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2026 KASL Clinical Practice Guidelines for Management of Chronic Hepatitis B

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KASL clinical practice guidelines for management of chronic hepatitis B

Endorsed by the East Asia Liver Alliance (EALA)

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PREAMBLE

Purpose of the revision

The prevalence of hepatitis B virus (HBV) in Korea has decreased to less than 3% since 2018 due to the results of national immunization and perinatal infection prevention projects, yet it shows a prevalence of 3–4% in the 40–60s age group, with a total of about 1.2 million infected individuals. Chronic hepatitis B (CHB) is a major risk factor of liver cirrhosis and hepatocellular carcinoma (HCC) in Korea, with the mortality rate related to liver disease caused by hepatitis B reaching 18.9 per 100,000 population. This rate is far beyond the World Health Organization (WHO)'s target of 4 or less, and therefore, active management is urgently needed. Although safe and effective oral antiviral therapies for CHB are available and have been shown to prevent HCC and reduce mortality with long-term treatment, the treatment rate among all hepatitis B patients in Korea remains low at 22.2%.

The existing hepatitis B guidelines limit the treatment target to the immune-active phase with elevated alanine aminotransferase (ALT) based on the immunological natural history classification. However, with the accumulation of recent studies on the natural history of CHB, it has been suggested that the existing immunological disease stage classification has limitations in fully reflecting the clinical course of all patients. With increasing reports on disease progression and HCC risks and efficacy of antiviral treatment for patients in the "gray zone" or "indeterminate phase" who are not clearly defined by conventional classifications, the necessity for guideline revisions has been raised. These updates should reflect the latest evidence across the entire spectrum of CHB management, including clinical judgment on treatment initiation and the continuation or termination of antiviral therapy.

The Korean Association for the Study of the Liver (KASL) has continuously developed and revised clinical practice guidelines to improve the level of care for liver diseases in Korea and to establish standardized medical guidelines. In response to the recent expansion of treatment indications in international guidelines related to hepatitis B and the growing need to respond to the WHO strategy for hepatitis B elimination, the existing guidelines announced in 2022 have been fully revised. In particular, this revision redefines the classification of the natural history of CHB based on the viral load according to the recent accumulated research results, reflecting the risk of liver disease progression and HCC. In addition, this new natural history classification is linked to the treatment target to expand the treatment indication by proposing a more simplified treatment strategy.

This guideline aims to provide practical guidance to medical staff in charge of the diagnosis and treatment of CHB patients in Korea, thereby supporting rational medical decision-making for each patient. Ultimately, it aims to reduce the liver-related mortality and occurrence of HCC caused by CHB, improve patient quality of life, and contribute to reducing the burden of socioeconomic diseases.

Target group

This guideline is mainly directed at patients with newly diagnosed or previously diagnosed CHB who are being treated. It also includes recommendations that can be used

Abbreviations:

AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; AGA, American Gastroenterological Association; AHB, acute hepatitis B; ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HAV, anti-hepatitis A virus; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; APASL, Asian Pacific Association for the Study of the Liver; APRI, aspartate aminotransferase-to-platelet ratio index; ART, antiretroviral therapy; ASO, antisense oligonucleotide; AST, aspartate aminotransferase; BCP, basal core promoter; BMD, bone mineral density; BSV, besifovir dipivoxil maleate; CAM, capsid assembly modulator; CAR, chimeric antigen receptor; CBC, complete blood count; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CI, confidence interval; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; EBRT, external beam radiation therapy; ETV, entecavir; FIB-4, fibrosis-4 index; FXR, farnesoid X receptor; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HAIC, hepatic artery infusion chemotherapy; HBcAg, hepatitis B core antigen; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; IgM, immunoglobulin M; KASL, Korean Association for the Study of the Liver; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NA, nucleos(t)ide analogue; NAP, nucleic acid polymer; NTCP, sodium taurocholate cotransporting polypeptide; PC, precore; PCR, polymerase chain reaction; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Peg-IFNα, pegylated interferon-alpha; PT/INR, prothrombin time/international normalized ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; RFA, radiofrequency ablation; siRNA, small interfering RNA; SVR, sustained virological response; SWE, shear wave elastography; TACE, transarterial chemoembolization; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TKI, tyrosine kinase inhibitor; TLR, toll-like receptor; TNF, tumor necrosis factor; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; WHO, World Health Organization

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as a reference for clinical decision-making for patients with diverse clinical situations, such as those with HCC, receiving immunosuppressive treatment or chemotherapy, who have undergone hematopoietic stem cell transplantation (HSCT), liver or other organ transplantation, HCC, acute hepatitis B (AHB), coinfection, pregnant women, and children.

Readership

This guideline is mainly intended for medical staff in primary, secondary, and tertiary medical institutions who treat patients with CHB, and is designed to be used by medical professionals, public health physicians, and health care policymakers.

Development group and conflict of interest information

The 2026 CHB Treatment Guidelines Revision Committee consisted of 19 experts in related fields (Appendix 1) under the auspices of the KASL. All members reported conflict of interest information in advance during the development of the guidelines, and the details were presented in Appendix 2. Reported conflicts of interest were managed so as not to affect the process of revising the guidelines and the formulation of recommendations.

Financial resources and potential impact

This guideline was developed with the support of the "Patient-Centered Clinical Research Coordinating Center (PACEN)" (project specific number: RS-2025-02217627) with funding from the Ministry of Health and Welfare. The financial support agency did not have any direct or indirect influence on the content composition or development process of the recommendation, and the Guideline Revision Committee strictly maintained independence and objectivity throughout the writing process.

Literature search to collect evidence

To collect evidence, a systematic literature search was conducted on major domestic and foreign medical databases (PubMed, MEDLINE, Embase, Cochrane Central, KoreaMed, KMbase, etc.). The languages of the searched literature were limited to English and Korean, and the search terms were based on CHB and terms related to each subtopic. The scope of the search was based on the results of studies published in the last decade, but previous studies were included if clinically significant. Among the selected literature, studies with a limited level of evidence, such as expert opinions and case reports, and non-clinical studies were excluded.

Systematic literature review and classification of level of evidence and recommendation grade

The collected literature was evaluated through a systematic literature review method, and the level of evidence was classified by revising and applying the definition of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system based on comprehensive consideration of the certainty of evidence, consistency of results, and clinical significance (Table 1).[1-3]

The level of evidence was determined according to the type of study, with randomized control studies (RCTs) assigned the highest level of evidence and observational

Table 1. Classification of levels of evidence and strengths of recommendation

Level of evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate (B)	Further research may change confidence in the estimate of the clinical effect
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect
Strength of recommendations	**Criteria**
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

studies the lowest; in addition, the level of evidence was adjusted by evaluating factors that affect the quality of the study.[2] Levels of evidence were classified as follows: A (high), evidence is unlikely to change with further studies; B (moderate), evidence that may change; and C (low), evidence likely to change due to limited evidence.

The strength of recommendation was also modified and applied based on the GRADE system. The level of evidence for each study and socio-economic aspects such as clinical ramifications, costs, and patient acceptability of the study results was comprehensively considered. Accordingly, the grades of recommendations were divided into strong (1) and weak recommendations (2).[4] A strong recommendation is a rating that recommends implementing it in most patients because the likelihood of a desirable effect is higher, the quality of the evidence is high, the effectiveness, cost, and patient acceptability are superior compared to other interventions, and the likelihood of harm is low. A weak recommendation refers to the rather low evidence, varying degrees of desirable effects, or the difference between the benefits and harmful effects of the intervention is small. Although the degree of acceptability of patients varies, the grade is suitable for the use in a large number of patients due to its desirable effects. In the recommendation level is weak, other interventions may be chosen depending on the values and preferences of some patients or medical staff. The grade of each recommendation was determined by balancing the expected clinical benefits and potential harms, with the intention to increase its applicability in clinical practice.

External review

To ensure the objectivity and practicality of this guideline, it was consulted by an advisory committee formed independently of the guideline revision committee. The advisory committee included experts from related fields such as gastroenterology, infectious diseases, general internal medicine, family medicine, pediatrics, obstetrics and gynecology, surgery, and laboratory medicine who were not directly involved in the development process (Appendix 1) and independently reviewed the academic validity of the recommendations and their applicability in clinical practice. In addition, a public hearing was held on April 22, 2026, with the participation of various experts and the public, to offer different opinions. The revision committee reviewed the opinions presented during the external review and public hearing process and reflected them in the revision and supplementation of the recommendations. The guidelines completed through this process were finally approved by the Board of Directors of the KASL (Appendix 1).

Publication of guidelines

The revised 2026 KASL clinical practice guidelines for management of chronic hepatitis B will be officially announced at The Liver Week 2026 on June 13, 2026. The Korean version of these guidelines will be available on the website of the KASL (http://www.kasl.org), and the English version will be published in Clinical and Molecular Hepatology (http://www.e-cmh.org), the official journal of the society, and will be searchable in major medical databases such as PubMed.

Revision plan

These guidelines will be reviewed periodically as new clinical evidence and development of treatment strategies are developed, and further revisions may be made if significant changes are identified. In the future, if new medical evidence is accumulated and it is determined that it is necessary to promote the health of the Korean people, the KASL plans to revise this guideline.

EPIDEMIOLOGY

HBV infection remains a major cause of acute and chronic hepatitis, liver cirrhosis, and HCC in Korea, and constitutes a key target for national public health policies, including vaccination, screening, and infection prevention. As of 2020, approximately 1.2 million individuals were estimated to be chronically infected with HBV in Korea, and the liver disease-related mortality rate attributable to HBV is 18.9 per 100,000 population.[5] In addition, approximately 10,000 deaths from HCC occur annually, of which about 60% are attributed to HBV infection.[6-8] Furthermore, an estimated 254 million individuals worldwide were living with chronic HBV infection in 2022, with approximately 1.1 million deaths related to HBV-associated diseases.[9]

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Prior to the introduction of hepatitis B vaccination, the prevalence of HBV infection in Korea was reported to be as high as 8–10% during the 1980s.[10] However, following the implementation of nationwide vaccination programs—including neonatal vaccination in 1991, the National Immunization Program in 1995, and the perinatal transmission prevention program in 2002—this prevalence has declined substantially. Since 1998, hepatitis B surface antigen (HBsAg) testing has been incorporated into the Korea National Health and Nutrition Examination Survey (KNHANES), enabling periodic assessment of national-level indicators. According to the 2024 survey, the HBsAg positivity rate was 2.1%, and has remained below 3% since 2018.[11] Nevertheless, age-specific differences in prevalence remain evident. Among individuals younger than 40 years, this prevalence has markedly decreased due to the birth cohort effect associated with vaccination. In contrast, individuals aged 40–60 years, who were born before the introduction of vaccination, continue to show relatively high prevalence rates of 3–4%. Therefore, while primary prevention strategies focusing on vaccination should be maintained in younger populations, a comprehensive approach is required for individuals aged ≥40 years, including targeted screening to identify undiagnosed infections, timely antiviral treatment, and supplementary vaccination for susceptible individuals.

Despite the importance of these prevention strategies, the status of HBV management in Korea remains suboptimal compared with the targets proposed by the WHO for viral hepatitis elimination. The incorporation of HBsAg and antibody to hepatitis B surface antigen (anti-HBs) testing into the National Health Screening Program has contributed to improved diagnosis, with 83% of infected individuals having been diagnosed.[12] However, according to a nationwide data analysis conducted in 2020, the linkage to care rate was only 39.4%, with an antiviral treatment rate of 22.2% among all infected individuals, and 67.3% among those eligible for treatment.[5] These rates remain substantially below the WHO 2030 elimination targets of diagnosing 90% of infected individuals, treating 80% of diagnosed patients, and achieving a 65% reduction in liver disease-related mortality. Achieving these goals will require comprehensive measures to strengthen diagnosis, improve patient follow-up, and increase treatment uptake.

AHB is a notifiable infectious disease (class III) in Korea, subject to mandatory reporting and ongoing epidemiological surveillance. Although the annual number of reported cases has shown a general downward trend since 2021, 200–400 new cases continue to be reported each year, indicating the need for ongoing monitoring.[13] In addition, assessing the burden of past HBV infection—defined as HBsAg-negative and antibody to hepatitis B core antigen (anti-HBc)-positive status—is of clinical importance. Reported anti-HBc positivity rates in Korea vary according to population characteristics: 13.5% among blood donors,[14] and 39.3% in the general adult population (HBsAg positivity 4.0%, anti-HBs positivity 75.4%).[15] These differences are attributable to variations in the age distribution and health status of the study populations. Resolved HBV infection constitutes a potential risk factor for HBV reactivation in high-risk patients receiving immunosuppressive therapy or cytotoxic chemotherapy; therefore, assessment of prior HBV exposure and evaluation of reactivation risk are necessary.

The majority of patients with CHB in Korea are infected with HBV genotype C.[16-18] Compared with other genotypes, genotype C is associated with delayed hepatitis B e antigen (HBeAg) seroconversion and a higher frequency of basal core promoter (BCP) mutations, resulting in persistent viral replication even after seroconversion.[19,20] As a consequence, Korean patients with CHB are at higher risk of progression to liver cirrhosis and HCC, and have been reported to have higher rates of virological relapse following discontinuation of antiviral therapy, compared with patients infected with other HBV genotypes.[21,22]

Globally, hepatitis D virus (HDV) coinfection occurs in approximately 4.5% of patients with CHB,[23] but its prevalence in Korea has been reported to be relatively low. Studies conducted after 2000, including single-center analyses and data from the Health Insurance Review and Assessment Service, found that HDV coinfection among Korean patients with CHB was approximately 0.3%.[24,25] Meanwhile, a recent prospective multicenter study involving tertiary referral hospitals in Korea reported an anti-HDV positivity rate of 2.1%.[26] Notably, the positivity rate among foreign nationals residing in Korea was significantly higher at 7.4% compared with 1.9% among Korean nationals, and a higher frequency of coinfection was also observed in patients with an ALT level ≥40 U/L.

[Summary]

- Approximately 1.2 million individuals are chronically infected with HBV in Korea, and the treatment rate as well as HCC incidence and mortality remain suboptimal compared with WHO elimination targets.
- The prevalence of hepatitis B (HBsAg positivity) has remained below 3% in the general population since 2018 but over 3% among individuals aged 40–60 years, who were born before the introduction of vaccination.
- Most Korean patients with CHB are infected via perinatal transmission and harbor HBV genotype C, which is associated with long-standing infection and an increased risk of progression to cirrhosis and HCC.

NATURAL HISTORY

CHB is defined as the persistence of serum HBsAg for longer than 6 months after infection. Understanding the natural history of CHB plays is crucial for identifying populations at risk for disease progression and determining the appropriate timing of therapeutic intervention; it is also a fundamental prerequisite for diagnosis, treatment, and prognosis.[27] The natural history of CHB can be classified based on immunological, virological, and clinical characteristics.

The immunological natural history is classified into the immune-tolerant phase (CHB, immune-tolerant phase), HBeAg-positive immune-active phase (HBeAg-positive CHB, immune-active phase), immune-inactive phase (CHB, immune-inactive phase), HBeAg-negative immune-active phase (HBeAg-negative CHB, immune-active phase), and HBsAg loss phase (Supplementary Table 1, Supplementary Fig. 1). Although this immunological classification has been used for a long time, it is largely conceptual, lacks consistent criteria for distinguishing each phase, and the prognosis at each phase has varied among studies. Furthermore, the age and serum HBV DNA criteria defining the immune-tolerant phase are ambiguous or differ across guidelines.[28] Some studies have even included patients at high risk of HCC in the immune-tolerant phase.[29] Furthermore, the immunological natural history inevitably has a gray zone or indeterminate phase for those who do not fit into any specific phase.

To overcome these challenges, this guideline presents the natural history based on viral load, reflecting recent research findings. The advantage of this new classification is that it is based on an objective indicator, eliminates gray zone or indeterminate phase, reflects long-term prognosis, and can be linked to treatment indications.

Immunological natural history of CHB

The immune-tolerant phase is associated with vertical transmission and characterized by young age, HBeAg positivity, and very high serum HBV DNA levels. Yet, this phase defined as a phase with low immune response to the virus, persistently normal serum ALT, and no or minimal inflammation in liver tissue.[30,31] However, the definition and criteria of the immune-tolerant phase differ across guidelines (Supplementary Table 2), and accordingly, study results regarding the risk of HCC show considerable variation.[27,29,32,33] In a study that followed 946 patients in the immune-tolerant phase for 10 years, only 1% progressed to cirrhosis and 1.7% developed HCC.[34] In contrast, HBV DNA integration and clonal hepatocyte expansion comparable to those of immune-active patients have been identified in the liver tissue of immune-tolerant patients.[35] The risk of HCC in untreated immune-tolerant patients was approximately 2.5 times higher than that in treated immune-active patients.[36] Most patients in the immune-tolerant phase transition with age to the HBeAg-positive immune-active phase, characterized by repeated fluctuations in serum HBV DNA levels and intermittent or persistent elevation of serum ALT while maintaining HBeAg positivity.[37,38] Liver biopsy during this phase shows moderate or greater inflammation and varying degrees of fibrosis.[39] These changes result from increased activity of cytotoxic T lymphocytes against hepatitis B core antigen (HBcAg) or HBeAg, causing the destruction of infected hepatocytes.[40] As HBV DNA replication is suppressed, HBeAg seroconversion occurs in some patients. The immune-inactive phase is characterized by HBeAg negativity, anti-HBe positivity, normal serum ALT, and undetectable or low serum HBV DNA (<2,000 IU/mL).[41-43] This phase generally persists for a long time and is associated with a favorable prognosis, although liver biopsy may show minimal inflam-

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mation and fibrosis reflecting prior liver injury.[44] Approximately 20% of patients who achieve HBeAg seroconversion subsequently transition to the HBeAg-negative immune-active phase, characterized by serum HBV DNA ≥2,000 IU/mL, elevated ALT, and active necroinflammation.[45] Compared with the HBeAg-positive immune-active phase, this phase occurs at an older age and has a lower rate of spontaneous remission, leading to persistent inflammation and progression to fibrosis and cirrhosis in most patients.[46-48] Approximately 1–2% of patients in the immune-inactive phase annually progress to the HBsAg loss phase, and HBsAg loss may also occur rarely in patients receiving antiviral therapy.[49-52]

Limitations of the immunological natural history

Immunological classification has limitations because disease phases do not always progress sequentially in clinical practice. Moreover, it cannot adequately classify patients with normal ALT but moderate HBV DNA levels, or those with persistently elevated ALT but low HBV DNA (<2,000 IU/mL), who are therefore categorized as belonging to the "gray zone" or indeterminate phase, accounting for approximately 30% of patients with CHB.[53-55] The presence of the gray zone introduces ambiguity in definition and classification, leading to clinical uncertainty in patient stratification and treatment decision-making,[55-57] and treatment decisions are often difficult without a liver biopsy.[58] Patients in the gray zone are often older and may have comorbidities such as diabetes or metabolic dysfunction-associated steatotic liver disease (MASLD), as well as additional risk factors such as viral mutations associated with disease progression. A recent meta-analysis including 103 studies demonstrated that patients in the indeterminate phase also have a risk of progressive liver disease and HCC, with annual incidence rates of 0.32% for HCC, 0.67% for cirrhosis, and 0.34% for cirrhosis-related complications.[58]

Another limitation of the immunological classification is the lack of clear immunological markers for phase distinction and its reliance primarily on serum ALT. Although ALT is widely used as a marker of liver injury, it has limited sensitivity and specificity and high variability, which limits its use for classification. In patients with persistently normal ALT, liver biopsy revealed significant liver injury in 37%, fibrosis stage ≥2 in 18%, and moderate-to-severe inflammation in 34%.[59] Ideally, all patients at risk of HCC should meet criteria for antiviral therapy. However, a multicenter Korean study reported that a substantial proportion of patients who developed HCC did not meet treatment criteria according to the guidelines (64.0% for the APASL [Asian Pacific Association for the Study of the Liver], 46.0% for the AASLD [American Association for the Study of Liver Diseases], and 33.5% for the EASL [European Association for the Study of the Liver]), suggesting that current criteria fail to adequately identify patients at risk.[60] The upper limits of normal ALT also differ across guidelines. KASL recommends upper limits of normal ALT of 34 IU/L for men and 30 IU/L for women, whereas AASLD recommends 35 IU/L for men and 25 IU/L for women, and EASL proposes 40 IU/L for men and women.[27,29,61]

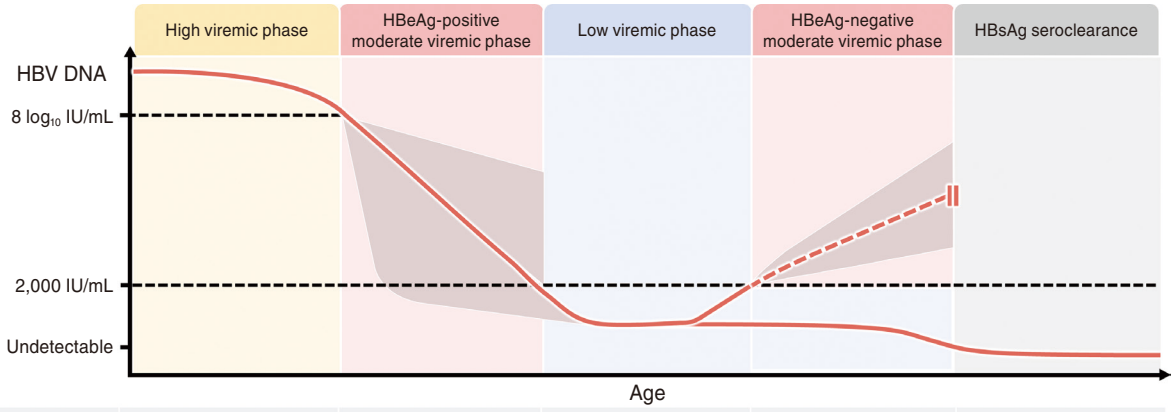
Natural history based on viral load

In this guideline, the natural history is newly classified according to viral load, based on serum HBV DNA levels, to overcome the limitations of the conventional immunological classification and to provide a simpler and more practical framework (Fig. 1). Recent studies have shown that, even when ALT levels are within the normal range, the risk of HCC is the highest in moderate viremia and is rather lower in high viremia.[62-66] This has been comprehensively demonstrated to show the non-linear relationship between serum HBV DNA level and HCC risk. Furthermore, it explains the low HCC risk in the immune-tolerant phase. In addition, biopsy-based studies have confirmed that the risk of liver injury is highest in moderate viremia.[67-69]

The phenomenon of the highest risk of HCC observed in moderate viremia can be explained by clonal hepatocyte expansion and integration of HBV DNA into the host genome, which are direct pathways of HBV-related hepatocarcinogenesis.[70,71] In the early stage of infection, HBV infects nearly all hepatocytes, and the amount of HBV DNA that can be produced by the whole liver during this period is known to be approximately 9 $\log_{10}$ IU/mL or higher.[70] In addition, HBV has been reported to undergo integration into the host genome from the early stage of infection.[35] Integration of HBV DNA into the host genome may induce the development of hepatocyte clones that acquire resistance to HBV infection or harbor variants with decreased secretion of HBV antigens. During the immune clearance

process at a certain stage, in which HBV-infected hepatocytes are eliminated by immune cells,[72,73] hepatocytes with these variants may relatively evade immune attack by producing less or no HBV antigen and thereby gain a survival advantage over normal hepatocytes. Consequently, immune pressure creates the so-called "bottleneck effect" in somatic mosaicism, and only certain hepatocyte clones survive and proliferate,[74] which may lead to an increased risk of HCC.[75] In contrast, the amount of HBV DNA that can be produced by the whole liver decreases when hepatocyte clones that are resistant to HBV infection or have reduced HBV antigen secretion expand.[76] Therefore, serum HBV DNA levels may act as an indirect marker of clonal hepatocyte expansion, and this may explain why the risk of HCC can be higher in moderate than in high viremia. Furthermore, recent studies have confirmed that moderate viremia is an independent risk factor for histological liver injury such as hepatic inflammation and fibrosis, regardless of ALT levels.[67,68] This suggests that immune-mediated tissue injury is relatively increased in moderate viremia, and the immune pressure required for clonal hepatocyte expansion in this range may be greater, contributing to the increased risk of HCC.

