with creatinine clearance rates <30 mL/min.
3. When TDF/TAF cannot be used, ETV should be added to the HAART regimen. For pregnant women co-infected with HIV and HBV, a regimen containing lamivudine (or FTC) + TDF is recommended.[182]

Recommendation 30: For HIV-HBV co-infected patients, a regimen against both HIV and HBV (including two drugs for HBV) is recommended (A1).

Patients with HBV-related liver failure

Patients with HBV-related acute, subacute, acute-on-chronic, and chronic liver failure are known to have a high mortality rate. Therefore, antiviral therapy is recommended for patients with HBsAg positivity.

Anti-HBV therapy has been demonstrated to improve the long-term prognosis of HBV-associated ACLF.[183,184] Additionally, many clinical studies have shown that ETV, TDF, and TAF can treat HBV-related ACLF.[185–187] In particular, TAF offers the advantage of reducing renal toxicity compared to TDF while maintaining antiviral efficacy.[128] Furthermore, early and rapid reduction of HBV DNA levels is the key point of treatment in this context, as the survival rate of patients

can be improved if the HBV DNA level is reduced by $2\log_{10}$ IU/mL within 2–4 weeks.[184,186,188] Consequently, antiviral therapy should be continued for an extended duration in patients following recovery from liver failure.

Recommendation 31: For HBsAg-positive patients with acute, subacute, acute-on-chronic, or chronic liver failure, NAs (ETV, TDF, or TAF) are recommended (A1).

HBV-related HCC patients

Anti-HBV therapy plays a critical role in the management of HBV DNA-positive HCC patients, as it can effectively reduce HCC recurrence after surgery and improve overall survival.[189] Among the available options, NAs (ETV, TDF, or TAF) with rapid and high efficacy are preferred. In patients without contraindications, IFN-α can also be considered as a treatment option.

HBV reactivation may occur in patients with HCC who are HBsAg-positive but HBV-DNA-negative during liver resection, hepatic arterial chemoembolization, radiotherapy, or systemic chemotherapy. In these patients, antiviral therapy using ETV, TDF, or TAF is recommended.

Recommendation 32: For HBsAg-positive patients with HBV-related HCC, NAs (ETV, TDF, or TAF) are recommended (A1).

Liver transplant patients

When patients undergo liver transplantation due to HBV-related diseases (including liver failure and HCC), anti-HBV regimens should be selected appropriately to reduce the risk of HBV re-infection in the transplanted liver. The selection of a specific anti-HBV therapy regimen for HBV-infected patients undergoing transplantation depends on the primary risk factor for re-infection, which is determined by the HBV DNA level prior to transplantation.

Undetectable HBV DNA before transplantation indicates a low risk of re-infection. NAs (ETV, TDF, or TAF) can be applied as early as possible before surgery to prevent HBV reactivation, and HBIG is not needed after surgery.[190] If HBV DNA is positive before transplantation, it indicates a high risk of re-infection, and NAs (ETV, TDF, or TAF) can be applied as early as possible before surgery to reduce HBV DNA levels. HBIG should be injected intravenously during the anhepatic period of surgery.

In addition to the long-term application of NAs after surgery, low-dose HBIG should be injected simultaneously for 0.5–1.0 years.[191] Notably, a recent study found that shortening the course of HBIG in patients treated with ETV remains effective.[192] However, close monitoring of HBV DNA is required to detect drug resistance and promptly adjust the treatment regimen when patients have already been administered other NAs. In addition, some studies reported that hepatitis B vaccination after liver transplantation could prevent recurrence; however, its clinical application remains controversial.[190]

Recommendation 33: For HBsAg-positive patients undergoing liver transplantation for HBV-related disease, antiviral therapy with ETV, TDF, or TAF should be initiated before surgery (A1).

Clinical needs requiring further study and resolution

1. Explore and develop novel markers that can accurately reflect the natural history of chronic HBV infection or the stage of disease progression.
2. Explore the impact of concomitant diseases (i.e., MAFLD, diabetes) on the efficacy of antiviral therapy and the development of HCC in patients with HBV infection.
3. Explore the potential publicity and organizational implementation models for large-scale HBV screening in the population to identify and treat patients.
4. Explore the feasibility and cost-effectiveness of large-scale treatment initiatives, including the consideration of a "treat all" policy, and provide evidence for public health decision making.
5. Explore innovative approaches using new technology for disease management in the medical system, with a focus on improving treatment and compliance, monitoring disease progression, and detecting HCC early.
6. Explore the effective use of real-world clinical data to evaluate the long-term safety, efficacy, and cost-effectiveness of approved drugs.
7. Explore the efficacy and cost-effectiveness of using approved drugs to achieve clinical cure in eligible populations (especially in treated populations).
8. Explore new virological and immunological mechanisms of HBV infection and discover new targets for clinical treatment.
9. Explore new clinical trial designs and organizational approaches to conduct high-quality clinical trials for new drugs and expedite the approval process for achieving clinical cure in HBV management.

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