Based on these findings, this guideline classifies the natural history into four phases based on HBV DNA levels. This system classifies the natural history into 1) high viremic phase (>8 $\log_{10}$ IU/mL), 2) HBeAg-positive moderate viremic phase (2,000 IU/mL–8 $\log_{10}$ IU/mL), 3) low viremic phase (<2,000 IU/mL), and 4) HBeAg-negative moderate viremic phase (2,000 IU/mL–8 $\log_{10}$ IU/mL). According to the systematic review and meta-analysis conducted by the committee of the KASL guideline (Key Question 1), the annual incidence of HCC per 100 person-years was identified as 0.19 in high viremia using 8 $\log_{10}$ IU/mL as the cutoff, and 0.41 in an additional analysis using 7 $\log_{10}$ IU/mL as the cutoff. Accordingly, 8 $\log_{10}$ IU/mL, at which the risk of HCC begins to decrease markedly, was set as the criterion for the high viremic phase. The high viremic phase corresponds to the immune-tolerant phase and some of the immune-active phase; the HBeAg-positive moderate viremic phase corresponds to the HBeAg-positive immune-active phase; the low viremic phase corresponds to the immune-inactive phase; and the HBeAg-negative moderate viremic phase corresponds to the HBeAg-negative immune-active



HBsAg	Positive	Positive	Positive	Positive	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
cccDNA	+++++	+++++	++	+++	+
ALT levels	Normal or elevated	Elevated or normal	Normal or elevated	Elevated or normal	Normal or elevated
Liver histology (necroinflammation)	Minimal	Moderate/severe	Minimal	Moderate/severe	None/minimal
Liver histology (fibrosis)	Minimal	Variable degree (progressing)	Variable degree	Variable degree (progressing)	Variable degree (sequelae)
HCC risk	Low	High	Low	High	Very low

Figure 1. Natural history of chronic hepatitis B based on viral load. The dashed line indicates the HBeAg-negative moderate viremic phase, observed in approximately 20% of patients. The shaded area represents the potential variability of HBV DNA levels within the moderate viremic phase. ALT, alanine aminotransferase; cccDNA, covalently closed circular DNA; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

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phase. Compared with the conventional immunological classification of natural history, the viral load-based natural history is expected to provide practical help in clinical judgment regarding treatment indications and in establishing treatment strategies by eliminating the gray zone or indeterminate phase, using clearer and simplified criteria, and linking them with the prediction of the risk of HCC and cirrhosis-related complications.

High viremic phase

The high viremic phase is defined as a serum HBV DNA level >8 $\log_{10}$ IU/mL (10^8 IU/mL). In a Korean study including 6,949 treatment-naive non-cirrhotic CHB patients with ALT levels ≤2 times the upper limit of normal (ULN), the risk of HCC was lowest in the high viremic phase, with a hazard ratio (HR) of 0.90 compared with patients with HBV DNA ≤4 $\log_{10}$ IU/mL.[63] In a multicenter cohort study from Taiwan, Hong Kong, and Korea applying the same selection criteria, the HCC risk was also lowest in the high viremic phase.[64]

In a Korean multicenter study of 4,693 patients with CHB who initiated treatment with tenofovir disoproxil fumarate (TDF) or entecavir (ETV) because serum ALT levels were elevated to ≥2× ULN, patients in the high viremic phase also had the lowest HCC risk.[66] In a multicenter cohort study including 20,826 patients from Taiwan, Hong Kong, and Korea under the same inclusion criteria, the HCC risk was the lowest in the high viremic phase.[77] In a study that developed an artificial intelligence-based HCC risk prediction model involving 13,508 treated CHB patients, those who were in the high viremic phase before treatment had the lowest risk of HCC.[78]

Moderate viremic phase

The HBeAg-positive moderate viremic phase is defined as HBeAg positivity with a serum HBV DNA level of ≥2,000 IU/mL and ≤8 $\log_{10}$ IU/mL. In a Korean study involving treatment-naive non-cirrhotic CHB patients with ALT levels ≤2× ULN, HBV DNA levels of 6–7 $\log_{10}$ IU/mL showed the highest HR of 4.98 for HCC development, compared with HBV DNA ≤4 $\log_{10}$ IU/mL, and the result was consistent when limited to HBeAg-positive patients.[63] In the validation cohort of a multinational multicenter cohort study applying the same inclusion criteria, HBeAg-positive patients with HBV DNA levels of 6–7 $\log_{10}$ IU/mL had the highest HCC risk with an HR of 6.08, compared with patients with HBV DNA ≤3 $\log_{10}$ IU/mL.[64]

In a Korean multicenter cohort study involving 2,703 HBeAg-positive CHB patients who initiated treatment with TDF or ETV because of ALT levels ≥2× ULN, pretreatment HBV DNA levels of 5–6 $\log_{10}$ IU/mL were associated with an HCC risk 6.1 times higher than that of the high viremic phase.[65] In a multinational cohort study of 7,545 patients using the same selection criteria, pretreatment HBV DNA levels of 6–7 $\log_{10}$ IU/mL were associated with an 8.05-fold higher risk of HCC compared with the high viremic phase.[79] Pretreatment HBV DNA levels of 6–7 $\log_{10}$ IU/mL in HBeAg-positive patients were also associated with an 4.31 time-fold higher risk of HCC compared with the high viremic phase.[66] A study including 3,585 treated HBeAg-positive patients from 23 institutions identified HBV DNA levels of 5–8 $\log_{10}$ IU/mL as an independent risk factor for HCC and a new HCC prediction score of the PAGED-B was developed.[80]

In studies including liver biopsy results, HBV DNA levels of 5–7 $\log_{10}$ IU/mL were identified as an important risk factor for intrahepatic inflammation even when ALT was normal and there was no significant liver fibrosis.[67-69] The risk of histological liver disease, including inflammation and fibrosis, was 4.3 time-fold in patients with HBV DNA levels of 5–7 $\log_{10}$ IU/mL compared with those with HBV DNA <3 $\log_{10}$ IU/mL.[68]

The HBeAg-negative moderate viremic phase is defined as HBeAg negativity with a serum HBV DNA level of ≥2,000 IU/mL and ≤8 $\log_{10}$ IU/mL. In a multinational multicenter cohort study, HBV DNA levels of 5–6 $\log_{10}$ IU/mL in HBeAg-negative patients were associated with the highest risk of HCC with an HR of 8.14, compared with the high viremic phase.[64]

In a Korean multicenter study of patients treated with TDF or ETV because of ALT levels ≥2× ULN, HBeAg-negative patients with pretreatment HBV DNA levels of 6–7 $\log_{10}$ IU/mL had the highest risk of HCC.[66] In a multinational cohort study including 20,826 patients with CHB, HBeAg-negative patients with pretreatment HBV DNA levels of 6–7 $\log_{10}$ IU/mL had the highest risk of HCC.[77]

The risk of HCC was the highest in the moderate viremic phase regardless of HBeAg positivity.[63,64,66,77] Although HBeAg positivity has been considered a major factor in assessing HCC risk, recent studies have reported that HBeAg

positivity may not necessarily be associated with the risk of HCC.[81-83]

According to the systematic review and meta-analysis conducted by the committee of the KASL guideline (Key Question 1), HBV DNA levels were significantly associated with the risk of HCC in CHB patients. In particular, the risk of HCC was highest in the moderate viremic phase (HBV DNA 2,000 IU/mL–8 $\log_{10}$ IU/mL). The annual HCC incidence per 100 person-years was 0.35 in the low viremic phase, 0.81 in moderate viremic phase, and 0.19 in high viremic phase.

Low viremic phase

The low viremic phase is defined as a serum HBV DNA level <2,000 IU/mL. In a study involving treatment-naive non-cirrhotic CHB patients with ALT levels ≤2× ULN, the risk of HCC in the low viremic phase was lowest and comparable to that of the high viremic phase.[63] In a multinational multicenter cohort study using the same selection criteria, the HCC risk was the lowest in patients with HBV DNA <3 $\log_{10}$ IU/mL.[64] Studies including liver biopsy results confirmed that intrahepatic inflammation and fibrosis were lowest in patients with HBV DNA <3 $\log_{10}$ IU/mL.[67,68]

Factors affecting the natural history of chronic hepatitis B and progression of liver disease

In CHB, the 5-year cumulative incidence of cirrhosis is known to be 8–20%,[84] and the annual incidence of HCC is known to be 2–5%.[85] In Korea, the 5-year cumulative incidence of cirrhosis is reported to be 23%, with an annual incidence of 5.1%, whereas the 5-year cumulative incidence of HCC is 3%, with an annual incidence of 0.8%.[86] Factors affecting the development of cirrhosis and HCC include host factors, viral factors, and socio-environmental factors. Host factors include cirrhosis, chronic intrahepatic necroinflammation, age >30 years,[85,87-91] male sex, family history of HCC, and coinfection with other hepatitis viruses or human immunodeficiency virus (HIV). Viral factors include moderate serum HBV DNA levels,[62,64,77] high quantitative serum HBsAg levels,[88] HBV genotype C,[92] and specific viral mutations.[22,93,94] Socio-environmental factors include chronic alcohol consumption, metabolic syndrome,[95] diabetes,[80,96] obesity, and smoking[97,98] (Table 2). Coffee,[99-101] metformin,[102] aspirin,[103,104] statins,[105-108] sodium-glucose co-transporter 2 (SGLT-2) inhibitors,[109] and glucagon-like peptide-1 receptor agonists (GLP-1 RAs)[110] are known to reduce the risk of HCC. Various HCC prediction models using age, sex, ALT, HBeAg positivity, serum HBV DNA, platelet count, treatment status, and other variables have been developed and are currently used in practice.[111,112]

[Summary]

- This guideline presents a natural history based on viral load that overcomes the limitations of immunological natural history.
- The natural history based on viral load classify patients into the high viremic phase (serum HBV DNA >8 $\log_{10}$ IU/mL), the HBeAg-positive moderate viremic phase (≥2,000 IU/mL and ≤8 $\log_{10}$ IU/mL), the low viremic phase (<2,000 IU/mL), and the HBeAg-negative moderate viremic phase (≥2,000 IU/mL and ≤8 $\log_{10}$ IU/mL).
- The risk of HCC is highest in the moderate viremic phase.

Table 2. Factors associated with the development of cirrhosis and HCC in patients with chronic hepatitis B

Risk factor	Host	Viral	Miscellaneous
HCC and cirrhosis	Age >30 years Persistent ALT elevation Male Concurrent infection (HCV, HDV, HIV)	Moderate HBV DNA (2,000 IU/mL–8 $\log_{10}$ IU/mL) High serum HBsAg titer Genotype C Basal core promoter mutation	Alcohol Metabolic syndrome Diabetes Obesity Aflatoxin Smoking
HCC	Presence of cirrhosis Family history of HCC		

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

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PREVENTION

The prevention of hepatitis B is divided into primary, secondary, and tertiary prevention according to the stage of disease progression, with different strategies applied at each stage. Primary prevention aims to block HBV infection itself, mainly through vaccination, and combined administration of hepatitis B immune globulin (HBIG) and vaccine to newborns born to HBsAg-positive mothers is particularly effective in preventing vertical transmission. Secondary prevention focuses on minimizing the occurrence of complications such as liver cirrhosis and HCC through early diagnosis and regular follow-up of patients with CHB. Tertiary prevention aims to prevent disease deterioration and improve prognosis in patients who have already developed advanced liver disease such as cirrhosis or HCC, and includes ongoing antiviral therapy after curative treatment, surveillance for recurrence, and management to maintain liver function. This section presents specific clinical management strategies to block HBV infection, focusing on the strategies for primary prevention of hepatitis B.

In Korea, where the prevalence of hepatitis B is relatively high, HBV serologic markers (HBsAg, anti-HBs, and immunoglobulin G [IgG] anti-HBc) should be tested in individuals at risk or suspected of having the disease.[113] Through the national immunization program led by the Korea Disease Control and Prevention Agency, hepatitis B vaccination is provided to all newborns and infants, and it is also recommended in children, adolescents, and adults who do not have a history of complete vaccination or in whom immunity has not been documented. In adults who are HBsAg negative and have anti-HBs levels <10 mIU/mL (negative), hepatitis B vaccination is recommended.[27,32,114] In particular, HBV serologic markers should be tested and vaccination should be recommended if all markers are negative in the following situations: 1) in individuals with chronic liver diseases such as hepatitis C, MASLD, alcohol-associated liver disease, autoimmune hepatitis, or cirrhosis, or in those with unexplained elevations of serum AST or ALT; and 2) in individuals at high risk of HBV exposure, including healthcare workers, residents and staff of residential facilities, people with physical disabilities living in group homes and their caregivers, family members of patients with CHB, sexual partners of patients with CHB, hemodialysis patients, injection drug users, persons at high risk of sexually transmitted infections, and people living with HIV.[27,32,114] According to the national immunization guidelines, intramuscular hepatitis B vaccine should be administered into the deltoid muscle in children and adults, whereas the anterolateral thigh is recommended as the injection site in infants. Hepatitis B vaccines are classified into three generations according to the manufacturing method and antigen composition: first-generation plasma-derived HBsAg vaccines, second-generation recombinant HBsAg vaccines, and third-generation vaccines that additionally contain pre-S1 and pre-S2 antigens on HBsAg.[115] In adults, 20 μg of a second-generation recombinant vaccine is administered intramuscularly at 0, 1, and 6 months for a total of three doses (Supplementary Table 3).[116] In children without a history of hepatitis B vaccination, 10 μg of a second-generation recombinant vaccine is administered intramuscularly at 0, 1, and 6 months for a total of three doses without prior screening tests.[117] In newborns, vaccination is performed according to the HBsAg status of the mother.[114] Newborns born to HBsAg-negative mothers should receive 10 μg of a second-generation recombinant vaccine within 24 hours of birth, followed by additional doses at 1 and 6 months of age, for a total of three doses. Newborns born to HBsAg-positive mothers or mothers with unknown HBsAg status should receive 10 μg of a second-generation recombinant vaccine and HBIG (0.5 mL or 100–150 IU/kg) at separate sites as soon as possible, preferably within 12 hours of birth, followed by 10 μg of the vaccine at 1 and 6 months for a total of three doses. In Korea, administration of HBIG and vaccination for newborns born to HBsAg-positive mothers is supported through the national perinatal hepatitis B prevention program. In hemodialysis patients, immunocompromised individuals, and patients with liver cirrhosis, the immune response to hepatitis B vaccination may be suboptimal, and adjustment of vaccination strategies is therefore required.[27,32,114] In hemodialysis patients, high-dose (40 μg) second-generation recombinant vaccine is recommended, administered as three doses at 0, 1, and 6 months or as four doses at 0, 1, 2, and 6 months.[118-120] In patients with cirrhosis and in immunocompromised individuals, standard-dose (20 μg) vaccination at 0, 1, and 6 months is recommended, and high-dose (40 μg) vaccination may be considered if the antibody response is inadequate.[121-124] Third-generation vaccines (e.g., Heplisav-B,

PreHevbrio) have been reported to elicit stronger immune responses than second-generation vaccines in hemodialysis patients, patients with chronic liver disease, and immunocompromised individuals;[125,126] however, these vaccines are not currently licensed in Korea and are therefore not available for use.

Completion of hepatitis B vaccination results in seroconversion in more than 90% of individuals (anti-HBs >10 mIU/mL).[127] When an additional three-dose series of vaccination is given to anti-HBs nonresponders, seroconversion occurs in 44–100% of cases.[116,117] In immunocompetent individuals, routine testing for anti-HBs after completion of hepatitis B vaccination is not necessary. However, anti-HBs testing at 9–12 months of age is recommended in infants born to HBsAg-positive mothers or in those with family members who have CHB. In healthcare workers, hemodialysis patients, staff working in dialysis units or operating rooms, immunocompromised individuals (e.g., people living with HIV, hematopoietic stem cell transplant recipients, and patients receiving chemotherapy), and sexual partners of patients with hepatitis B, anti-HBs should be measured 1–2 months after completion of vaccination to determine the need for revaccination.[27,116] In adults with anti-HBs levels <10 mIU/mL after vaccination, booster vaccination should be administered as follows.[27,32,114] Among adults, including those with chronic liver disease, immunocompromised individuals, and people living with HIV, anti-HBs nonresponders (anti-HBs <10 mIU/mL) should receive a repeat three-dose series of standard-dose (20 μg) second-generation recombinant vaccine at 0, 1, and 6 months. In patients undergoing hemodialysis and with anti-HBs <10 mIU/mL, high-dose (40 μg) second-generation recombinant vaccine should be administered as three doses at 0, 1, and 6 months, or as four doses at 0, 1, 2, and 6 months. Although anti-HBs titers gradually decline or may become undetectable over time after vaccination, additional booster doses are not required in immunocompetent individuals. In contrast, in hemodialysis patients, annual measurement of anti-HBs is recommended, and booster vaccination should be given if the level falls to ≤10 mIU/mL because the risk of HBV infection increases at this threshold.[114,116] In addition, booster vaccination should be administered in patients with cirrhosis and in immunocompromised individuals when anti-HBs levels are ≤10 mIU/mL.[27,114]

In individuals without anti-HBs who are exposed to blood or body fluids contaminated with HBV, HBIG (0.06 mL/kg) should be administered intramuscularly as soon as possible, preferably within 24 hours, and hepatitis B vaccination should be initiated either simultaneously or within 1 week in the case of percutaneous exposure and within 2 weeks in the case of sexual exposure.[114,128] In individuals who have never undergone HBV serologic testing, have not completed vaccination, or do not have anti-HBs, condom use is recommended during sexual contact with patients with CHB to avoid the risk of infection.[114,129]

In individuals who are negative for HBsAg and anti-HBs but positive for IgG anti-HBc alone, the most common cause in countries like Korea, where the prevalence of HBsAg-positive individuals is not low, is past HBV infection. Vaccination is not required in such past infection cases; however, hepatitis B vaccination may be considered in those who are at high risk of HBV exposure.[130,131] Furthermore, in individuals with isolated IgG anti-HBc positivity who also have abnormal liver function, the possibility of detectable HBV DNA should be considered.

[Recommendation]

1. In adults who are negative for both HBsAg and anti-HBs, hepatitis B vaccination should be administered using 20 μg of a second-generation recombinant vaccine intramuscularly at 0, 1, and 6 months for a total of three doses. (A1) In particular, in high-risk groups for HBV infection, including healthcare workers, hemodialysis patients, staff in dialysis units and operating rooms, immunocompromised individuals, and sexual partners of HBV-infected persons, HBV serologic markers (HBsAg, anti-HBs, and IgG anti-HBc) must be tested, and vaccination should be provided if all markers are negative. (A1) However, in individuals who are anti-HBc-positive only, or in those who previously completed vaccination but subsequently lost anti-HBs, vaccination is not always mandatory; nevertheless, vaccination or booster doses may be considered if they belong to high-risk groups for HBV infection. (B1)
2. In children without a history of hepatitis B vaccination, 10 μg of vaccine should be administered intramuscularly at 0, 1, and 6 months for a total of three doses without prior screening tests. (A1)

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3. Newborns born to HBsAg-negative mothers should receive 10 μg of vaccine within 24 hours of birth, followed by additional doses at 1 and 6 months for a total of three doses. (A1) Newborns born to HBsAg-positive mothers or mothers with unknown HBsAg status should receive HBIG (0.5 mL or 100–150 IU/kg) and 10 μg of vaccine at separate sites as soon as possible, preferably within 12 hours of birth, followed by 10 μg of vaccine at 1 and 6 months for a total of three doses. (A1)
4. In patients undergoing hemodialysis, high-dose (40 μg) second-generation recombinant vaccine should be administered as three doses at 0, 1, and 6 months, or as four doses at 0, 1, 2, and 6 months. (B1) In patients with cirrhosis and in immunocompromised individuals, standard-dose (20 μg) vaccination at 0, 1, and 6 months is recommended, and high-dose (40 μg) vaccination should be considered when the response is inadequate. (B1)
5. In adult nonresponders with anti-HBs titers <10 mIU/mL measured 1–2 months after completion of hepatitis B vaccination, a repeat three-dose series of 20 μg second-generation recombinant vaccine at 0, 1, and 6 months is recommended. In hemodialysis patients, high-dose (40 μg) vaccine should be administered as three doses at 0, 1, and 6 months, or as four doses at 0, 1, 2, and 6 months. (B1)

DIAGNOSIS AND ASSESSMENT

Serum HBsAg and anti-HBc are performed as screening tests to determine the presence of HBV infection. CHB is defined as HBsAg positivity persisting for 6 months or longer, or the presence of HBsAg positivity and IgG anti-HBc positivity. Patients with CHB require a thorough history and physical examination, including assessment of alcohol consumption, medication use, and family history of HBV infection and HCC. Furthermore, co-infection with other viruses, such as hepatitis C virus (HCV) and HIV, should be tested. In high-risk populations, the possibility of HDV should also be considered. In addition, comorbid conditions including obesity, diabetes, metabolic syndrome, and MASLD should be evaluated to establish the causal relationship between HBV infection and liver disease, and long-term regular follow-up is necessary. Serological viral markers, biochemical tests, and non-invasive liver fibrosis assessments are performed to evaluate the degree of viral replication, liver damage, and accompanying liver fibrosis in patients with CHB. Liver ultrasonography and serum alpha-fetoprotein (AFP) testing are also conducted to determine the presence of cirrhosis and HCC (Table 3).

Diagnostic tests for chronic hepatitis B

Qualitative measurement of HBsAg using immunoassay is an essential and accurate serological test for the diagnosis of hepatitis B, with a sensitivity and specificity exceeding 98%. The presence of HBsAg is a definitive marker of HBV infection, and detection of HBsAg in serum for 6 months or longer is sufficient to establish the diagnosis of CHB. Simultaneous serological testing for viral markers of HBV infection, including anti-HBs and anti-HBc, enables differentiation among acute, chronic, and resolved infections, as well as identification of vaccinated individuals.

In acute HBV infection, HBsAg appears 1–10 weeks after exposure and disappears 4–6 months after recovery from hepatitis.[132] In the absence of prior exposure to hepatitis B, acute HBV infection can be diagnosed by HBsAg and immunoglobulin M (IgM) anti-HBc positivity. However, in some cases, only IgM anti-HBc is positive, which may correspond to the window period between HBsAg disappearance and anti-HBs detection. Anti-HBc typically persists for life; IgM anti-HBc usually persists for approximately 6 months after recovery from the acute phase, and anti-HBc detected thereafter is predominantly composed of IgG anti-HBc. Notably, IgM anti-HBc may be detected at very low levels even in chronic HBV infection, and particularly during acute exacerbation, IgM anti-HBc may become positive at low titers.[117] Therefore, when IgM anti-HBc is detected in the setting of markedly elevated liver enzymes, the signal-to-cutoff (S/CO) ratio of IgM anti-HBc and HBV DNA levels could be evaluated to differentiate between AHB and acute exacerbation of CHB.[133,134]

Isolated IgG anti-HBc positivity may indicate either a decline in anti-HBs titer to undetectable levels following resolved infection, or occult HBV infection.[135-137] In such cases, measurement of serum HBV DNA may be helpful. Patients exhibiting this serological pattern should undergo

repeat testing for HBsAg, anti-HBc, and anti-HBs within 3–6 months to differentiate between these possibilities.

Individuals who have recovered from HBV infection are characterized by HBsAg negativity with positivity for both anti-HBs and anti-HBc. In contrast, vaccinated individuals demonstrate anti-HBs positivity alone without detectable anti-HBc. This distinction arises because anti-HBc is an antibody directed against the core protein of HBV, which is produced only upon direct viral infection and persists in the serum even after recovery.

Initial evaluation of patients with chronic hepatitis B

Serum HBV DNA

Serum HBV DNA evaluation directly measures the degree of viral replication. Quantification of HBV is essential for assessing the status of infection, establishing the diagnosis of CHB, determining treatment eligibility, and conducting serial monitoring. Furthermore, it is important for predicting the risk of progression to cirrhosis and the development of HCC. The global standard for expressing serum HBV DNA levels is IU/mL,[138] where 1 IU/mL is approximately equivalent to 5 copies/mL, although this conversion factor varies depending on the assay platform (Roche Diagnostics: 5.8 copies/mL; Abbott Diagnostics: 3.4 copies/mL). Viral quantification is performed using real-time polymerase chain reaction (PCR), which offers a broad detection range of 10–10^9 IU/mL and high sensitivity.[139] In clinical practice, the same HBV DNA assay should be used consistently when monitoring patients with CHB.

Biochemical tests

Biochemical tests including serum aspartate aminotransferase (AST), ALT, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, and creatinine, along with complete blood count (CBC) and prothrombin time/international normalized ratio (PT/INR), are

Table 3. Initial evaluation for patients with chronic hepatitis B

Essential	Recommendation
History taking and physical examination	History taking and physical examination should be performed in patients with chronic hepatitis B, including coinfection with other viruses, alcohol use, pregnancy, comorbidity, medication history, and family history of HBV infection and HCC.
Quantitative HBV DNA assay	Serum quantitative HBV DNA assay should be performed as a marker of HBV replication.
Biochemical tests	Laboratory tests including CBC, AST/ALT, ALP, GGT, bilirubin, albumin, creatinine, and PT should be performed.
HBeAg/anti-HBe	HBeAg/anti-HBe should be performed as markers of HBV replication.
Serum AFP	Serum AFP should be performed to evaluate for the presence of HCC.
Liver ultrasonography	Liver ultrasonography should be performed to evaluate for the presence of liver cirrhosis and HCC.
Non-invasive liver fibrosis tests	Non-invasive liver fibrosis tests should be performed to evaluate liver fibrosis.
Optional	**Recommendation**
Quantitative HBsAg assay	Quantitative HBsAg assay may be considered to assess disease activity and predict prognosis.
IgG anti-HAV	IgG anti-HAV is recommended to determine the need for vaccination.
Anti-HCV, Anti-HIV, Anti-HDV (or HDV RNA)	Testing for anti-HCV, HIV, and anti-HDV (or HDV RNA) may be considered to evaluate for coinfection.
Liver protocol CT or MRI	Liver protocol CT or MRI may be performed when evaluation of liver cirrhosis and hepatocellular carcinoma is difficult by ultrasonography.
Liver biopsy	Liver biopsy may be performed to assess the degree of necroinflammatory activity and liver fibrosis.

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CT, computed tomography; GGT, gamma-glutamyl transpeptidase; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PT, prothrombin time.

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necessary to differentiate the etiology and assess the severity of liver disease. Thrombocytopenia accompanied by a progressive decline in serum albumin levels and prolongation of PT are characteristic findings observed during progression to cirrhosis.

Serum ALT has been widely used as an important criterion for evaluating liver disease and selecting candidates for treatment.[140] ALT levels are generally higher than AST levels; however, this ratio may be reversed with the progression to cirrhosis. In patients with CHB, normal or mildly elevated ALT levels are generally consistent with the absence of or mild necroinflammation in the liver parenchyma, where elevated ALT levels may suggest increased hepatic necroinflammatory activity. However, the degree of ALT elevation does not always correlate with the histological severity of liver injury, and caution is therefore warranted in its interpretation.[141]

Several studies have reported that the true normal ALT levels are significantly lower than the previously established upper limits (40 IU/L for males and 30 IU/L for females). A cohort study proposed that the ULN for AST and ALT should be lowered to 30 IU/L for males and 19 IU/L for females.[141] A Korean retrospective study analyzing data from approximately 12,000 patients with CHB proposed thresholds of 34 IU/L for men and 30 IU/L for women as predictive cutoff values for liver disease-related mortality.[142] Although this study has the inherent limitation of a retrospective design, it encompassed a wide range of age groups and was not restricted to individuals without mild fatty liver disease, thereby reflecting realistic values for Korean patients with chronic HBV infection and addressing the practical need for predicting liver disease-related prognosis. Therefore, until prospective validation is available, it is reasonable to adopt 34 IU/L for men and 30 IU/L for women as the ULN of ALT in patients with CHB. However, serum ALT is known to be influenced by age, body mass index, sex, lipid and carbohydrate metabolism disorders, and uremia.[141,143] Therefore, relying solely on ALT elevation as a prerequisite for initiating treatment is problematic, and careful interpretation is warranted.

Serum HBeAg/Anti-HBe

It is necessary to determine whether patients with CHB are HBeAg-positive or HBeAg-negative, as HBeAg status may change over time. In general, HBeAg positivity indicates active viral replication and high infectivity. During the natural course of CHB, spontaneous seroconversion from HBeAg to anti-HBe may occur, accompanied by a reduction in viral replication and normalization of ALT levels. In such cases, liver histology typically shows mild inflammation and fibrosis. However, inactive cirrhosis may be present if significant hepatic injury occurred during the immune-active phase. Patients who are HBeAg-negative but have HBV DNA levels ≥2,000 IU/mL with elevated ALT are considered to be in the HBeAg-negative immune-active phase, which is attributable to precore or BCP mutations that prevent HBeAg production.[49] BCP mutations are associated with more severe hepatocyte inflammation and necrosis, lower remission rates, and an increased risk of HCC development.

Quantitative serum HBsAg

Quantitative serum HBsAg testing is a method that detects all three sizes of hepatitis B surface protein particles: S (small), M (middle), and L (large). Quantitative HBsAg has been reported to correlate with intrahepatic covalently closed circular DNA (cccDNA) levels, as determined by liver biopsy. In HBeAg-negative patients with HBV DNA levels <2,000 IU/mL, a quantitative HBsAg level <1,000 IU/mL was associated with a low probability of subsequent HBV reactivation,[144,145] and a relatively lower risk of HCC development.[88,146,147] In HBeAg-positive patients, very high quantitative HBsAg levels (>25,000 IU/mL) were associated with a low likelihood of significant fibrosis and consequently a lower risk of HCC.[148] Monitoring changes in quantitative HBsAg levels in treatment-naïve HBeAg-positive patients may provide information regarding changes in the natural course of disease, the risk of HCC development, and the potential for subsequent HBsAg seroclearance.[149,150] During antiviral therapy, quantitative HBsAg may help predict which patients can safely discontinue treatment, because the probability of reactivation is low.[151-153]

IgG anti-HAV antibody

When patients with CHB are infected with acute hepatitis A, the infection is predominantly symptomatic with jaundice rather than asymptomatic, requires a longer recovery period, and is associated with a higher incidence of fulminant hepatic failure. Importantly, several studies have identified underlying chronic liver disease as a significant risk factor

for fulminant hepatic failure and death due to acute hepatitis A.[154-156] Over the past 30 years, the seroprevalence curve for anti-hepatitis A virus (anti-HAV) antibodies in Korea has shifted approximately 20 years to the right, indicating that hepatitis A can occur across all age groups.[157] Therefore, it is recommended that patients with CHB undergo IgG anti-HAV testing and receive vaccination if antibodies are absent.

Co-infection

Anti-HCV testing should be performed to determine the presence of HCV co-infection. HIV testing should be conducted in individuals at high risk for HIV infection, including men who have sex with men, persons with a history of injection drug use, those with multiple sexual partners, or those with a recent history of sexually transmitted infections. In individuals at high risk for HDV co-infection (those originating from HDV-endemic regions, those with unexplained transaminase elevations disproportionate to their HBV DNA levels, or those with rapid fibrosis progression or early decompensation), anti-HDV or HDV RNA PCR testing should be considered.

In cases of acute hepatitis of unclear etiology, IgM anti-hepatitis E virus (HEV) or HEV RNA testing should be considered to exclude co-infection. In addition, IgM anti-HAV testing is recommended for patients who are IgG anti-HAV-negative. A prospective multicenter study conducted across 12 centers in Korea during 2020–2021 reported that hepatitis A virus was the most common cause of acute viral hepatitis (78.8%), followed by HEV (7.5%).[158]

Liver ultrasonography

Liver ultrasonography is performed as the primary imaging modality to assess the presence of cirrhosis and HCC in patients with CHB, as it is readily available, non-invasive, less expensive than computed tomography (CT) or magnetic resonance imaging (MRI), allows real-time examination, and does not expose patients to the adverse effects of intravenous contrast agents or radiation. Because CHB is a major risk factor for HCC development, evaluation for the presence of HCC is necessary from the initial assessment. Characteristic ultrasonographic findings of cirrhosis include a nodular or irregular surface and coarsened hepatic echotexture; in advanced cirrhosis, the liver appears atrophic and multinodular. A previous study reported that ultrasonography could diagnose cirrhosis in patients with CHB with a sensitivity of 77.8% and specificity of 92.5%.[159] In patients in whom liver ultrasonography is inadequate for evaluating the presence of cirrhosis or HCC, CT or MRI may be performed as an alternative.

Non-invasive liver fibrosis tests

Assessment of liver fibrosis plays an important role in treatment decisions and prognostic prediction in CHB. Recently, non-invasive tests such as serum markers, vibration-controlled transient elastography (VCTE), shear wave elastography (SWE), and magnetic resonance elastography (MRE) have been preferentially considered over invasive liver biopsy for the initial evaluation. For detailed descriptions and recommendations regarding the diagnostic performance, utility, and advantages and limitations of these modalities, refer to the KASL clinical practice guidelines for non-invasive tests to assess liver fibrosis in chronic liver disease, published in 2024.[160]

In patients with CHB, serum markers such as the AST to platelet ratio index (APRI) and fibrosis-4 (FIB-4) demonstrate high specificity for the diagnosis of significant fibrosis and cirrhosis and can be used as convenient tools to exclude these conditions. However, these markers may be affected by hepatitis activity and extrahepatic factors, and caution is warranted in their interpretation. VCTE is a highly accurate diagnostic test with an area under the receiver operating characteristic curve of 0.80 or higher and has been the most extensively studied among non-invasive liver fibrosis assessments. Although heterogeneity among studies has resulted in some variation in reported cutoff values and diagnostic performance, two recent meta-analyses reported optimal liver stiffness measurement (LSM) cutoff values of 7.0 kPa for significant fibrosis, 8.0–9.5 kPa for advanced fibrosis, and 11.0–12.5 kPa for cirrhosis.[161,162] Although further research is needed, point SWE and two-dimensional SWE also demonstrate diagnostic accuracy comparable to that of transient elastography. Notably, two-dimensional SWE showed similar LSM cutoff values for diagnosing each stage of liver fibrosis.[160] MRE is also an excellent diagnostic modality for assessing liver fibrosis in patients with CHB.[160]

Liver biopsy

Liver biopsy is the traditional gold standard that enables

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direct assessment of the degree of intrahepatic necroinflammation and fibrosis. Although liver biopsy has been performed as the reference standard for fibrosis assessment, this procedure is invasive and associated with complications such as bleeding and pain and is limited by sampling error and interobserver variability among pathologists.[163] Therefore, non-invasive liver fibrosis tests have recently been preferentially considered as alternatives to invasive liver biopsy. Nevertheless, liver biopsy continues to play an important clinical role. Liver biopsy should be considered when the results of non-invasive tests are discordant with the clinical findings, when the decision to initiate treatment remains unclear, or when concomitant liver disease of a different etiology is suspected and requires differentiation.

Novel viral markers

Although quantitative serum HBsAg has been shown to correlate with intrahepatic cccDNA levels, this correlation is weak in HBeAg-negative patients because HBsAg in these patients is predominantly derived from integrated viral genomes. Recently, novel non-invasive markers that reflect the intrahepatic pool of transcriptionally active HBV cccDNA have been proposed, including serum hepatitis B core-related antigen (HBcrAg) and quantitative HBV RNA.[164] These novel biomarkers are expected to better reflect the size of the cccDNA pool and the transcriptional activity of intrahepatic cccDNA, thereby facilitating prognostic prediction in patients with CHB.[165] Furthermore, quantitative anti-HBc has a potential marker reflecting HBV-specific immune responses, and has been reported to be associated with disease activity and reactivation risk.[166,167] However, all of these markers currently require laboratory-level techniques for quantification and are therefore not yet used in routine clinical practice. Additional studies are needed to define the potential role of these novel biomarkers in the monitoring and prediction of disease progression in patients with CHB.

[Recommendation]

1. Serum HBsAg and anti-HBc should be performed as screening tests to determine HBV infection status. (A1)
2. Quantitative serum HBV DNA testing and HBeAg/anti-HBe testing should be performed as markers of viral replication in serum HBsAg-positive patients with CHB. (A1)
3. Blood tests including CBC, AST/ALT, ALP, GGT, bilirubin, albumin, creatinine, PT/INR, and serum AFP should be performed in patients with CHB. (A1)
4. IgG anti-HAV testing should be performed in patients with CHB, and vaccination should be administered if the test is negative. (B1)
5. Anti-HCV testing should be performed in patients with CHB to assess for HCV co-infection. (B1) Anti-HDV (or HDV RNA) and HIV testing are recommended to evaluate for HDV and HIV co-infection. (B2)
6. Liver ultrasonography should be performed in patients with CHB to assess for the presence of cirrhosis and HCC. (A1)
7. Non-invasive liver fibrosis tests should be performed to evaluate fibrosis in patients with CHB. (B1)

Monitoring of patients not eligible for treatment

Reactivation may occur in approximately 15–33% of HBeAg-negative carriers who are not receiving antiviral therapy and in patients following spontaneous HBeAg/anti-HBe seroconversion during long-term follow-up, with a higher risk observed in patients with HBV DNA levels >2,000 IU/mL and in those who underwent HBeAg/anti-HBe seroconversion at an age of 40 years or older.[87,168] Therefore, even in patients not eligible for treatment, clinical findings, laboratory results, imaging studies, and non-invasive liver fibrosis assessments should be periodically monitored to determine whether they meet the criteria for treatment initiation (Table 4).

In general, ALT and HBV DNA are monitored at 3–6-month intervals, and HBeAg/anti-HBe is monitored at 6–12-month intervals. In cases where treatment eligibility remains unclear, more frequent monitoring of ALT and HBV DNA at 1–3-month intervals and HBeAg/anti-HBe at 2–6-month intervals may be conducted to determine treatment eligibility. Alternatively, treatment decisions can be guided by liver fibrosis assessment using non-invasive tests or liver biopsy. Spontaneous HBeAg/anti-HBe seroconversion can occur at any time up to 30–40 years of age (mean age, 31 years) and becomes less frequent thereafter.[169] Spontaneous HBsAg seroclearance in CHB is rare, reported at an annual

rate of 1.1% overall in untreated patients,[170] and 2.3% per year in HBeAg-negative patients not eligible for treatment.[171] However, the rate increases with age, and serial quantitative HBsAg testing should be considered for prediction. This is useful for predicting HBsAg seroclearance and HCC development along with HBV reactivation, thereby facilitating more accurate patient monitoring strategies.[172] Qualitative serum HBsAg testing may be performed when quantitative testing is unavailable.

Because CHB is a major risk factor for HCC, screening for HCC is necessary from the initial evaluation, and regular HCC surveillance is required regardless of whether antiviral treatment is being administered. The standard method for HCC surveillance is the performance of serum AFP testing and ultrasonography at regular 6-month intervals.[173] The primary targets for HCC surveillance are patients with CHB who are aged 40 years or older, or those younger than 40 years who are at high risk for HCC development, such as those with accompanying cirrhosis. Even in patients who have achieved HBsAg seroclearance, HCC surveillance should be continued if they have cirrhosis, a family history of HCC, or if HBsAg seroclearance occurred at an age of 40 years or older in males and 50 years or older in females.[174,175] Regular surveillance improves patient survival and increases the likelihood of early HCC diagnosis.[176,177]

Follow-up non-invasive liver fibrosis tests could be considered in patients not eligible for treatment to monitor fibrosis progression. Although further research is needed regarding the optimal testing interval and individualization based on patient status is necessary, testing at 2–3-year intervals may be considered for patients in a stable condition, whereas testing intervals of 1 year should be considered for patients with unclear treatment eligibility.[27]

Table 4. Monitoring for the patients with chronic hepatitis B who are not meeting treatment criteria

Interval	Tests
Every 3–6 months	ALT, HBV DNA*
Every 6 months	HCC surveillance†—AFP, liver ultrasonography
Every 6–12 months	HBeAg/anti-HBe*
Every 12 months	Quantitative or qualitative HBsAg‡

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
*Testing intervals may be shortened when treatment eligibility is uncertain.
†For individuals at high risk of HCC, including those aged ≥40 years or those with cirrhosis regardless of age.
‡Testing may be tailored to individual patients when clinically indicated for specific purposes, such as identifying infection phase transitions, stratifying HCC risk, or detecting spontaneous HBsAg loss.

[Recommendation]

1. Serum ALT and HBV DNA should be monitored at 3–6-month intervals to determine whether patients not eligible for treatment meet the criteria for treatment initiation. (B1)
2. In cases where treatment eligibility remains unclear, serum ALT and HBV DNA markers could be monitored at 1–3-month intervals, or liver fibrosis assessment could be performed to determine treatment eligibility. (B1)
3. In patients with CHB aged 40 years or older, or those younger than 40 years who are at high risk for HCC development such as those with cirrhosis, HCC surveillance consisting of serum AFP testing and ultrasonography should be performed at 6-month intervals. (A1)

TREATMENT GOAL AND OBJECTIVES

In patients with CHB, the goal of clinical management and antiviral therapy is to decrease liver-related mortality and improve overall survival by preventing cirrhosis, decompensation, and HCC. To achieve this, the ideal therapeutic objective should be a “sterilizing cure,” characterized by the complete eradication of the HBV—including serum HBV DNA, intrahepatic cccDNA, and integrated DNA—as well as the induction of HBsAg seroclearance or seroconversion before the onset of clinically significant fibrosis. However, HBsAg seroclearance or seroconversion is rarely observed with currently approved antiviral agents, and the eradication of cccDNA and integrated DNA remains an elusive challenge.[52] Consequently, the realistic short-term objective of current antiviral therapy is to maintain sustained suppression of HBV replication to achieve undetectable serum HBV DNA levels. The long-term objective is to achieve a “functional cure,” defined by HBsAg seroclearance and seroconversion. Prolonged antiviral treatment

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can alleviate hepatic inflammation, prevent or reverse fibrosis, and lower the incidence of cirrhosis and HCC, thereby reducing liver-related mortality.[178-180] Furthermore, another objective of antiviral therapy is to prevent vertical mother-to-child transmission during pregnancy and to forestall HBV reactivation during immunosuppressive therapy and chemotherapy.

[Summary]

- The goal of CHB treatment is to reduce liver-related mortality and improve patient survival. To achieve this, the primary objectives are to suppress HBV replication, alleviate or prevent hepatic inflammation and fibrosis, thereby forestalling the development of cirrhosis and HCC.
- The realistic short-term objective of antiviral therapy is to induce the sustained undetectable serum HBV DNA, whereas the long-term objective is to achieve a "functional cure," defined as HBsAg seroclearance or seroconversion.
- Another objective of antiviral therapy is to prevent vertical mother-to-child transmission during pregnancy and to forestall HBV reactivation during immunosuppressive therapy.

TREATMENT INDICATIONS AND STRATEGIES

Active replication of HBV can lead to liver injury and increases the risk of liver disease progression and complications.[44] Potent nucleos(t)ide analogues (NAs) that effectively suppress HBV replication are available.[181] Suppression of viral replication with these antiviral agents results in improvement of hepatic inflammation, normalization of ALT levels, regression of liver fibrosis, and a reduction in the risks of HCC and liver-related mortality.[182] In the past, evidence supporting the impact of antiviral therapy on long-term clinical outcomes—such as HCC development, progression to cirrhosis, and mortality—was limited. In addition, due to issues with antiviral resistance, relatively poor tolerability, and suboptimal antiviral efficacy of first-generation NAs, treatment goals were primarily focused on short-term surrogate endpoints, including normalization of liver enzymes, suppression of viral replication, HBeAg seroconversion, and histological improvement. Consequently, CHB was largely approached as an inflammatory liver disease. However, accumulating evidence from large-scale longitudinal observational studies, as well as RCTs, has demonstrated that antiviral therapy significantly improves long-term outcomes, including reducing the incidence of HCC, preventing progression to cirrhosis, and decreasing liver-related mortality.[27]

The decision to initiate antiviral therapy is made based on a comprehensive assessment of multiple factors, including: (1) the stage of liver disease, (2) the level of HBV replication, and (3) the presence of additional risk factors for HCC. The stage of liver disease can be broadly categorized into chronic hepatitis, compensated cirrhosis, and decompensated cirrhosis, according to the extent of liver fibrosis. Cirrhosis is the strongest predictor of HCC development, even after viral suppression.[85,183] Liver fibrosis can be assessed using liver biopsy, serum biomarkers (e.g., APRI, FIB-4 index),[184,185] or noninvasive methods such as transient elastography (e.g., FibroScan®).[186,187] Significant fibrosis is generally defined as stage F2 or higher on liver biopsy.[188] According to meta-analyses, a liver stiffness cutoff of 7 kPa has been suggested for the diagnosis of ≥F2 fibrosis using transient elastography.[161,162,189,190] The level of HBV replication, as measured by serum HBV DNA, is a key determinant of disease progression and HCC risk. The REVEAL study conducted in Taiwan demonstrated that the risk of cirrhosis and HCC increases significantly when HBV DNA levels exceed 2,000 IU/mL.[191,192] However, it should be noted that the REVEAL study population predominantly consisted of individuals aged ≥40 years, who were HBeAg-negative and had HBV DNA levels below 2,000 IU/mL. In addition, due to technical limitations at the time of the study, further quantification above approximately 10^5 IU/mL was not feasible.

Recent studies that complement and extend the findings of the REVEAL study have consistently demonstrated a non-linear (parabolic) relationship between HBV DNA levels and the risk of HCC, regardless of antiviral treatment status.[62-64] The risk of HCC is highest in patients with moderate viremia, whereas it is relatively lower in those with low and high viremia. Importantly, this non-linear relationship persists even among patients receiving antiviral therapy. In particular, patients who initiate treatment during the moder-

ate viremia phase continue to exhibit an elevated risk of HCC that does not normalize, even after long-term viral suppression.[66,77] These observations can be explained by the complex pathophysiological mechanisms described in the natural history of CHB, including HBV DNA integration into the host genome, clonal expansion of hepatocytes, and immune-mediated liver injury. Notably, the finding that baseline HBV DNA levels at the time of treatment initiation continue to influence HCC risk even after antiviral therapy suggests that the cumulative hepatocarcinogenic risk established through prolonged virus–host interactions may not be fully reversible.[66,77] This underscores the importance of HBV DNA levels at treatment initiation as a key predictor of long-term HCC risk and supports the need for earlier initiation of antiviral therapy before substantial hepatocarcinogenic risk has accumulated, irrespective of ALT levels.

NAs, the current standard antiviral therapy, directly inhibit HBV reverse transcription, thereby reducing circulating serum HBV DNA levels. At the same time, this therapy decreases the production of double-stranded linear DNA, which serves as a substrate for HBV DNA integration into the host genome, and thus may indirectly interrupt a key oncogenic pathway leading to HCC.[71] In other words, beyond their direct antiviral effect of suppressing viral replication, NAs may also exert indirect effects by reducing HBV DNA integration into the host genome and the subsequent clonal expansion of hepatocytes, thereby lowering the risk of HCC. In the TORCH-B study, analysis of patients treated with TDF for 3 years demonstrated an approximately 3.3-fold reduction in the frequency of HBV DNA integration compared with baseline.[193] Furthermore, in a separate analysis of patients who participated in previous clinical trials in Hong Kong, antiviral therapy was associated with a significant reduction in HBV DNA integration frequency, and even after just 1 year of treatment, the size of hepatocyte clones was reduced by approximately 50%.[194]

Based on this evidence, the present guideline moves beyond an ALT-centered framework for assessing liver injury in the treatment of CHB and introduces a new classification system based on HBV DNA levels. By adopting an early treatment strategy focused on viral activity itself, this approach aims to more effectively prevent HCC and proposes simplified treatment criteria that more intuitively identify patients eligible for treatment (Fig. 2). This strategy of expanding treatment eligibility is expected to help bridge the gap between the relatively high diagnostic rate and the comparatively low rates of linkage to care and treatment reported in Korea, in the context of the WHO 2030 viral

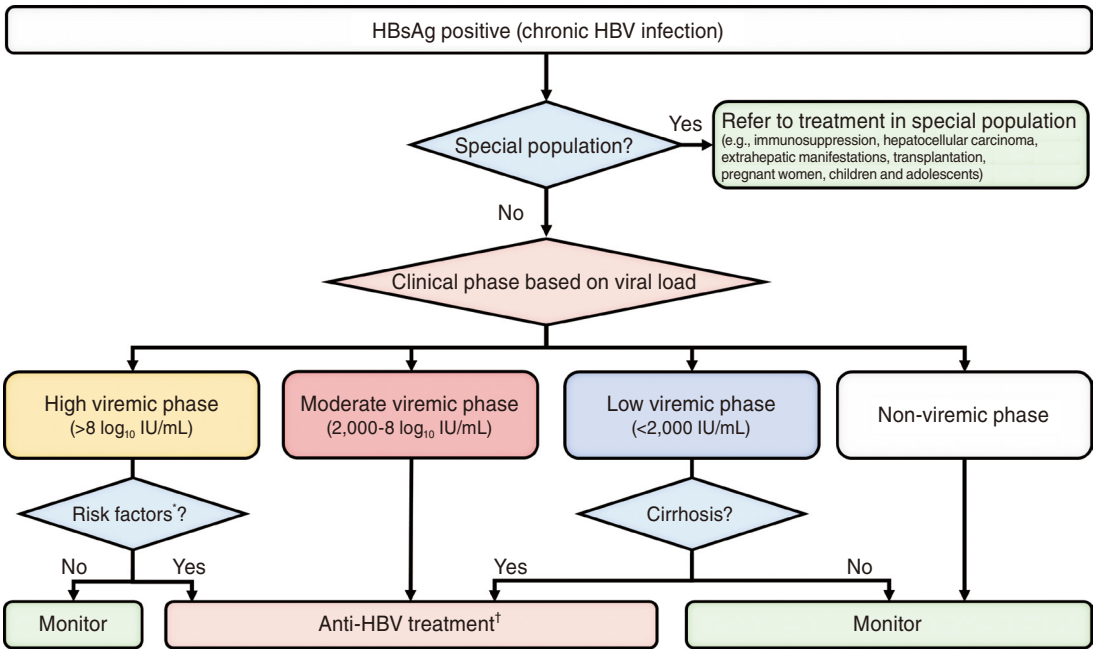

Figure 2. Simplified algorithm for management of chronic hepatitis B. *Risk factors for disease progression or HCC: ALT >ULN, age >30 years, or significant fibrosis (≥F2). †Anti-HBV treatment refers to oral nucleos(t)ide analogues as standard first-line therapy. ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ULN, upper limit of normal.

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hepatitis elimination goals. However, the expanded treatment criteria proposed in this guideline encompass a broader population than that currently covered by national health insurance reimbursement policies, which may limit their implementation in real-world clinical practice. Addressing this discrepancy will require future revisions of reimbursement criteria based on accumulating clinical evidence and cost-effectiveness analyses.

High viremic phase

High viremic phase is defined as a serum HBV DNA level exceeding 8 $\log_{10}$ IU/mL and includes the majority of patients traditionally classified as being in the immune-tolerant phase, as well as a subset of those in the immune-active phase. Recent large-scale cohort studies from Korea and other countries have consistently shown that, among patients with CHB who are non-cirrhotic, treatment-naïve, and have ALT levels ≤2× ULN, those with high viremia have the lowest risk of HCC compared with other viremia categories.[63,64] This pattern has also been observed in patients treated with TDF or ETV, with the lowest HCC risk seen in those with high viremia at treatment initiation.[36,65,66,77,79] These findings suggest that the high viremic phase itself is associated with a relatively low short-term risk of HCC. However, this should not be interpreted as indicating long-term safety, as this population may include individuals with additional risk factors—such as older age, elevated ALT levels, or progression of liver fibrosis—that increase the risk of liver-related complications over time.[88,91,195-200]

High viremia, or the immune-tolerant phase, has traditionally been recognized as a phase predominantly observed in relatively young individuals, typically under 30 years of age. In a prospective study following 240 patients, HBeAg seroconversion occurred most frequently around the age of 30, with anti-HBe detected in approximately 81% of patients by age 31.[169] In Korea, most patients with CHB are infected with genotype C, in which HBeAg seroconversion is known to occur approximately 10 years later than in genotype B.[19,201] According to a study analyzing prognosis based on the timing of HBeAg seroconversion, patients who achieved seroconversion before the age of 30 had an excellent prognosis. In contrast, those with seroconversion after the age of 40 had significantly higher risks of HBeAg-negative hepatitis, cirrhosis, and HCC, with hazard ratios (HRs) of 2.95, 17.6, and 5.22, respectively, compared with those who seroconverted before age 30.[87] Consistent with these findings, HBeAg positivity beyond the age of 30 has been identified as an independent risk factor for HCC. Age is one of the most important determinants of HCC risk, and although there are some sex-related differences, the risk of HCC generally increases with advancing age starting from approximately 30–35 years.[88,91] Notably, even among patients classified as having high viremia, those of relatively older age are more likely to have significant histologic disease, including ≥F2 fibrosis or ≥A2 necroinflammation on liver biopsy.[202] Furthermore, long-term follow-up studies have shown that these patients are at increased risk of developing cirrhosis and HCC.[36,203,204] These findings indicate that patients classified as having high viremia or being in the immune-tolerant phase are not necessarily in a histologically stable state. With increasing age, the likelihood of spontaneous immune clearance may decrease, while the underlying risk of disease progression may persist. Meanwhile, among patients in the immune-tolerant phase, higher HBsAg levels have been associated with a lower short-term risk of HCC and a delayed timing of HCC occurrence.[146] However, this should not be interpreted as indicating that the risk of HCC is absent or remains persistently low; rather, it is more appropriately understood as reflecting a temporal delay in the onset of HCC. Given that hepatocarcinogenesis requires sufficient time for the accumulation of genetic alterations, even patients previously classified as being in the immune-tolerant phase cannot be considered free from HCC risk during long-term follow-up. Furthermore, as HBV-specific immune responses decline with advancing age, the likelihood of spontaneous immune clearance may also decrease.[205,206] From the perspective of HCC prevention, these findings suggest that even among patients classified as having high viremia, there may be a rationale for considering earlier initiation of antiviral therapy beyond a certain age threshold. In this context, a recent multicenter retrospective study from China reported that, among immune-tolerant patients who were HBeAg-positive, aged ≤30 years, had HBV DNA ≥8 $\log_{10}$ IU/mL, normal ALT levels, and no significant fibrosis or family history of HCC, antiviral therapy was associated with a markedly reduced risk of HCC (HR, 0.03).[89] However, the overall risk of HCC in patients younger than 30 years is very low,

and in that study, only 46 cases of HCC occurred among 7,566 patients, with just a single case observed in the antiviral treatment group. In addition, the progression of 117 patients to cirrhosis within 5 years suggests the possibility that baseline fibrosis may have been underestimated, and that a substantial proportion of patients may already have had significant fibrosis (≥F2). Taken together, these considerations warrant cautious interpretation, and the benefits of antiviral therapy in patients with high viremia under the age of 30 should not be generalized based solely on these findings. Furthermore, in an RCT evaluating TDF monotherapy in immune-tolerant patients with high viremia, the rate of virologic response (HBV DNA <69 IU/mL) at 192 weeks was approximately 55%.[207] This finding suggests that the antiviral efficacy in terms of viral suppression may be relatively limited in patients with high viremia, and this should be carefully considered when initiating treatment.

ALT is an important biomarker of hepatic necroinflammation, and among patients with high viremia, persistently normal ALT levels are indicative of relatively low inflammatory activity. However, when ALT levels are near the ULN or mildly elevated, patients are more likely to have advanced fibrosis or necroinflammation on liver biopsy compared with those with very low ALT levels, and are at increased risk of liver-related complications, including HCC, during long-term follow-up.[202,203] Furthermore, in the TORCH-B study, antiviral therapy significantly suppressed fibrosis progression even in patients with mildly elevated ALT levels (1–2× ULN).[208] In the subsequent TORCH-B rollover study, patients in the initial placebo group were switched to TDF, and treatment was extended for 3 years in newly treated and previously treated patients. Approximately 60% of patients showed improvement in liver fibrosis, accompanied by a significant reduction in necroinflammation.[209] These findings demonstrate that antiviral therapy confers long-term histological benefits even in patients with only mildly elevated ALT levels.

In a Korean study comparing 87 immune-tolerant patients who received antiviral therapy with 397 patients who were observed without treatment, the untreated group had more favorable baseline liver function; nevertheless, the treated group showed a significantly lower risk of HCC and cirrhosis.[210] In addition, among patients with high viremia, a propensity score–matched analysis compared those with ALT <2× ULN who did not receive antiviral therapy with those who initiated antiviral therapy due to elevated ALT. After adjustment for key clinical variables—including age, sex, and baseline liver disease status—1,113 matched pairs were analyzed. Antiviral therapy was associated with a significantly lower risk of HCC (HR, 0.41).[66] As noted above, a recent multicenter retrospective study from China evaluated the preventive effect of antiviral therapy on HCC in so-called "gray-zone" patients (HBeAg-positive, HBV DNA ≥6 $\log_{10}$ IU/mL, normal ALT, and no advanced fibrosis). The study included 7,730 treated patients and 7,874 untreated patients, with mean HBV DNA levels of 8.6 and 8.5 $\log_{10}$ IU/mL, respectively—both within the high viremia range. Propensity score–matched analysis demonstrated a significant reduction in HCC risk in the treated group (HR, 0.17).[89] Furthermore, based on studies evaluating the long-term outcomes of immune-tolerant patients, a recent cost-effectiveness analysis reported that initiating antiviral therapy during the immune-tolerant phase is more cost-effective, in terms of reducing HCC incidence, than deferring treatment until transition to the immune-active phase.[211]

These findings suggest that in patients with high viremia, spontaneous immune clearance may be observed for a certain period in those younger than 30 years. However, antiviral therapy should be considered in patients older than 30 years, or in those with elevated ALT levels or evidence of significant fibrosis on invasive or noninvasive assessment, given the increased risk of long-term liver-related complications. In contrast, in the absence of these risk factors, careful monitoring is recommended.

[Recommendation]

1. In patients with high viremia (serum HBV DNA >8 $\log_{10}$ IU/mL), antiviral therapy should be considered in those older than 30 years, those with elevated liver enzymes, or those with significant liver fibrosis. In the absence of these risk factors for disease progression or HCC, close monitoring is recommended. (B1)

Moderate viremic phase

Traditionally, the indications for antiviral therapy in CHB have been defined based on two key axes: the level of viral replication and the degree of hepatic inflammatory activity. Specifically, patients have been classified as being in the

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immune-active phase when there is evidence of active viral replication, reflected by elevated serum HBV DNA levels, together with elevated serum ALT levels or histologically confirmed moderate or greater necroinflammation and significant fibrosis, and antiviral therapy has been recommended in such cases. These criteria are supported by evidence from multiple RCTs and observational studies demonstrating that antiviral therapy in immune-active patients significantly reduces the risks of cirrhosis, hepatic decompensation, and HCC.[182]

Active viral replication is primarily assessed by serum HBV DNA levels; however, the presence of detectable HBV DNA does not necessarily indicate a level of replication that warrants treatment. Among patients with low-level viremia (HBV DNA <2,000 IU/mL), many have normal ALT levels and minimal histologic inflammation and fibrosis, and may therefore have a relatively favorable prognosis without treatment.[191] Accordingly, although arbitrary, serum HBV DNA thresholds have been used to define levels of viral replication at which antiviral therapy may be considered: ≥20,000 IU/mL in HBeAg-positive patients and ≥2,000 IU/mL in HBeAg-negative patients.[183,191,192]

Serum ALT has long been used clinically as a marker of hepatic inflammatory activity, and according to a general consensus, antiviral therapy should be initiated when ALT levels exceed twice the ULN.[27,32] However, ALT does not always correlate with the extent of histologic liver injury and can be influenced by factors such as body mass index, sex, comorbidities, and other causes of liver injury.[141,212,213] Moreover, even in patients with normal or only mildly elevated ALT levels, significant fibrosis or necroinflammation may be detected on liver biopsy,[59,214] highlighting the limitations of treatment decisions based solely on serum ALT. Furthermore, recent studies suggest that while ALT reflects inflammatory activity, it does not adequately capture the oncogenic processes associated with hepatocarcinogenesis. Notably, no significant difference in the frequency of HBV DNA integration into the host genome has been observed between the “chronic infection” and “chronic hepatitis” phases as defined by the EASL guidelines based on ALT levels.[215] This finding implies that oncogenic processes, such as HBV DNA integration, may already be ongoing even when ALT levels are within the normal range.[71,76,215] Taken together, these data suggest that an ALT-centered framework for disease classification and treatment strategy may be insufficient for effective HCC prevention.[60]

Recent studies have demonstrated the presence of clinically high-risk populations that are not captured by existing treatment criteria based on the degree of viral replication (HBV DNA) and inflammatory activity (ALT). According to large-scale cohort studies from Korea and other countries involving non-cirrhotic, treatment-naïve patients, the highest risk of HCC has been consistently observed in patients with CHB who have moderate viremia, defined as HBV DNA levels of 4–8 $\log_{10}$ IU/mL, regardless of serum ALT levels.[63,64] Similar findings have been reported in studies of patients initiating antiviral therapy.[65,66,77,79] In Korean and multinational multicenter cohort studies of HBeAg-positive patients treated with TDF or ETV, those with moderate viremia (HBV DNA 5–8 $\log_{10}$ IU/mL) prior to treatment initiation had a higher risk of HCC than those with high viremia.[65,79] Based on these observations, new HCC risk prediction models incorporating this relationship have been proposed.[80] This pattern has also been observed in analyses including HBeAg-negative patients, in whom the highest risk of HCC was reported among those with baseline HBV DNA levels in the moderate range.[66,77]

Recent large-scale observational studies provide clinical evidence that antiviral therapy significantly reduces the risk of HCC in patients with moderate viremia. In a propensity score–matched analysis of patients with HBV DNA levels of 5–8 $\log_{10}$ IU/mL, comparing those with ALT <2× ULN who did not receive antiviral therapy with those who initiated antiviral therapy due to elevated ALT, 1:1 matching was performed after adjustment for key clinical variables, including age, sex, and baseline liver disease status (total 1,916 pairs). Antiviral therapy was associated with a significantly lower risk of HCC (HR, 0.46).[66] Furthermore, in a retrospective, multicenter, multiethnic study of 855 indeterminate-phase patients without advanced fibrosis, antiviral therapy was associated with an approximately 70% reduction in HCC risk.[216] However, although antiviral therapy significantly reduced HCC risk in patients with HBV DNA levels >1,000 IU/mL, this effect was not clearly observed in those with HBV DNA ≤1,000 IU/mL. The guideline revision committee also conducted a systematic review and meta-analysis (Key Question 2) to evaluate the effect of antiviral therapy in patients in the gray zone or indeterminate phase. Among the 37 studies (56,379 patients) included in a meta-analysis, 11 evaluated the effect of antiviral therapy in pa-

tients with moderate viremia. The annual incidence of HCC was 0.23 and 0.73 per 100 person-years in the treated and untreated groups, respectively, corresponding to an incidence rate ratio of 0.30, indicating a significantly lower risk in the treated group. In addition, a recent cost-effectiveness analysis conducted in non-cirrhotic patients with moderate viremia demonstrated that initiating antiviral therapy during moderate viremia, regardless of ALT levels, was more cost-effective than deferring treatment until progression to the immune-active phase accompanied by ALT elevation. Notably, from a societal perspective that incorporates productivity losses due to premature mortality, this strategy was found to be cost-saving.[217] Furthermore, expanding treatment eligibility to patients without cirrhosis based on HBV DNA ≥2,000 IU/mL—irrespective of ALT levels or HBeAg status—was projected to be cost-effective and to prevent approximately 43,300 cases of HCC and 37,000 deaths in Korea by 2035.[218]

The interim analysis of the recently reported ATTENTION study provides the first RCT evidence that early antiviral therapy in patients with moderate viremia can reduce the risk of HCC and major liver-related clinical events.[219] The ATTENTION study is a multicenter, RCT that enrolled non-cirrhotic adults aged 40–80 years with CHB who had moderate viremia (HBV DNA 4–8 $\log_{10}$ IU/mL) and normal or mildly elevated ALT levels. Participants were randomly assigned in a 1:1 ratio to receive tenofovir alafenamide (TAF) or to undergo observation. At the time of the first prespecified interim analysis (median follow-up, 17.7 months), the composite primary endpoint—including HCC, hepatic decompensation, liver transplantation, or all-cause mortality—occurred at a lower rate in the TAF group (n=369) compared with the observation group (n=365) (0.33 vs. 1.57 per 100 person-years; HR, 0.21). These findings suggest that antiviral therapy can lead to a reduction in clinically meaningful events even in patients with moderate viremia without significant ALT elevation. Building on the randomized evidence from the ATTENTION trial within the 4–8 $\log_{10}$ IU/mL range, together with the preceding observational cohort data and the guideline revision committee's own systematic review and meta-analysis, antiviral therapy is recommended in patients with CHB and moderate viremia to minimize the risks of liver disease progression and HCC, regardless of ALT levels or other risk factors.

[Recommendation]

1. In patients with moderate viremia (serum HBV DNA ≥2,000 IU/mL and ≤8 $\log_{10}$ IU/mL), antiviral therapy is recommended, as they are at high risk for liver disease progression and HCC. (B1)

Low viremic phase

Low viremic phase is defined as a serum HBV DNA level <2,000 IU/mL and generally includes patients traditionally classified as being in the inactive phase. In patients with low viremia and no evidence of advanced fibrosis, a favorable prognosis is generally observed even without antiviral therapy.[191] According to recent large-scale cohort studies from Korea and other countries, among non-cirrhotic, treatment-naïve patients with CHB and ALT levels ≤2× ULN, those with low viremia—along with those with high viremia—have a lower risk of HCC.[63,64] However, even in patients with low HBV DNA levels (<2,000 IU/mL), the presence of markers suggestive of advanced fibrosis, such as elevated FIB-4 or APRI, has been associated with an increased risk of liver-related complications, including HCC.[55,57,60,220] Nevertheless, there is currently insufficient evidence to support that antiviral therapy improves clinical outcomes, including HCC prevention, in these patients. In a recent multicenter retrospective study from China evaluating the preventive effect of antiviral therapy on HCC among HBeAg-negative patients with normal ALT, no advanced fibrosis, and HBV DNA levels <2,000 IU/mL or 2,000–20,000 IU/mL, no significant benefit was observed in either group.[89] Similarly, in a systematic review and meta-analysis conducted by the guideline revision committee (Key Question 2), seven studies assessed the effect of antiviral therapy in patients with low viremia. The annual incidence of HCC was 0.33 and 0.29 per 100 person-years in the treated and untreated groups, respectively (incidence rate ratio, 1.13), indicating no significant difference between the two groups.

A subset of patients with low viremia may experience fluctuations between reactivation to active hepatitis with ALT elevation and the inactive phase.[45] Therefore, careful assessment of fibrosis stage and the presence of cirrhosis is warranted in these patients, along with regular monitoring of serum ALT and HBV DNA levels to confirm the per-

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sistence of the inactive phase. In patients with low viremia who have no evidence of fibrosis but exhibit persistent ALT elevation, alternative causes of ALT elevation should be evaluated, including MASLD and coexisting viral infections such as hepatitis C or hepatitis D.

Patients with low viremia are known to progress to HBsAg loss, the functional cure of hepatitis B, at an annual rate of approximately 1–2%.[50,221] This rate has been reported to increase to as high as 7% per year in older individuals or in those with low baseline HBsAg levels (e.g., <100 IU/mL or <250 IU/mL).[222,223] These rates are substantially higher than the annual HBsAg loss rates reported in patients receiving antiviral therapy (≤0.33% per year).[224,225] In prior studies of patients with low viremia, pegylated interferon–based therapy has been suggested to induce HBsAg loss.[226,227] However, the magnitude of this effect varied considerably depending on study design, and RCTs have demonstrated relatively modest rates of HBsAg loss. Furthermore, most of this evidence is limited to combination regimens including pegylated interferon and therefore may not be generalizable to clinical benefits such as HBsAg loss achieved with currently used NA monotherapy.

Therefore, when currently available NA monotherapy is applied to patients with low viremia, the clinical benefits—including functional cure, such as HBsAg loss, or prevention of HCC—are likely to be limited. Accordingly, the decision to initiate treatment should be made cautiously, taking into comprehensive consideration the degree of liver fibrosis, patterns of ALT changes, and coexisting conditions in each individual patient.

[Recommendation]

1. In patients with low viremia (serum HBV DNA <2,000 IU/mL), cirrhosis should be assessed, and if absent, patients should be monitored without antiviral therapy while alternative causes of liver disease are evaluated in the presence of ALT elevation. (B1)

Compensated cirrhosis

In patients with compensated cirrhosis, antiviral therapy has been shown in multiple studies, including meta-analyses, to reduce the risk of liver disease progression and HCC.[182] Studies with repeat liver biopsy have also demonstrated improvement in liver fibrosis.[228,229] Patients with cirrhosis often have normal or only mildly elevated ALT levels, and the risk of complications remains high even when ALT is within the normal range.[230] Therefore, in patients with evidence of active viral replication, antiviral therapy is recommended regardless of ALT levels. Cirrhosis is the most important risk factor for HCC. Even when virologic response is achieved with antiviral therapy, patients with cirrhosis remain at risk for HCC and require regular surveillance.[231]

In patients with compensated cirrhosis, active viral replication has traditionally been defined using the same threshold as in patients with chronic hepatitis, namely a serum HBV DNA level ≥2,000 IU/mL. However, in patients with compensated cirrhosis who have low viremia (<2,000 IU/mL), the evidence is inconsistent regarding whether their clinical outcomes differ from those with persistently undetectable HBV DNA and whether antiviral therapy confers clinical benefit.[231-237] Some studies have reported that, in patients with compensated cirrhosis and low viremia, the risks of HCC and liver-related complications may be higher than in those with undetectable HBV DNA, regardless of antiviral treatment status.[231-234,238] In contrast, a Korean study of 567 untreated patients with compensated cirrhosis found that intermittent low viremia was not associated with an increased risk of HCC, complications, or mortality compared with persistently undetectable HBV DNA.[235] Similarly, in a study including more than 2,300 patients with compensated cirrhosis from Korea, Singapore, and Japan, untreated patients with low viremia did not show a significant difference in the risk of complications or HCC compared with those with undetectable HBV DNA, whether achieved spontaneously or during antiviral therapy.[236]

Nevertheless, given the high risk of HCC in patients with compensated cirrhosis, the well-established long-term safety of currently available NAs, and the substantial risk of hepatic decompensation in the event of hepatitis flare, a more proactive treatment strategy is warranted. Accordingly, in patients with compensated cirrhosis, antiviral therapy is recommended in those with active viral replication (serum HBV DNA ≥2,000 IU/mL) and those with low viremia (<2,000 IU/mL) if HBV DNA is detectable. Further high-quality studies are needed to assess the risk–benefit of antiviral therapy in patients with advanced fibrosis or cirrhosis and low viremia.

[Recommendation]

1. In patients with compensated cirrhosis, antiviral therapy is recommended if serum HBV DNA is detectable, regardless of the level of viremia (HBV DNA ≥2,000 IU/mL [A1]; <2,000 IU/mL [B1]).

Decompensated cirrhosis

Decompensated cirrhosis is defined by the presence of cirrhosis-related complications such as ascites, variceal bleeding, hepatic encephalopathy, or jaundice.[239] Patients with decompensated cirrhosis should be managed at centers capable of providing comprehensive care for these complications and should be evaluated for liver transplantation. In this population, oral antiviral therapy improves hepatic function, reduces the need for transplantation, and favorably alters the natural course of the disease.[240-244] However, even with antiviral therapy, time is required to achieve virologic response and clinical improvement, and in some patients with severely impaired liver function, recovery may not occur and progression to liver failure may necessitate liver transplantation.[245,246] Patients with decompensated cirrhosis have a particularly high risk of liver failure in the setting of HBV reactivation; therefore, prompt initiation of antiviral therapy is warranted even in the presence of low-level viremia. Accordingly, antiviral therapy should be initiated promptly when serum HBV DNA is detectable, regardless of the level of viral replication.

[Recommendation]

1. In patients with decompensated cirrhosis, antiviral therapy should be initiated when serum HBV DNA is detectable, and liver transplantation should be considered in the event of progression to liver failure. (A1)

THERAPEUTIC AGENTS

The selection of an antiviral agent should be based on a comprehensive evaluation of several factors: patients-related factors, short-term objectives (undetectable serum HBV DNA, the incidence of drug resistance and adverse events), long-term objectives (functional cure), and the long-term goal (efficacy in reducing HCC, decompensation and liver-related mortality).

Currently approved and clinically available antiviral agents include oral NAs—TAF, TDF, ETV, besifovir dipivoxil maleate (BSV), lamivudine, telbivudine, clevudine, and adefovir—as well as the injectable pegylated interferon-alpha (Peg-IFNα). Peg-IFNα has the advantage of a finite treatment duration and the potential for sustained response even after cessation of therapy, provided a therapeutic response is elicited. However, it is limited by the inconvenience of injection, a high frequency of drug-related adverse effects, and overall suboptimal treatment responses. Furthermore, it is contraindicated in patients with liver decompensation or severe heart disease. Notably, the efficacy of Peg-IFNα therapy varies significantly according to the HBV genotype. In genotype C, which accounts for the vast majority of CHB cases in South Korea, treatment outcomes are particularly poor (HBeAg loss rates: 40–47% for genotype A, 30–44% for B, vs. 20–30% for C; HBsAg loss rates: 14–17% for genotype A, 7–9% for B, vs. 1–3% for C).[247-249] Additionally, limited accessibility due to its current unavailability in the domestic market poses a challenge. Therefore, Peg-IFNα is difficult to recommend as a first-line treatment for hepatitis B in South Korea. Although Peg-IFNα may be selectively considered for pediatric patients or those with HDV coinfection.

Although most oral NAs can achieve undetectable serum HBV DNA, the incidence of drug resistance during NA treatment varies significantly among different agents. Oral antivirals with a high risk of developing resistance are classified as having a low genetic barrier. This group includes lamivudine, telbivudine, clevudine, and adefovir, which are no longer recommended as first-line therapies for CHB. In contrast, agents with a negligible or very low risk of resistance are categorized as having a high genetic barrier. This category includes TAF, TDF, ETV, and BSV. Due to their high rates of achieving HBV DNA undetectability and their minimal risk of long-term resistance, these agents are currently recommended as the preferred first-line treatments. Although not based on direct head-to-head comparative studies, the administration methods, therapeutic clinical outcomes, and preferred clinical scenarios for each agent are summarized in Table 5.

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Patient comorbidities or conditions to consider when selecting antiviral agents

Patients with renal impairment or metabolic bone disorders

Long-term administration of TDF may lead to a decrease in bone mineral density (BMD) and has been associated with adverse effects such as acute or chronic renal failure, hypophosphatemia, and Fanconi syndrome. Therefore, TDF is not recommended for patients with underlying renal dysfunction or risk factors for bone metabolism diseases; instead, TAF, ETV, or BSV are recommended.[250-252] Patients with CHB who are at high risk for osteoporosis include those on chronic steroid therapy, those taking concomitant medications that may adversely affect BMD, and patients with osteopenia. Patients at risk for renal dysfunction include those with a baseline glomerular filtration rate (GFR) <60 mL/min/1.73m², proteinuria or albuminuria (urine albumin-to-creatinine ratio >30 mg/g), hypophosphatemia (<2.5 mg/dL), uncontrolled diabetes or hypertension. When administering these antiviral agents to patients with renal impairment, dosage adjustments are required for TDF, ETV, and BSV according to their renal function. For TAF, no dosage adjustment is required for patients with renal impairment, including those on dialysis. However, its use is not recommended in patients with a GFR <15 mL/min/1.73m² who are not undergoing hemodialysis. BSV is not recommended for patients with a creatinine clearance <15 mL/min/1.73m² due to insufficient clinical data. Detailed protocols regarding renal decline or bone metabolism disorders emerging during treatment are described in the "Monitoring During Antiviral Therapy" section.

Antiviral treatment status: Naive vs. Experienced

Reports of resistance to TAF and TDF are extremely rare. Therefore, tenofovir-based regimens are prioritized for patients with existing drug resistance or a risk of resistance. Genotypic resistance to ETV is rare in treatment-naïve patients, with a reported cumulative resistance rate of only 1.2% after five years.[253] However, in patients with prior Lamivudine experience, the resistance rate to ETV was significantly higher, reaching 6% after one year and exceeding 50% after five years.[253-255] Therefore, ETV should be avoided whenever possible in patients with confirmed lamivudine resistance or those previously treated with lamivudine, adefovir, or telbivudine. If ETV must be used, the dose should be doubled to 1 mg/day.[256,257] In patients who previously discontinued ETV, the drug may be reintroduced provided that complete viral suppression was maintained, and no resistance was suspected during the previous treatment period. However, switching to tenofovir can also be considered to minimize the potential risk of drug resistance development.

Women of childbearing potential, pregnant, or lactating

When initiating antiviral therapy in patients planning for pregnancy or those who are pregnant, the choice of medication must be made cautiously, considering the safety of the fetus and the mother. In this condition, TAF or TDF is recommended. Sufficient data regarding the use of TAF and TDF during pregnancy have been accumulated, primarily from HIV-positive patient cohorts and HBV-infected mothers, supporting their safety for use in pregnant women and fetus.[258] Conversely, ETV is not recommended for pregnant women due to the potential for increased teratogenicity observed in animal studies. BSV is also not recommended due to a lack of clinical data in this population. Detailed information regarding the management of CHB in this population is provided in the section "Treatment in Special Situations (Pregnant Patients or Patients Planning Pregnancy)."

Long-term outcomes of specific agents for informed treatment selection

The achievement rate of functional cure, defined as the loss of HBsAg (with or without the acquisition of anti-HBs), is very low at approximately 1–5% for the four primary medications recommended in these guidelines.[258-261] And, there is a lack of studies directly comparing the functional cure rates between these specific agents. In a network meta-analysis of RCTs (42 studies, 921 patients), there were no significant differences in the HBsAg loss rates among ETV, TDF, and TAF.[262] Furthermore, a recent Korean multicenter study compared ETV and TDF with adjusted variables; the results showed no significant difference in the functional cure rate (HBsAg loss) between the two groups during a median follow-up period of 5.5 years (2.8% vs. 1.9%).[263]

Regarding the preventive effects of TDF and ETV against HCC in CHB, conflicting results have been reported in do-

Table 5. Instruction, efficacy, and preferred conditions of high genetic barrier NAs

NAs	TAF	TDF	ETV	BSV
Dosage and administration instructions				
Dosage and frequency	25 mg once daily regardless of meal	300 mg once daily regardless of meal	0.5 mg once daily on an empty stomach	150 mg with L-carnitine 550 mg once daily regardless of meal
HBeAg positive (2-year efficacy)				
Undetectable HBV DNA (%)	73 (<29 IU/mL)	75 (<29 IU/mL)	70–80 (<60 IU/mL)	64–81 (<69 IU/mL)
HBeAg loss (%)	22	18	39	14–21
HBeAg seroconversion (%)	18	12	31–33	8–21
ALT normalization (%)	75	68	82–87	64–79
HBsAg loss (%)	1	1	4–5	0
HBsAg seroconversion (%)	1	0	2	0
HBeAg negative (2-year efficacy)				
Undetectable HBV DNA (%)	90 (<29 IU/mL)	91 (<29 IU/mL)	91–95 (<60 IU/mL)	97 (<29 IU/mL)
ALT normalization (%)	81	71	78–88	88
HBsAg loss (%)	<1	0	0–1	0
HBsAg seroconversion (%)	<1	0	0	0
Preferred conditions				
Bone disease	Recommended	Not recommended	Recommended	Recommended
Renal disease	Recommended	Not recommended	Recommended	Recommended
Pregnancy or preparing pregnancy	Recommended	Recommended	Not recommended	Not recommended
Treatment experienced	Recommended	Recommended	Not recommended	Not recommended

ALT, alanine aminotransferase; BSV, besifovir dipivoxil maleate; CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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mestic and international studies. In 2019, a study utilizing data from a single domestic institution and National Health Insurance Service (NHIS) claims reported that after propensity score matching, the TDF group showed a significantly lower risk of developing HCC compared to the ETV group, with HRs of 0.68 and 0.62, respectively.[264] Subsequently, several follow-up studies, domestically and internationally, have presented conflicting findings regarding the difference in HCC risk between the two agents,[265-269] and meta-analyses have also reported inconsistent results.[270,271] In a meta-analysis utilizing individual patient data, the difference in the risk of developing HCC between the TDF and ETV groups was particularly pronounced among patients who were aged 50 or older, male, and HBeAg-positive.[272] Furthermore, research findings regarding the risk of HCC for newer agents, including TAF and BSV, have recently been published.[273-275] Therefore, as controversy persists regarding whether long-term outcomes, such as the incidence of HCC, differ by specific agent, the Clinical Practice Guideline Revision Committee conducted a systematic review and meta-analysis (Key Question 3) targeting the four primary medications. This systematic review and meta-analysis included 37 studies involving 243,577 patients. Compared to the ETV group, the risk of developing HCC was significantly lower in the following groups: TAF group (HR, 0.65; 95% confidence interval [CI], 0.49–0.86), TDF group (HR, 0.80; 95% CI, 0.70–0.91), BSV group (HR, 0.46; 95% CI, 0.28–0.74). However, since most of the studies included in the meta-analysis were retrospective cohort studies with a moderate level of evidence for tenofovir and low level evidence for BSV, there remains insufficient justification to strongly recommend the use of TAF, TDF, or BSV over ETV for the purpose of HCC prevention. Furthermore, although reducing the risk of HCC is one of the most critical goals of antiviral therapy, the selection of an antiviral agent must involve a comprehensive evaluation of other therapeutic objectives and the potential risk of adverse events.

In contrast, some reports suggest that antiviral therapy may also reduce the risk of developing extrahepatic malignancies.[276] Although one study indicate a potential difference in the risk reduction between ETV and tenofovir,[277] other contradictory report showed no such difference.[263] Consequently, there is insufficient evidence to determine whether the reduction in the risk of extrahepatic malignancies should be an additional consideration when selecting an antiviral agent for CHB.

[Recommendation]

1. For treatment-naive patients with CHB, oral antiviral agents with a high genetic barrier—specifically TAF, TDF, ETV, and BSV—are recommended as first-line therapy (A1).
2. When selecting a therapeutic agent, TAF, ETV, or BSV are preferentially recommended for patients who have pre-existing renal impairment or bone metabolic disease (A1), as well as for those at an increased risk of developing such conditions (B1).
3. In patients previously exposed to lamivudine, adefovir, or telbivudine, TAF or TDF is recommended (A1). Similarly, TAF or TDF is recommended for patients who are pregnant or planning to become pregnant (A1).

NEW DRUGS FOR A FUNCTIONAL CURE

The ideal goal of the treatment of CHB is a “sterilizing cure,” characterized by the complete eradication of HBsAg and HBV DNA from the serum, alongside the total elimination of cccDNA and integrated HBV DNA from the host genome. This state would essentially restore the patient to a pre-infection biological status. However, achieving this remains elusive due to current technological and pharmacological limitations.[278]

Consequently, the medical community has shifted its focus toward a more realistic alternative endpoint: “functional cure.” Functional cure is defined as the sustained loss of HBsAg and undetectable HBV DNA in the serum, regardless of whether anti-HBs seroconversion occurs. Although cccDNA and integrated HBV DNA may persist in the liver during this stage, it represents a state of successful immunological control—functionally analogous to the recovery seen after AHB infection.[278,279] Despite this, existing standard-of-care therapies, including NAs and Peg-IFNα, rarely induce satisfactory rates of HBsAg loss.[280] To bridge this therapeutic gap, various novel agents with diverse mechanisms of action are currently undergoing clinical trials (Supplementary Table 4). These agents are generally cate-

gorized into two strategies: those directly targeting the HBV life cycle and those aimed at augmenting the host's immune response (Fig. 3). Given that NA, with its proven efficacy and safety, has been established as the standard treatment, these new drugs must possess a significant HBsAg elimination effect and good tolerability.

Direct-acting antiviral agents

Direct-acting antivirals (DAAs) aim to suppress the viral life cycle by reducing viral antigens and genomic templates, thereby facilitating a decline in cccDNA activity or HBsAg levels.

RNA targeted therapeutics

Viral RNA serves as the essential template for the synthesis of all HBV antigens and proteins. By degrading or interfering with these RNA transcripts, these agents can inhibit viral replication and HBsAg production, potentially restoring HBV-specific immune responses.[281] Currently, antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are the primary modalities in this class. ASOs are 15–20-nucleotide-long single-stranded DNA oligomers, that binds complementarily to target viral RNA, triggering degradation via ribonuclease H. Furthermore, siRNAs are double-stranded RNA molecules (20–25 nucleotides) that utilize the RNA-induced silencing complex (RISC) to degrade target mRNA.[282,283]

Clinical trials of agents like bepirovirsen and xalnesiran have demonstrated functional cure rates of up to 10% and 23%, respectively.[284,285] Safety considerations include potential vehicle toxicity (using lipid nanoparticles or GalNAc-conjugates), off-target effects, and the risk of reactivation from residual cccDNA.[286] Clinicians should also be vigilant for ALT flares during treatment, which resemble acute hepatitis episodes.[287]

Other novel approaches include inhibitors of PAPD5/7, host enzymes that protect HBV RNA from degradation.[288]

DNA transcription inhibitors

These agents inhibit the transcription of viral DNA into RNA. Farnesoid X receptor (FXR) agonists are being explored in this context; although FXR primarily regulates bile acid homeostasis, it also modulates HBV transcription

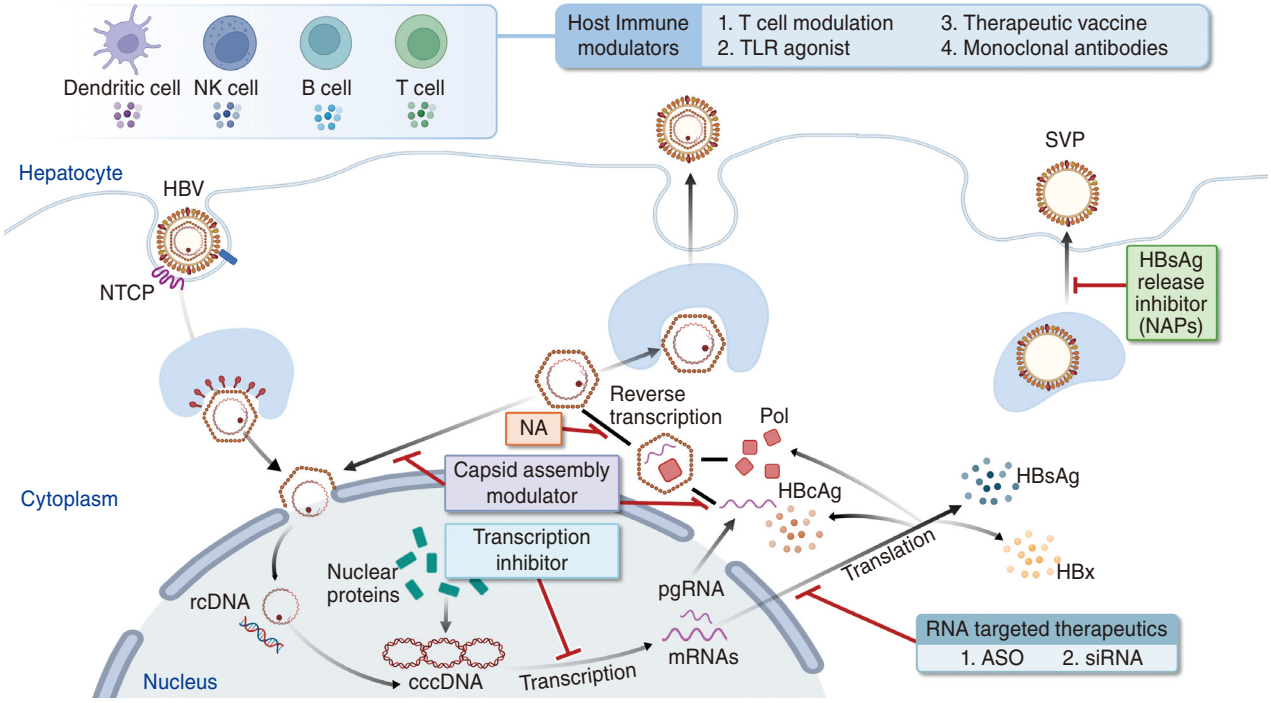

Figure 3. Mechanisms of novel antiviral agents for the functional cure. ASO, antisense oligonucleotide; cccDNA, covalently closed circular DNA; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; NA, nucleos(t)ide analogue; NAPs, nucleic acid polymers; NK, natural killer; NTCP, sodium taurocholate co-transporting polypeptide; Pol, polymerase; rcDNA, relaxed circular DNA; siRNA, small interfering RNA; SVP, subviral particle; TLR, toll-like receptor.

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through interactions with the enhancer II/core promoter regions and the HBV X protein.[289]

Capsid assembly modulator/core inhibitor

The HBV core protein (183–185 amino acids) is vital for nucleocapsid assembly and the packaging of pregenomic RNA. Capsid assembly modulators (CAMs) disrupt this process, preventing the synthesis of relaxed circular DNA and the replenishment of the cccDNA pool in the nucleus.[290,291] They are categorized into CAM-A (inducing aberrant, non-capsid structures) and CAM-E (forming "empty" capsids devoid of genetic material). Although CAMs significantly reduce serum HBV DNA, their impact on HBsAg levels is limited, making them unlikely to achieve functional cure as monotherapy.

HBsAg release inhibitor

These agents, primarily nucleic acid polymers (NAPs), inhibit the assembly and secretion of subviral particles. By reducing the circulating HBsAg burden, they may alleviate "immune exhaustion" and enhance HBV-specific immunity.[292] Notably, NAPs have shown significant efficacy in treating HBV/HDV coinfection, positioning them as a potential therapeutic agent for hepatitis D.[293]

Immune modulators

A primary mechanism of CHB is the evasion or neutralization of the host's immune surveillance, often manifesting as "immune tolerance" or "T-cell exhaustion." Immune modulators aim to reverse this suppressive state.

T cell modulation

This strategy involves immune checkpoint inhibitors (ICIs), such as anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies (e.g., nivolumab, envafolimab), along with other modulators designed to reactivate exhausted T cells. Recent research also explores degrading inhibitor of apoptosis proteins (IAPs) to promote the clearance of infected hepatocytes and boost virus-specific T-cell counts. [294,295]

Toll-like receptor agonist

Toll-like receptors (TLRs) are critical components of the innate immune system that detect pathogen-associated molecular patterns. Agonists for TLR-7 and TLR-8 (e.g., selgantolimod) are being evaluated for their ability to induce interferon production and stimulate therapeutic cytokine release.[296-298]

Therapeutic vaccine

Unlike preventative vaccines, therapeutic vaccines use various HBV antigens (HBsAg, HBcAg, pre-S1, pre-S2) to stimulate an active, virus-specific immune response in patients with CHB. Although early HBsAg-only vaccines showed limited efficacy, next-generation multi-antigen vaccines are currently in development.[299,300]

Monoclonal antibodies

HBV-specific monoclonal antibodies neutralize virions directly and potentially induce broader T-cell and B-cell responses through passive immunization, representing a novel therapeutic strategy for functional cure.[301,302]

Combination treatment

Despite the promise of these novel agents, clinical data indicate that monotherapy over a limited duration is generally insufficient to achieve high rates of HBsAg loss. Consequently, current research is gravitating toward combination regimens involving NAs, Peg-IFNα, and one or more novel classes. The prevailing hypothesis is that functional cure requires a synergistic approach: potent suppression of viral replication and a significant reduction in HBsAg levels must precede or accompany the restoration of long-term HBV-specific T-cell and B-cell immunity.[52] The optimal combination regimen remains to be elucidated through forthcoming clinical investigations.

TREATMENT RESPONSE AND MONITORING DURING ANTIVIRAL THERAPY

Definitions of antiviral treatment response and monitoring

Definitions of treatment response

Virologic response is defined as undetectable serum HBV DNA by real-time PCR assay (Table 6). Maintained virologic response refers to sustained undetectable serum

HBV DNA during follow-up after achieving virologic response. Partial virologic response is defined as a decrease in serum HBV DNA that remains detectable using a real-time PCR assay. In patients with good adherence, partial virologic response can be assessed at week 24 for agents with a low genetic barrier and at week 48 for those with a high genetic barrier, based on HBV DNA detectability. Serologic response is defined in two ways depending on the antigen type. HBeAg serologic response refers to HBeAg loss or HBeAg/anti-HBe seroconversion in patients with HBeAg-positive CHB, whereas HBsAg serologic response is defined as HBsAg loss or HBsAg/anti-HBs seroconversion. Virologic breakthrough is defined as an increase in serum HBV DNA by more than 1 $\log_{10}$ IU/mL from the lowest level during antiviral therapy, or re-detection of HBV DNA after having been undetectable. It generally precedes biochemical breakthrough. Biochemical response refers to normalization of ALT to within the ULN, whereas biochemical breakthrough is defined as re-elevation of ALT above the ULN after having been normalized during antiviral therapy.

Monitoring during antiviral therapy

Persistent viral replication during antiviral therapy is a risk factor for disease progression and the development of drug-resistant mutations.[303] Monitoring serum HBV DNA during treatment allows assessment of virologic response and enables modification of the treatment strategy; therefore, serum HBV DNA should be measured every 1–6 months during therapy. Even when HBV DNA levels are ≤2,000 IU/mL during treatment, patients with persistently or intermittently detectable HBV DNA have a higher risk of HCC than those with consistently undetectable levels, and thus require close monitoring.[231] Accordingly, HBV DNA should continue to be measured every 3–6 months even after a virologic response has been achieved. It is recommended that serum HBV DNA be suppressed to below the lower limit of detection by real-time PCR assay.[304] Patients who receive long-term antiviral therapy have been reported to have a significantly lower risk of HCC development compared with untreated patients.[178,305] However, the risk of HCC is not completely eliminated despite prolonged antiviral therapy, as multiple factors—including underlying liver disease status, age, sex, alcohol consumption, and metabolic comorbidities, in addition to inflammation and fibrosis caused by viral hepatitis—contribute to hepatocarcinogenesis. Therefore, regular surveillance for HCC using serum AFP measurement and liver ultrasonography should be performed every 6 months during antiviral therapy.[306,307]

The degree of HBV DNA reduction during treatment is proportional to the degree of HBsAg decline.[308] A low baseline quantitative HBsAg level or a rapid decline in HBsAg levels after 24 weeks of therapy has been reported as a predictor of virologic response.[309-311] Baseline HBsAg <1,000 IU/mL and an annual decline in HBsAg >0.166 $\log_{10}$ IU/mL were each associated with HBsAg seroclearance.[312] Furthermore, a low HBsAg level of approximately 10–200 IU/mL at the end of treatment has been shown to be associated with sustained virologic response and HBsAg loss after treatment discontinuation.[152,313-316] These findings suggest that quantitative HBsAg measurement is useful for monitoring patients receiving oral antiviral agents.

Since one of the goals of antiviral therapy in patients with CHB is to slow or reverse the progression of fibrosis, non-

Table 6. Definition of response to antiviral therapy for chronic hepatitis B

Virologic response	Decrease in serum HBV DNA to undetectable level by real-time PCR assay
Partial virologic response	Decrease in serum HBV DNA of more than 2 $\log_{10}$ IU/mL but detectable HBV DNA by real-time PCR assay after at least 12 months of therapy with high-potency NAs, or after at least 6 months of therapy with low-potency NAs in compliant patients
Virologic breakthrough	Increase in serum HBV DNA of more than 1 $\log_{10}$ IU/mL compared to nadir (lowest value) or detection of serum HBV DNA in patients with undetectable serum HBV DNA level
HBeAg serologic response	HBeAg loss or HBeAg seroconversion
HBsAg serologic response	HBsAg loss or HBsAg seroconversion
Biochemical response	Normalization of ALT level
Biochemical breakthrough	Increase in serum ALT level >ULN after ALT normalization on antiviral therapy

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; PCR, polymerase chain reaction; ULN, upper limit of normal.

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invasive measurement of liver stiffness can be useful for evaluating treatment response and prognosis.[317-319] In CHB patients with histologically confirmed fibrosis of F3 or greater and HBV DNA ≥2,000 IU/mL who underwent annual liver stiffness measurement by transient elastography during antiviral therapy, the mean liver stiffness value decreased progressively from a baseline of 14.5 kPa to 8.3 kPa after 5 years; furthermore, patients with lower baseline liver stiffness (<12.0 kPa) were more likely to achieve significant fibrosis improvement (<7.2 kPa).[318] Non-invasive liver stiffness measurement may also assist in predicting the risk of future HCC development in patients with CHB. HCC risk models incorporating liver stiffness values have demonstrated superior predictive performance compared with conventional models.[320-322] With the widespread use of antiviral agents with a high genetic barrier, effective suppression of HBV DNA is now commonly achieved; thus, liver stiffness, which reflects the degree of fibrosis, may serve as a more important prognostic indicator.[320] Although non-invasive fibrosis assessment may be performed at intervals of 24 months in patients with mild to moderate fibrosis, further studies are needed to determine the optimal monitoring interval. Additionally, it should be noted that the accuracy of non-invasive fibrosis tests may be reduced in the setting of active hepatic inflammation, and results should therefore be interpreted with caution.[323]

Most oral antiviral agents are primarily excreted through the kidneys. Therefore, dose adjustment is required when administering antiviral agents other than TAF in patients with impaired renal function, and regular monitoring of kidney function is recommended. In particular, treatment with adefovir or TDF may lead to a decline in GFR,[324,325] and this risk is further increased in older patients or those receiving concomitant diuretics.[326] Renal impairment occurring during TDF therapy may be partially reversible upon switching to ETV or TAF.[251,327,328] In an extension study of a phase 3 clinical trial comparing BSV with TDF, the change in GFR during 48 weeks of TDF treatment was –7.8 mL/min; however, upon switching to BSV, the change in GFR was –0.8 mL/min at 144 weeks, indicating partial recovery to baseline levels.[329] Long-term TDF therapy may impair renal function and interfere with phosphate reabsorption, thereby increasing the risk of hypophosphatemia, decreased BMD, and osteoporosis.[325] In a recent large retrospective study, patients treated with TDF had a significantly higher risk of fractures compared with those treated with ETV.[330] This difference was particularly pronounced in patients aged 60 years or older and became apparent after 2 years of antiviral therapy. In contrast, TAF was associated with significantly smaller reductions in BMD and GFR, as well as a significantly lower risk of fracture, compared with TDF.[331-333] Improvements in GFR and BMD were observed in patients who switched from TDF to TAF.[334] In another extension study of a phase 3 clinical trial comparing BSV with TDF, patients in the TDF group showed changes in spinal and hip BMD of –1.12% and –0.62%, respectively, at week 48; however, upon switching to BSV with an additional 48 weeks of treatment, BMD recovered to baseline levels, with no significant difference compared with the group that continued BSV.[335] Therefore, regular follow-up including assessment of renal function, BMD, and serum phosphate levels is recommended in patients receiving adefovir or TDF. If a decline in GFR, osteoporosis, or hypophosphatemia is identified, switching to TAF, ETV, or BSV is recommended. However, in patients with prior exposure to low genetic barrier agents such as lamivudine, the use of ETV is not recommended due to an increased risk of resistance.[336]

According to several large cohort studies and meta-analyses, TAF has been associated with greater increases in serum lipid levels compared with TDF-based therapy. In a real-world cohort of more than 6,400 patients who switched from TDF to TAF, low-density lipoprotein cholesterol levels increased steadily over approximately 9 months, whereas triglyceride levels increased over 9–16 months and then plateaued.[337] Meta-analyses have shown that TAF is associated with an increased risk of dyslipidemia compared with TDF and ETV, particularly in patients with CHB who have comorbid diabetes or hypertension.[338,339] However, recent studies have not identified a significant difference in the risk of major adverse cardiovascular events between TAF and TDF.[340-342] In a nationwide cohort study conducted in Korea, TAF did not increase the risk of cardiovascular events compared with TDF, and some analyses even reported a trend toward lower risk with TAF.[340,343] Furthermore, a pooled analysis of two RCTs showed that, despite differences in lipid levels, there were no significant differences between the two agents in terms of predicted 10-year cardiovascular risk or the incidence of actual cardiovascular events.[341] Based on the current evidence, the association of TAF therapy with a definite increase in the

risk of cardiovascular events remains unclear. Nevertheless, further long-term follow-up studies addressing cardiovascular risk are warranted. Given the nature of CHB requiring long-term treatment, continuous assessment of lipid profiles and cardiovascular risk is recommended in patients with underlying metabolic risk factors.

[Recommendation]

1. Regular surveillance for HCC using serum AFP measurement and liver ultrasonography should be performed every 6 months during antiviral therapy. (A1)
2. During antiviral therapy, liver function and serum HBV DNA should be tested at intervals of 1–6 months. Quantitative HBsAg testing may be performed annually to predict treatment response and guide decisions on treatment cessation. (B1)
3. Even after achieving a virologic response, serum HBV DNA may be monitored every 3–6 months, and non-invasive fibrosis assessment may be performed every 12–24 months. (B1)
4. Renal function should be monitored regularly during antiviral therapy. (A1) In patients receiving TDF, renal function, serum phosphate levels, and BMD should be monitored periodically. If a decline in GFR, hypophosphatemia, or osteoporosis occurs, switching to TAF, ETV, or BSV is recommended. (A1) However, ETV is not recommended in patients with prior exposure to other antiviral agents. (A1)

Management of antiviral resistance and partial virologic response

Management of antiviral resistance

Although the risk of antiviral drug resistance has substantially decreased with the use of agents with a high genetic barrier such as ETV and tenofovir as first-line therapy, it remains an important factor that can significantly influence treatment outcomes. When antiviral resistance emerges, previously suppressed HBV replication resumes, serum liver enzyme levels that had improved begin to rise, and liver disease progression recommences. Therefore, early detection and appropriate management are crucial. Once amino acid substitutions occur, the viral genome becomes more prone to additional mutations and may lead to cross-resistance, thereby substantially limiting subsequent antiviral treatment options and treatment efficacy.[344] Moreover, even when switching to agents without cross-resistance, the rate of resistance to subsequent therapy is generally higher than that observed in treatment-naïve patients.[344-346] Therefore, selecting antiviral agents with a low risk of resistance at the initiation of therapy is crucial for preventing the development of resistance mutations.

When virologic breakthrough occurs in patients with CHB receiving antiviral therapy, adherence to the prescribed regimen should be assessed first. A substantial proportion of virologic breakthroughs are attributable to poor adherence, and patients with low adherence have worse clinical outcomes compared with those with good adherence. In a study of 894 treatment-naïve patients receiving ETV with a median follow-up of 5.4 years, the mean adherence rate was 89.1%, and those with poor adherence had significantly higher rates of HCC, cirrhosis-related complications, and mortality.[347] Once adherence has been confirmed, genotypic resistance testing may be considered. However, resistance testing is time-consuming, and if serum HBV DNA levels are insufficient for amplification and sequencing, results may not be obtainable. Delays in switching antiviral therapy resulting from this limitation may increase the risk of clinical deterioration. Therefore, in patients with confirmed virologic breakthrough and suspected drug resistance despite good adherence, it is reasonable to switch promptly to an antiviral agent with a high genetic barrier without waiting for the results of genotypic resistance testing, to avoid delays in rescue therapy. When a patient whose HBV DNA had previously been undetectable experiences a virologic breakthrough with HBV DNA rising to ≥60 IU/mL, this may be regarded as an early sign of virologic breakthrough.[348,349] To avoid unnecessary delays due to the technical limitations of resistance testing, immediate switching to tenofovir without awaiting resistance test results is a clinically reasonable strategy in such patients.

For resistance to nucleoside analogues, including lamivudine, telbivudine, clevudine, and ETV, switching to tenofovir monotherapy is recommended. In patients with lamivudine resistance, TDF monotherapy achieved a serum HBV DNA undetectable rate (<69 IU/mL) of 89.4% at week 96, which was not significantly different from that of combination therapy with TDF and emtricitabine (86.3%).[350] Although data on the management of resistance to telbivudine and clevu-

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dine are limited, their resistance mutation profiles are highly similar to that of lamivudine; therefore, management strategies similar to those for lamivudine resistance are recommended. In an RCT of patients with ETV resistance, the rate of undetectable serum HBV DNA (<15 IU/mL) at week 48 was 71% with TDF monotherapy and 73% with combination therapy using TDF and ETV, with no significant difference between the two groups.[348] In another study, the rates of undetectable serum HBV DNA (<20 IU/mL) at 24 months were 85.4% and 89.2%, respectively, also showing no significant difference.[351] Accordingly, in patients who achieve a virologic response with tenofovir/ETV combination therapy as rescue treatment for drug resistance, switching to tenofovir monotherapy may be considered.[352]

For CHB with resistance to the nucleotide analogue adefovir, switching to tenofovir monotherapy is also recommended. Among adefovir resistance mutations, rtN236T has been reported to reduce susceptibility to tenofovir in vitro; however, it is generally considered to remain susceptible in clinical settings.[353] In an RCT comparing TDF monotherapy with TDF/emtricitabine combination therapy in patients with adefovir resistance or adefovir treatment failure, the rates of undetectable serum HBV DNA (<69 IU/mL) at week 168 were 82% and 84%, respectively, with no significant difference between the two groups.[354] In another RCT of patients with confirmed adefovir resistance, the rates of undetectable serum HBV DNA (<15 IU/mL) at week 48 were 62.0% with TDF monotherapy and 63.5% with combination therapy of TDF and ETV, again showing no significant difference.[355] When participants from two clinical trials, which compared TDF monotherapy versus TDF/ETV combination therapy in patients with ETV or adefovir resistance, were all switched to TDF monotherapy after the initial 48-week period and followed for a further 5 years, the rate of undetectable HBV DNA (<15 IU/mL) was higher than at week 48, despite declines in renal function and BMD.[356] Although data on BSV resistance are limited, rtL180M and rtM204V mutations were identified in patients who experienced virologic breakthrough during BSV therapy; these mutations conferred resistance to ETV but susceptibility to tenofovir was retained.[357] Resistance to tenofovir is extremely rare,[358] and in such cases, the addition of ETV may be considered.

Multidrug resistance has not been clearly defined internationally, but is generally considered to refer to the presence of resistance mutations to two or more antiviral agents from different classes.[344] Studies on the treatment of multidrug resistance are mostly limited by small sample sizes, heterogeneous resistance mutation profiles, and diverse treatment combinations. Although no established standard of care exists, tenofovir monotherapy or tenofovir/ETV combination therapy may be considered. In a prospective multicenter study involving 64 patients with multidrug resistance, combination therapy with TDF and ETV achieved an undetectable serum HBV DNA rate (<12 IU/mL) of 62.5% at 48 weeks.[359] In another prospective multicenter study, no significant difference in virologic response rates was observed between TDF monotherapy and TDF/nucleoside analogue combination therapy.[360] In patients with resistance to ETV or adefovir, the 48-week virologic response rates were 66.3% with TDF monotherapy and 68.0% with TDF/ETV combination therapy, with no significant difference between the two groups.[349] Based on these findings, TDF monotherapy may be considered as a rescue strategy in patients with multidrug resistance.

Management of partial virologic response during antiviral therapy

Persistent viral replication during antiviral therapy for hepatitis B is a risk factor for disease progression and the emergence of drug-resistant mutations. Therefore, periodic measurement of serum HBV DNA using sensitive real-time PCR assays during treatment is necessary to monitor virologic response.

In patients receiving antiviral agents with a low genetic barrier who demonstrate a partial virologic response with confirmed medication adherence, switching to an agent with a high genetic barrier is recommended. In an RCT of patients with a partial response to lamivudine, switching to ETV 1 mg resulted in a serum HBV DNA undetectable rate (<60 IU/mL) of 67.6% at 96 weeks.[361] However, caution is warranted when switching to ETV in patients with prior lamivudine exposure, given the increased risk of ETV resistance in this population.[336] Tenofovir has been reported to achieve excellent antiviral responses regardless of prior lamivudine exposure or resistance.[362] In patients who initiated and are maintained on high genetic barrier agents such as ETV or tenofovir, drug resistance rarely develops even in the presence of a partial virologic response, and further virologic improvement may still occur. Therefore, if serum HBV DNA continues to show a declining trend, continua-

tion of the current regimen with close monitoring is acceptable.[363] If a partial virologic response persists after 12 months of ETV therapy, switching to tenofovir may be considered. In an RCT of patients with a partial response after more than 12 months of ETV therapy, switching to TDF resulted in a serum HBV DNA undetectable rate (<20 IU/mL) of 55% at 12 months, compared with 20% in those who continued ETV.[364] A meta-analysis similarly demonstrated the effectiveness of switching to TDF in this setting.[365]

[Recommendation]

1. When virologic breakthrough or partial virologic response is confirmed during antiviral therapy, medication adherence should be assessed. (A1)
2. In patients with virologic breakthrough and confirmed adherence, switching to tenofovir can be considered regardless of resistance test results if clinical deterioration is a concern while awaiting those results. (B1)
3. In patients with confirmed antiviral resistance, switching to tenofovir monotherapy is recommended. (A1)
4. In patients with partial virologic response, switching to tenofovir monotherapy is recommended. (A1) However, in patients receiving agents with a high genetic barrier with confirmed adherence and no evidence of virologic breakthrough, continuation of the current therapy may be considered. (B1)

TREATMENT CESSATION AND POST-TREATMENT MONITORING

Clinical indicators for treatment cessation

The goal of antiviral therapy in patients with CHB is to achieve sustained suppression of HBV replication, reducing liver-related mortality and improving long-term survival. In principle, this could be accomplished by complete eradication of HBV from the host; however, currently available antiviral agents cannot eliminate cccDNA residing in infected hepatocytes, making viral eradication an unrealistic expectation in clinical practice. Accordingly, the decision to discontinue antiviral therapy must be approached with great caution. In lieu of viral eradication, surrogate endpoints that are readily measurable during treatment and reflective of treatment objectives have been adopted to guide cessation decisions. These include normalization of ALT, undetectable serum HBV DNA, HBeAg loss or seroconversion, and HBsAg loss or seroconversion. Emerging evidence suggests that quantitative serum HBsAg, quantitative HBcrAg, and serum HBV RNA may further aid in predicting sustained treatment response and determining the optimal timing of treatment discontinuation.[184,366]

When antiviral therapy is discontinued prior to HBsAg loss or seroconversion, virological relapse rates range from approximately 20 to 70%, depending on patient characteristics at the time of cessation and the duration of follow-up.[367-371] Several studies have reported that hepatitis flares following treatment discontinuation may paradoxically enhance host immune responses, potentially increasing the likelihood of functional cure defined as HBsAg loss; this phenomenon has been observed more frequently in non-Asian populations.[369,372,373] Nonetheless, the decision to stop therapy should be made judiciously, with consideration of safety and the anticipated likelihood of sustained response. In patients with cirrhosis, treatment cessation carries a substantial risk of acute exacerbation and progression to hepatic decompensation, necessitating a particularly cautious approach; discontinuation of antiviral therapy is not recommended in patients with decompensated cirrhosis.[369,374-377] Recent evidence has also highlighted the influence of HBV genotype on post-cessation outcomes. In the COIN-B study, genotypes C, D, and E were associated with higher rates of virological relapse and acute exacerbation, whereas no severe flares were observed among patients with genotype A.[378] Given that genotype C predominates among CHB patients in Korea, an especially prudent approach to treatment discontinuation is warranted in this population.[249] Notably, the recent EASL guidelines more actively endorse planned discontinuation of NAs in selected non-cirrhotic, HBeAg-negative patients after sustained virological suppression as a strategy to increase the likelihood of HBsAg loss, accompanied by intensive off-treatment monitoring at 1–3-month intervals during the first year.[27] In contrast, given the predominance of genotype C in Korea—a genotype associated with higher rates of virological relapse and severe flares after cessation—and the limited validation of existing predictive models in Korean cohorts, we recommend a more cautious, individualized approach to treatment discontinuation.

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These differences are particularly relevant to functional-cure–oriented strategies, as the controlled off-therapy flare leveraged elsewhere as a potential route to HBsAg loss may be less predictable in genotype C–predominant populations; prospectively validated, genotype-specific stopping criteria are warranted.

ALT normalization

Normalization of ALT during antiviral therapy reflects a reduction in intrahepatic inflammatory activity, typically accompanies the achievement of undetectable HBV DNA, and is associated with a lower risk of clinical deterioration.[379] ALT normalization can serve as a useful indicator for assessing treatment efficacy. However, 14–40% of patients with persistently normal ALT levels have been shown to harbor significant fibrosis (≥F2), and various confounding factors—including MASLD and alcohol-associated liver disease—can independently influence ALT levels.[228] For these reasons, ALT normalization alone has limited value as a sole criterion for treatment cessation.

Undetectable HBV DNA

Serum HBV DNA level is the most robust predictor of disease progression and long-term prognosis in the natural history of CHB.[191,192] During antiviral therapy, HBV DNA levels generally correlate with histological activity, and patients who maintain low HBV DNA levels have fewer episodes of hepatic decompensation and better survival outcomes.[380,381] Antiviral treatment reduces HBV DNA levels, with the degree of histological improvement correlating with the magnitude of viral suppression, which in turn attenuates disease progression and lowers the risk of HCC development. HBV DNA therefore represents a clinically relevant surrogate endpoint that aligns well with the overarching goals of therapy.[381-384] In HBeAg-negative CHB patients who maintain prolonged virological suppression, sustained off-treatment response and higher rates of HBsAg loss have been reported even after treatment discontinuation, lending support to the notion that long-term undetectable HBV DNA may be a reasonable target for guiding cessation decisions. Lower HBV DNA levels are generally associated with a more favorable prognosis; notably, patients with HBV DNA levels between 60 and 2,000 IU/mL exhibit rates of cirrhosis and HCC development comparable to those with undetectable HBV DNA, although definitive thresholds for this low-viremia range remain to be established.[191,192] Furthermore, HBV DNA becomes detectable again in the majority of patients following treatment discontinuation, which limits the utility of undetectable HBV DNA as the sole criterion for stopping therapy.[220,367-369]

HBeAg loss or seroconversion

In HBeAg-positive patients, HBeAg seroconversion is accompanied by ALT normalization and histological improvement and occurs in proportion to the degree of HBV DNA suppression achieved during therapy. Following HBeAg seroconversion, the annual rate of subsequent HBsAg loss increases to approximately 1.15%, making HBeAg loss or seroconversion a meaningful surrogate endpoint in this patient population.[385,386] However, sustained virological response (SVR) after treatment cessation following HBeAg loss or seroconversion is suboptimal, reported at approximately 62.5% at 1 year, 53.4% at 2 years, and 51.5% at 3 years.[387] Moreover, some patients may develop HBeAg-negative hepatitis, HBeAg reversion, or in severe cases, acute exacerbation with jaundice. These observations indicate that HBeAg loss or seroconversion alone is insufficient as the sole criterion for stopping therapy.[388] The duration of consolidation therapy—defined as continued treatment after achieving HBeAg loss or seroconversion with sustained undetectable HBV DNA and normal ALT—is an important determinant of durable off-treatment response, although the optimal duration has not been clearly defined.[371,389] A minimum of 12 months of consolidation therapy is generally recommended, though the supporting evidence remains limited.[27,390] More recently, incorporating quantitative HBsAg levels (particularly <100 IU/mL) at the time of treatment cessation has been proposed as an additional criterion that may improve the safety of discontinuation decisions.[391]

Quantitative HBsAg, quantitative HBcrAg, and HBV RNA

HBsAg is a surface protein encoded by the S gene region of HBV. During viral replication, three forms of HBs protein—small (S), middle (M), and large (L)—are produced from transcribed mRNA, and quantitative HBsAg assays measure all three forms collectively.[392] A growing body of evidence supports the use of quantitative HBsAg levels to predict sustained response to antiviral thera-

py.[172,393-395] In the context of peginterferon treatment, quantitative HBsAg has proven to be a reliable predictor of future treatment response and has been incorporated into stopping rules, thereby helping to avoid unnecessary continuation of ineffective therapy.[172] In patients receiving antiviral agents, low HBsAg levels at the time of treatment cessation have also been shown to predict SVR and subsequent HBsAg loss.[372,394-396] The RETRACT-B study identified HBsAg ≥100 IU/mL at the time of cessation as a major risk factor for hepatitis flare, with a 5-year cumulative incidence of acute exacerbation reaching 33%.[396] The CREATE study demonstrated that patients with HBsAg <50 IU/mL had the most favorable outcomes, although substantial differences were observed between Asian and non-Asian populations, highlighting the need for ethnicity-specific thresholds.[395] In a study of 117 patients followed for a mean of 2 years after ETV discontinuation, those with HBsAg <100 IU/mL had a clinical relapse rate of only 9.3%, with SVR maintained in 45.5%.[316] Similarly, another study reporting outcomes over a median follow-up of 156 weeks after cessation of ETV or tenofovir confirmed that HBsAg <100 IU/mL at cessation was a significant predictor of HBsAg loss.[397] A recent meta-analysis encompassing 24 studies with a total of 3,732 patients demonstrated that HBsAg thresholds of <100 and <1,000 IU/mL at the time of cessation were strong predictors of HBsAg loss, though their ability to predict virological relapse was limited, suggesting the need for combination with additional biomarkers.[394]

HBcrAg is a composite serological marker that simultaneously measures three proteins derived from the precore/core gene—HBeAg, HBcAg, and p22cr—and correlates well with intrahepatic cccDNA, intrahepatic HBV DNA, and serum HBV DNA levels, thus serving as an indicator of intrahepatic viral replicative activity.[392,398] Quantitative HBcrAg has been shown to be useful in predicting sustained response after antiviral therapy, and more recently, its combination with quantitative HBsAg has been proposed as a means of predicting SVR and HBsAg loss following treatment cessation.[399] The SCALE-B score (Surface antigen, Core-related antigen, Age, ALT, and tenofovir for HBV), which integrates age, ALT, tenofovir use, quantitative HBsAg, and quantitative HBcrAg (calculated as 35 × HBsAg [log IU/mL] + 20 × HBcrAg [log U/mL] + 2 × age [years] + ALT [IU/L] + 40 for tenofovir use), has been developed as a predictive model for clinical relapse after antiviral cessation.[395] In the CREATE study, a SCALE-B score <260 was associated with a SVR rate of 62%, an HBsAg loss rate of 11%, and an acute exacerbation rate of only 3%, suggesting that treatment cessation may be considered in this group. Conversely, a SCALE-B score >320 was associated with a SVR rate of 35%, an HBsAg loss rate of 1%, and an acute exacerbation rate of 31%.[395] It should be noted, however, that these predictive models were primarily developed from multinational or non-Asian cohorts, and external validation studies in Korean patients—among whom genotype C predominates—remain limited. Further validation in Korean cohorts is needed, and caution is advised when applying these models to the domestic patient population.

HBV RNA is also under investigation as a potential biomarker to guide treatment cessation decisions. In a study of 114 Asian patients, those with HBV RNA ≥44.6 U/mL had a relapse rate as high as 93.2%, indicating unsuitability for treatment discontinuation. In contrast, patients who simultaneously met the criteria of undetectable HBV RNA and HBsAg <10 IU/mL had a relapse rate of only 9.1%, suggesting that cessation may be feasible in this subgroup.[400] Based on these findings, a risk stratification framework has been proposed: high-risk (HBV RNA ≥44.6 U/mL), intermediate-risk (HBV RNA <44.6 U/mL or undetectable), and low-risk (undetectable HBV RNA and HBsAg <10 IU/mL). The combination of HBV RNA with quantitative HBsAg and HBcrAg has also been explored as a composite predictor of sustained off-treatment response.[366,401] However, HBV RNA measurement has not been standardized for routine clinical use, and assay standardization is a prerequisite for its broader clinical application. Taken together, current evidence favors a multi-biomarker risk stratification approach combining HBsAg, HBcrAg, and HBV RNA over reliance on any single biomarker, with ethnicity-specific criteria warranting further attention. Recent studies have confirmed that such a multi-biomarker strategy may facilitate HBsAg loss and improve the precision of treatment cessation decisions.[402]

HBsAg loss

HBsAg loss is defined as the disappearance of HBsAg and HBV DNA from serum, irrespective of anti-HBs formation.[278] Although intrahepatic cccDNA may persist in this setting, disease progression is effectively halted and the risk of HCC is markedly reduced—a state commonly re-

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ferred to as “functional cure” and widely regarded as a realistic treatment goal. In patients who achieve spontaneous HBsAg loss before the development of cirrhosis, the subsequent incidence of cirrhosis and HCC has been reported to be very low,[403] and HBsAg loss occurring before the age of 50 is associated with a reduced risk of HCC.[404] Among patients who achieve HBsAg loss or seroconversion through antiviral therapy, transient HBsAg reappearance or HBV DNA re-detection may occasionally be observed; however, the majority maintain durable HBsAg loss with sustained undetectable HBV DNA, and HCC incidence in these patients is lower than in those who do not achieve HBsAg loss.[224,405-407] HBsAg loss or seroconversion therefore represents the clinical endpoint that most closely reflects the therapeutic objectives of antiviral treatment, and therapy may be discontinued once this has been confirmed.[224,407,408] To minimize the risk of HBsAg reversion, it is advisable to confirm that HBsAg loss is sustained on at least two consecutive measurements at a minimum interval of 6 months before stopping treatment.[407,408]

Monitoring after discontinuation of antiviral therapy

Although treatment response may be sustained after discontinuation of antiviral therapy, hepatitis flares and progression to serious hepatic decompensation can occur. Regular follow-up is therefore essential, including periodic assessment of liver function tests, HBeAg, anti-HBe, and HBV DNA to monitor for sustained response, detect relapse, and evaluate hepatic functional status.

Virological relapse, defined as HBV DNA >2,000 IU/mL, typically occurs within 6–12 months after treatment cessation,[369,375,396] although recent studies have revealed notable differences according to the antiviral agent used. Approximately 70% of patients who discontinue tenofovir experience relapse within 12 weeks, whereas fewer than 10% of those who stop ETV relapse during the same period.[409] ALT elevation tends to follow virological relapse with a time lag. Acute exacerbation after tenofovir cessation tends to be concentrated within the first 6 months, occurring earlier and with greater severity compared with ETV cessation, whereas relapse following ETV discontinuation characteristically has a more delayed onset.[410]

When HBV DNA rises after treatment cessation, close monitoring of HBV DNA and liver function tests including ALT is essential to determine the need for retreatment.[411] Virological relapse is defined as HBV DNA ≥2,000 IU/mL in most guidelines and clinical studies,[27,33,412] and this threshold has been adopted as the criterion for sustained remission in major RCTs and large multinational cohort studies.[413] Prospective data have shown that persistently elevated HBV DNA >2,000 IU/mL is associated with an approximately 7-fold increase in the risk of biochemical relapse.[414] Retreatment is therefore recommended when HBV DNA rises to ≥2,000 IU/mL following cessation. Regarding the choice of agent for retreatment, re-initiation of the previously used drug is the standard approach when no resistance mutations are present. However, switching to an alternative agent should be considered in the following situations: when the prior agent had a low genetic barrier to resistance (e.g., lamivudine, adefovir), when resistance mutations have been documented, or when clinical circumstances have changed—such as a decline in renal function. Data from the HBRN study indicated that the risk of ALT flare increases sharply once HBV DNA exceeds 4 $\log_{10}$ IU/mL (10,000 IU/mL).[375] The RETRACT-B study further showed that 44% of patients with HBV DNA >5 $\log_{10}$ IU/mL (100,000 IU/mL) within 12 weeks of cessation experienced acute hepatitis flare, identifying this as a high-risk group.[415] The rate of HBV DNA rise is faster after tenofovir than after ETV discontinuation (2.12 vs. 0.73 $\log_{10}$ IU/mL per month), and a monthly increase of ≥2.5 $\log_{10}$ IU/mL predicts severe exacerbation with a specificity of 76%, warranting immediate consideration of retreatment.[409]

At 24 weeks after cessation, patients who simultaneously meet the criteria of HBV DNA <100 IU/mL and HBsAg <100 IU/mL have a low clinical relapse risk of 9.9% and high probability of HBsAg loss at 58%.[416] Conversely, patients in whom both values exceed 100 IU/mL face a clinical relapse risk of 66.5%, with virtually no chance of achieving HBsAg loss (<1%).

In patients who have not achieved HBsAg loss, serial quantitative HBsAg monitoring is recommended to track the trajectory of HBsAg decline and loss.[172,393] Even after HBsAg loss has occurred, the possibility of late reversion—though rare—and the residual risk of HCC necessitate continued monitoring of HBsAg, anti-HBs, and ongoing HCC surveillance.[224,406-408,417] As the number of patients achieving HBsAg loss—whether spontaneously, with current antiviral therapy,

or through emerging functional-cure regimens—continues to grow, a risk-stratified rather than uniformly lifelong approach to HCC surveillance is preferable, reserving continued surveillance for those with residual risk factors. The appropriate intensity and duration of surveillance in these patients must be weighed against healthcare resource utilization and the psychological burden of indefinite monitoring; dedicated cost-effectiveness analyses in these specific cohorts are warranted to inform future recommendations.

[Recommendation]

1. Discontinuation of antiviral therapy in patients with CHB is recommended when HBsAg loss has been confirmed on at least two consecutive occasions. (A1)
2. Long-term antiviral therapy should be considered in patients with cirrhosis, and antiviral therapy should not be discontinued in patients with decompensated cirrhosis. (B1)
3. During the first 6 months after treatment discontinuation, liver function tests and serum HBV DNA should be performed at 1- to 3-month intervals. Thereafter, the monitoring interval may be gradually extended if virological response is maintained. The follow-up schedule may be adjusted in consideration of the differing relapse kinetics between antiviral agents. (B1)
4. Retreatment should be considered when HBV DNA rises to ≥2,000 IU/mL after discontinuation of antiviral therapy. (B1)

MANAGEMENT IN SPECIAL CONDITIONS

Patients on immunosuppression or chemotherapy

HBV reactivation

HBV reactivation refers to a resurgence of HBV replication and the development of active necroinflammatory disease in patients with inactive chronic HBV infection or resolved HBV infection. This can follow two different scenarios: exacerbation of chronic HBV infection in HBsAg-positive individuals, and relapse of past HBV infection in HBsAg-negative but anti-HBc-positive individuals.[418] Exacerbation of chronic HBV infection is defined as a ≥100-fold increase in serum HBV DNA from baseline in HBsAg-positive patients, whereas a relapse of past HBV infection is defined as HBsAg seroreversion or the detection of serum HBV DNA ≥100 IU/mL from an undetectable baseline.[419-421]

HBV reactivation occurring in the context of chemotherapy or immunosuppressive therapy is a life-threatening complication; without appropriate antiviral prophylaxis, the risk of reactivation in HBsAg-positive patients ranges from 15–50%, and can exceed 75% following HSCT.[27] Although the risk is less common in HBsAg-negative/anti-HBc-positive patients, it can exceed 10% with B cell–depleting therapies. Consequently, all patients scheduled for chemotherapy or immunosuppressive therapy should be screened for HBsAg and anti-HBc before initiation, with additional serum HBV DNA testing if either marker is positive. Even if HBsAg is negative, checking baseline HBV DNA in anti-HBc-positive patients can confirm occult HBV infection, whereas measuring anti-HBs aids in risk classification and identifying vaccination candidates. The risk of HBV reactivation is stratified based on serologic markers, HBV DNA levels, and the type and intensity of chemotherapy into high-risk (≥10%), moderate-risk (1–10%), or low-risk (<1%) categories (Table 7).[27,422,423]

HBV reactivation during chemotherapy for lymphoma and other hematologic malignancies

HBV reactivation is frequently reported in 24–67% of cases during lymphoma chemotherapy, likely due to the potent bone marrow-suppressive effects of the drugs used and a higher baseline HBsAg prevalence in these patients compared to the general population.[424-427] Rituximab, often administered with corticosteroids for lymphoma, is known to significantly increase the risk of HBV reactivation.[428] Specifically, in HBsAg-negative/anti-HBc-positive patients, the use of rituximab is associated with an approximately 5-fold higher relative risk of reactivation compared to non-use.[429] HBV reactivation rates in this population vary by study design, reported as 2.4% in one retrospective study,[430] but found to be 17% in prospective and 7% in retrospective meta-analyses.[431] Studies on rituximab-treated patients have shown a significant difference in HBV reactivation incidence between those who received antiviral prophylaxis and those who did not (13.3% vs. 60%).[432] Furthermore, a strategy of universal HBV screening for all patients before R-CHOP chemotherapy, rather than limiting it to high-risk groups, has reduced the risk of HBV reactivation by up to

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Table 7. Risk of HBV reactivation associated with immune-related therapies or systemic chemotherapies

	HBsAg positive or HBV DNA positive	HBsAg negative/anti-HBc positive/HBV DNA negative
High risk (>10%)	Anthracyclines (doxorubicin, daunorubicin, epirubicin) Anti-TNF therapy (infliximab, adalimumab, etanercept, certolizumab, golimumab) Anti-IL-6 therapy (tocilizumab) Anti-IL-17 therapy (secukinumab, ixekizumab) B cell-depleting agents (rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab, obinutuzumab) A human immunoglobulin G1 monoclonal antibody targeting CD38-expressing cells (daratumumab) CAR-T therapy (BCMA, CD19) Stem cell transplantation TACE Tyrosine kinase inhibitors (sorafenib, lenvatinib, regorafenib, imatinib, sunitinib, osimertinib, nilotinib, gefitinib, dasatinib, erlotinib, afatinib, ibrutinib, idelalisib, palbociclib, ribociclib) JAK inhibitor therapy (tofacitinib, baricitinib) Corticosteroid therapy (high-dose >20mg/d or moderate-dose 10–20 mg/d prednisone ≥4 weeks)	B cell-depleting agents (rituximab, ofatumumab, ocrelizumab, alemtuzumab, ibritumomab, obinutuzumab) Stem cell transplantation
Moderate risk (1–10%)	Cytotoxic systemic chemotherapies other than anthracycline derivatives Anti-T cell therapy (abatacept, belatacept) Cytokine-based therapies Immunophilin inhibitors (cyclosporine) Anti-IL-12/23 (ustekinumab) mTOR inhibitors (everolimus, temsirolimus) Proteasome inhibitors (bortezomib) Histone deacetylase inhibitors Immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, ipilimumab) Corticosteroid therapy (prednisone <10 mg/d, ≥4 weeks)	Anthracyclines (doxorubicin, daunorubicin, epirubicin) Anti-IL-6 therapy (tocilizumab) Anti-IL-12/23 therapy (ustekinumab) Cytokine-based therapies Anti-T cell therapy (abatacept, belatacept) Immunophilin inhibitors (cyclosporine) mTOR inhibitors (everolimus, temsirolimus) Proteasome inhibitors (bortezomib) A human immunoglobulin G1 monoclonal antibody targeting CD38-expressing cells (daratumumab) Histone deacetylase inhibitors Anti-IL-17 therapy (secukinumab, ixekizumab) CAR-T therapy (BCMA, CD19) Cyclophosphamide TACE T cell-depleting therapies Tyrosine kinase inhibitors (imatinib, sunitinib, osimertinib, nilotinib, gefitinib, dasatinib, erlotinib, afatinib, ibrutinib, idelalisib, palbociclib, ribociclib) JAK inhibitors (tofacitinib, baricitinib) Corticosteroid therapy (high-dose >20 mg/d or moderate-dose 10–20 mg/d prednisone ≥4 weeks)

Table 7. Continued

	HBsAg positive or HBV DNA positive	HBsAg negative/anti-HBc positive/HBV DNA negative
Low risk (<1%)	Azathioprine Methotrexate Mycophenolate mofetil Antimetabolites, 6-mercaptopurine, leflunomide, hydroxychloroquine, hydroxyurea, immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) Corticosteroid therapy (≤1 week)	Azathioprine Methotrexate Mycophenolate mofetil Antimetabolites, 6-mercaptopurine, leflunomide, hydroxychloroquine, hydroxyurea, immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) Anti-TNF therapy (infliximab, adalimumab, etanercept, certolizumab, golimumab) Immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, ipilimumab) Corticosteroid therapy (≤1 week)

anti-HBc, antibody to hepatitis B core antigen; CAR-T, chimeric antigen receptor T-cell; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IL, interleukin; JAK, Janus kinase; mTOR, mechanistic target of rapamycin; TACE, transarterial chemoembolization; TNF, tumor necrosis factor.

10-fold and is associated with economic benefits and improved survival.[428]

In a prospective study of HBsAg-positive diffuse large B-cell lymphoma patients, TDF was administered at least 1 week before chemotherapy and continued for at least 48 weeks after completion.[433] Although no HBV reactivation or HBV-related hepatitis was reported during TDF administration, HBV reactivation occurred in 23.3% and HBV-related hepatitis in 8.2% during the follow-up period after discontinuation, highlighting the necessity of HBV DNA and ALT monitoring for at least 6 months post-prophylaxis.

Chimeric antigen receptor (CAR)-T cell therapy, primarily used for relapsed or refractory hematologic malignancies, has a reported HBV reactivation rate of approximately 11%.[434] Since this therapy causes severe B-cell depletion and immunosuppression, antiviral prophylaxis is mandatory for HBsAg-positive patients. HBsAg-negative/anti-HBc-positive patients are considered at moderate risk with a reactivation rate of about 3%, requiring consideration of prophylaxis or close monitoring.

Although data on HBV reactivation incidence for bispecific antibodies are currently limited,[435-438] they should be managed as a high-risk group similar to rituximab or CAR-T cell therapy given their CD3-engaging and B-cell-targeting mechanisms.

HBV reactivation during chemotherapy for solid tumors

The incidence of HBV reactivation in patients with solid tumors is generally reported between 14 and 21%. However, breast cancer patients exhibit a significantly higher frequency of 41–70%. This higher frequency is likely attributed to the relatively higher doses of chemotherapeutic agents used, particularly the combination of anthracycline-based regimens and corticosteroids.[439,440] Corticosteroids are known to increase HBV reactivation risk through immunosuppression and by directly stimulating HBV replication.[441] The risk of HBV reactivation associated with systemic corticosteroid therapy depends on the dose and duration of treatment, with the highest risk observed when high doses (e.g., prednisolone ≥20 mg/day) are administered for ≥4 weeks.[441] High doses exceeding 40 mg/day can increase the risk of hepatitis exacerbation regardless of the duration, whereas moderate doses (20–40 mg/day) have been reported to increase HBV reactivation risk by approximately 10–17%. This risk is notably higher in HBsAg-positive pa-

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tients, whereas low-dose, short-term, or local corticosteroid treatments are generally considered as low-risk.

Meanwhile, tyrosine kinase inhibitors (TKIs) are primarily used for solid tumors such as gastrointestinal stromal tumors and renal cell carcinoma, as well as some leukemias. In HBsAg-positive patients, the risk of HBV reactivation during TKI treatment is reported at approximately 11%, classifying them as a high-risk group for which antiviral prophylaxis is recommended.[442-444] Conversely, although HBV reactivation cases in HBsAg-negative/anti-HBc-positive patients have not been clearly established in many studies, they are categorized as a moderate-risk group based on published case reports and biological plausibility.

HBV reactivation during immune-related therapy for inflammatory bowel disease or rheumatic diseases

Tumor necrosis factor (TNF) inhibitors (e.g., infliximab, etanercept, adalimumab) used for the treatment of inflammatory bowel disease or rheumatoid arthritis (RA) have also been reported to cause HBV reactivation.[445-447] In HBsAg-positive patients, the reactivation risk is approximately 33% (332 per 1,000), classifying them as high-risk, and antiviral prophylaxis is essential. Conversely, when HBsAg-negative/anti-HBc-positive patients receive anti-TNF therapy, the HBV reactivation risk is very low at approximately 0.2% (2 per 1,000), placing them in the low-risk group. In the context of TNF inhibitors and disease-modifying antirheumatic drugs for rheumatic diseases, HBV reactivation has been reported in 12.3% of HBsAg-positive patients.[448] Another study observed reactivation in 39% of HBsAg-positive patients and 5% of anti-HBc-only positive patients, with prophylaxis significantly reducing reactivation rates (23% vs. 62%).[449]

Anti-IL-6 agents (e.g., tocilizumab) are primarily used in RA,[450,451] and direct evidence regarding the risk of HBV reactivation remains limited. Nevertheless, on the basis of biological plausibility and expert consensus, major guidelines classify HBsAg-positive patients as high risk and recommend prophylactic antiviral therapy, while HBsAg-negative/anti-HBc-positive patients are classified as moderate risk and recommended for either monitoring or prophylactic therapy.

JAK inhibitors (e.g., tofacitinib, baricitinib) are mainly used for RA, psoriasis, and moderate-to-severe ulcerative colitis.[452] In HBsAg-positive patients, the baseline HBV reactivation risk is reported at approximately 33%, classifying them as high-risk, and antiviral prophylaxis is strongly recommended.[453-455] In HBsAg-negative/anti-HBc-positive patients, the HBV reactivation risk is estimated at 1–10%, classifying them as a moderate-risk group.

HBV reactivation during immune checkpoint inhibitor therapy

ICIs, such as anti-PD-1/PD-L1 and anti-CTLA-4 agents, are primarily used to treat solid tumors, and there have been reports of HBV reactivation associated with these therapies.[456-462] In HBsAg-positive patients, the risk of HBV reactivation is approximately 7%, classifying them as a moderate-risk group for which antiviral prophylaxis is suggested. According to a recent retrospective study involving various solid cancers and some lymphomas, HBV reactivation was observed in 0.14% of all patients receiving ICI chemotherapy, 1.0% of HBsAg-positive patients, and 0% of HBsAg-negative patients. The HBV reactivation rates were 0.4% in patients receiving antiviral prophylaxis compared to 6.4% in those without prophylaxis.[462] Among various ICIs, pembrolizumab showed a significant correlation with HBV reactivation.[463] Conversely, the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients was very low at <0.1%, categorizing them into a low-risk group.

Timing of initiation and termination of antiviral prophylaxis and monitoring strategies

Because HBV reactivation can lead to liver failure and death, prevention is of the utmost importance. To this end, universal screening for HBsAg and anti-HBc should be performed for all patients before starting immunosuppressive therapy or chemotherapy (Fig. 4). For patients who are HBsAg-positive or anti-HBc-positive, initial evaluations for CHB should be conducted (Table 3). If a patient is HBsAg-negative but anti-HBc-positive, a baseline serum HBV DNA test must also be performed. For those with no evidence of past HBV infection (HBsAg-negative and anti-HBc-negative), HBV vaccination may be considered. For patients who are HBsAg-positive or have detectable HBV DNA and are receiving high- or moderate-risk medications, antiviral prophylaxis should be started before or at the same time as the initiation of therapy; for those in the low-risk group, monitoring is recommended. In HBsAg-positive patients, antiviral prophylaxis is recommended regardless of serum

HBV DNA levels. Administering antivirals at the start of immunosuppression or 7 days prior to the start of chemotherapy has been reported to be more effective than waiting for HBV DNA levels to rise.[464,465]

HBV reactivation can occur in HBsAg-positive and HBsAg-negative/anti-HBc-positive patients. Under immunosuppressive conditions, patients who are positive only for anti-HBc have been reported to have a higher risk of reactivation than those positive for both anti-HBc and anti-HBs.[422,466] However, that the American Gastroenterological Association (AGA) suggests that anti-HBs status should not be used to guide prophylaxis recommendations. For HBsAg-negative/anti-HBc-positive patients with undetectable HBV DNA receiving high-risk medications, antiviral prophylaxis should be initiated before or at the start of therapy. A global consensus on the management of patients receiving moderate-risk medications is currently lacking. The AGA suggests antiviral prophylaxis over monitoring for these individuals, whereas other guidelines (such as EASL) may recommend periodic monitoring of HBsAg and HBV DNA every 1–3 months, starting "on-demand" treatment only when reactivation is confirmed.[27,423] These differences reflect varying clinical risk assessments between HBsAg-positive (including HBV DNA-positive) patients and anti-HBc-positive individuals upon reactivation. Furthermore, there is a lack of RCTs directly comparing prophylaxis with a preemptive monitoring strategy. Given the rapid increase in the introduction of new immunosuppressants and anticancer agents, these recommendations must be applied carefully. For patients using low-risk medications, HBsAg and HBV DNA should be monitored every 1–3 months, with preemptive antiviral therapy initiated if reactivation is confirmed.

Theoretically, antiviral prophylaxis should be maintained until the immune system has sufficiently recovered, though clear evidence for a specific termination point is lacking. However, caution is required as reactivation has been reported more than 6 months after the completion of chemotherapy, regardless of pre-treatment HBV DNA levels. Therefore, prophylaxis should be maintained for at least 6 months post-therapy, with extensions considered based on the risk of the chemotherapy regimen. Specifically, for treatments involving rituximab or other B-cell depleting agents, it is recommended to extend prophylaxis to at least 12 months after completion.[467,468] Finally, close follow-up for reactivation is necessary for at least 12 months after the termination of antiviral prophylaxis.

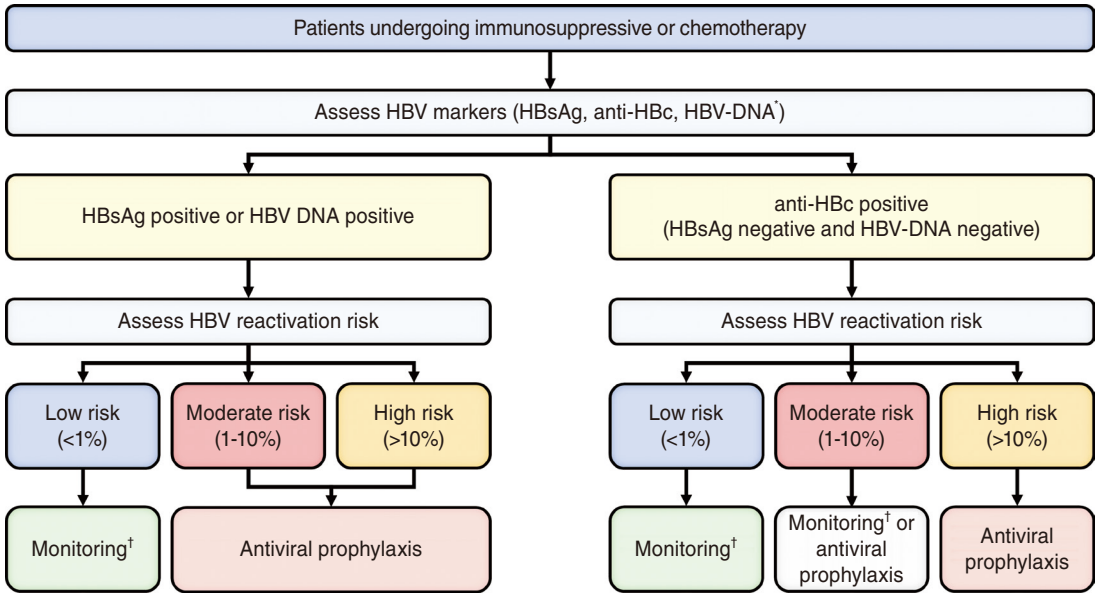

Figure 4. Prevention of HBV reactivation in patients undergoing immunosuppression or chemotherapy. *Assess when HBsAg or anti-HBc is positive. †HBV reactivation should be monitored with HBsAg, and/or HBV DNA every 1–3 months during and after immunosuppressive therapy. Because evidence for fixed risk-specific intervals is limited, the interval may be individualized according to reactivation risk and clinical context. anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

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Therapeutic agents

In an RCT involving HBsAg-positive or anti-HBc-positive patients scheduled for immunosuppressive therapy, antiviral prophylaxis based on ETV or TDF was administered until 6–12 months after the termination of immunosuppressive treatment.[469] No HBV reactivation was observed during the prophylactic antiviral treatment period. However, during the follow-up period after the termination of prophylaxis, HBV reactivation occurred in 4 patients (10.8%) in the ETV group and 5 patients (14.3%) in the TDF group. Meanwhile, in a retrospective study evaluating patients receiving immunosuppression or chemotherapy for solid tumors, lymphoma, or rheumatic diseases, the TAF group (n=11) showed similar effects compared to the ETV group (n=66) in terms of HBV DNA reduction (–2.83±1.45 log IU/mL vs. –3.05±2.47 log IU/mL) and the HBV non-detection rate (78.8% vs. 90.9%). No significant difference was observed between the two groups regarding the rate of renal function decline (–0.62±11.2 mL/min/1.73 m² vs. –3.67±13.2 mL/min/1.73 m²). Therefore, TAF can be considered a safe drug with good preventive effects.[470]

[Recommendation]

1. Patients scheduled for immunosuppressive therapy or chemotherapy should be screened for HBsAg and anti-HBc before initiation, with additional serum HBV DNA testing if either marker is positive. (A1)
2. For patients who are HBsAg-positive or have detectable HBV DNA and are receiving high-risk or moderate-risk medications, antiviral prophylaxis should be initiated before or at the start of therapy. (A1) The choice of antiviral agent, preferably TAF, TDF, or ETV, should be based on a comprehensive assessment of serum HBV DNA levels, the intensity and duration of immunosuppressive therapy or chemotherapy, and the risk of renal dysfunction or metabolic bone disease. (B1)
3. For patients who are HBsAg-negative, anti-HBc-positive, and have undetectable HBV DNA, antiviral prophylaxis should be initiated before or at the start of therapy with high-risk medications. (A1) For those receiving moderate-risk medications, either periodic monitoring of HBsAg and HBV DNA or antiviral prophylaxis should be considered. (B1) For those using low-risk medications, HBsAg and HBV DNA should be monitored periodically, and preemptive antiviral therapy should be initiated if HBV reactivation is confirmed. (B1)
4. Antiviral prophylaxis should be maintained for at least 6 months after the termination of immunosuppressive therapy or chemotherapy, and at least 12 months for regimens including B-cell depleting agents such as rituximab. (A1)
5. After the termination of antiviral prophylaxis, periodic monitoring of serum HBV DNA is recommended for at least 12 months to monitor for potential reactivation. (A1)

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Patients with CHB who require HSCT for hematologic malignancies are subject to prolonged immunosuppression due to high-dose chemotherapy and the underlying hematological diseases themselves, which increases the risk of HBV reactivation and can lead to a poor prognosis.[471,472] Therefore, all HSCT recipients should undergo universal screening for HBsAg, anti-HBc, and anti-HBs before transplantation. Quantitative serum HBV DNA testing must be performed for patients who are HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive, regardless of their anti-HBs status. Among all patients with hematologic malignancies, those who are HBsAg-negative and anti-HBc-negative should receive HBV vaccination, and their anti-HBs titers should be monitored. All HSCT recipients who are HBsAg-positive or HBV DNA-positive must initiate antiviral prophylaxis at the time of transplantation. In an 11-year allogeneic HSCT cohort, the risk of HBV reactivation in HBsAg-positive patients was reduced to approximately 9% after receiving antiviral prophylaxis including lamivudine or ETV.[473] In contrast, a prospective cohort study following 62 HBsAg-negative/anti-HBc-positive (resolved HBV) allogeneic HSCT recipients for 48 weeks reported a 2-year cumulative reactivation rate of 40.8%.[474] Retrospective studies in Korea have also reported a 2.6% HBV reactivation rate in HSCT recipients with past HBV infection over a median follow-up of 78 months; another retrospec-

tive study with a median follow-up of 21 months found that HBV reactivation occurred in 4 out of 96 patients who received 7 months of prophylaxis and in 8 out of 219 patients who did not.[474,475] According to reported observational studies, the 5-year cumulative incidence of HBV reactivation in HBsAg-negative/anti-HBc-positive allogeneic HSCT recipients is very high (10.5–43.0%), making antiviral prophylaxis appropriate for these patients.[476] Although various guidelines suggest maintaining antiviral prophylaxis for 6–18 months after the completion of HSCT, unified criteria have not yet been established. However, as HBV reactivation has been continuously reported even 5–7 years after the completion of HSCT,[476,477] maintaining long-term antiviral prophylaxis is considered safer, and further research and discussion regarding the timing of discontinuation are needed. Meanwhile, all HBsAg-positive solid organ and HSCT recipients should receive antiviral prophylaxis at the time of transplantation; considering the need for long-term therapy, TAF, TDF, or ETV are the preferred agents.

[Recommendation]

1. All HSCT recipients should be tested for HBsAg, anti-HBc, and anti-HBs before transplantation. (A1)
2. Quantitative serum HBV DNA testing should be performed for HSCT recipients who are HBsAg-positive or anti-HBc-positive. (B1)
3. For all hematologic malignancy patients who are HBsAg-negative and anti-HBs-negative, hepatitis B vaccination should be administered and anti-HBs titers should be monitored. (C1)
4. All HBsAg-positive or HBV DNA-positive HSCT recipients should receive prophylactic antiviral therapy at the time of transplantation (A1).
5. HSCT recipients who are HBsAg-negative, anti-HBc-positive, and HBV DNA-undetectable are recommended to start prophylactic antiviral therapy at the time of transplantation due to the high risk of HBV reactivation (B1).
6. Prophylactic antiviral therapy should be maintained for at least 12 months, and the choice of antiviral agent, preferably TAF, TDF, or ETV, should be based on a comprehensive assessment of serum HBV DNA levels, the intensity and duration of immunosuppression, and the risk of renal dysfunction or metabolic bone disease. (B1)

PATIENTS WITH HEPATOCELLULAR CARCINOMA

In patients with HBV-related HCC, the primary objective of antiviral therapy is to suppress HBV replication, preventing the progression of liver disease to enable active cancer treatment, and further reducing the risk of recurrence after curative therapy.

Various locoregional treatment modalities for HCC currently in use can impose a risk of HBV reactivation. According to recent systematic reviews, the risk of HBV reactivation in HBsAg-positive HCC patients not receiving antiviral therapy is categorized as moderate or high depending on the type of treatment applied.[478] Specifically, relatively high reactivation rates have been reported following surgery (16%), transarterial chemoembolization (TACE, 19%), and external beam radiation therapy (EBRT, 14%), whereas HBV reactivation has also been observed after local ablation such as radiofrequency ablation (RFA, 7%) and systemic chemotherapy (7%).

Antiviral therapy during curative treatment

In patients with CHB who are not taking oral antivirals, an increase in serum HBV DNA was observed in 20% of cases following surgical resection for HCC, with HBV reactivation accompanied by AST or ALT elevation occurring in approximately 9%.[478] In contrast, the rate of increase in serum HBV DNA was significantly lower, at approximately 2–4%, in those receiving oral antiviral agents. Similarly, following RFA or percutaneous ethanol injection, HBV reactivation occurred in 5–9% of the group not taking antivirals, whereas reactivation rates were extremely low in the group receiving antiviral therapy.[478-481] Even in HBsAg-positive patients with undetectable baseline HBV DNA, HBV reactivation occurred in 22–33% after surgical resection; however, the use of perioperative antiviral agents has been reported to significantly reduce this risk.[482-486] Furthermore, in patients with HBV-related HCC undergoing curative treatment, antiviral therapy has been confirmed to reduce the risk of tumor recurrence and significantly improve overall survival, even when baseline HBV DNA levels are low.[487] Among patients who underwent surgical resection for HBV-related HCC, TDF has been reported to significantly reduce the risk of recurrence and death compared to ETV.

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However, as long-term follow-up data, including those for TAF, remain limited, further research is required.[488,489]

Antiviral therapy during locoregional therapy

HBV reactivation has been reported in approximately 4–40% of patients with HBV-related HCC undergoing TACE.[478,490-494] Retrospective analyses have also reported approximately 9–11% HBV reactivation following TACE even in patients with resolved HBV infection (HBsAg-negative/anti-HBc-positive).[495,496] The AGA guideline assessed the risk of HBV reactivation in patients undergoing TACE based on data from three RCTs. One of these trials included HBsAg-positive patients, whereas the HBsAg status of the participants in the other two trials was not explicitly described.[423,492,497] Analysis of data from 91 patients estimated the baseline risk of HBV reactivation among individuals undergoing TACE to be 180 per 1000, categorizing this procedure as a high-risk exposure.[423] Several studies have shown that HCC patients receiving antiviral therapy experienced fewer liver-related events, such as HBV reactivation and the development of decompensated cirrhosis, and some studies observed improvements in survival rates.[478,496,498-500] Meanwhile, the incidence of HBV reactivation following hepatic artery infusion chemotherapy (HAIC) was reported at 24–67%, representing a relatively higher risk than TACE. This finding is potentially attributed to the larger total amount of cytotoxic chemotherapeutic agents administered during HAIC due to its shorter treatment intervals compared to TACE.[501-503] In a Korean propensity score-matched retrospective study evaluating patients undergoing transarterial chemotherapy (combining TACE and HAIC), the 10-year survival rate was significantly higher in the antiviral group compared to the control group (26.5% vs. 12.8%).[504] Additionally, a prospective study of 98 HBsAg-positive but HBV DNA-negative HCC patients undergoing TACE found that the incidence of HBV reactivation was significantly lower in the preemptive antiviral group than in the control group (5.9% vs. 23.4%).[505] HBV reactivation after EBRT was reported as 0% in the antiviral group compared to 18–21% in the control group, and the rate of associated ALT elevation was also significantly higher in the control group (12.5% vs. 2.3%).[478,506] A Korean multicenter retrospective study of EBRT patients also demonstrated that the absence of antiviral treatment significantly increased the risk of HBV reactivation (OR, 8.34; 95% CI, 2.53–27.47).[507] Furthermore, the combination of TACE and EBRT has been reported to more than double the risk of HBV reactivation compared to TACE alone.[508] Therefore, antiviral prophylaxis should be actively considered for these combined treatment strategies.

Antiviral therapy during systemic therapy

ICIs, which are the first-line treatment for HCC, theoretically enhance the body's immune response, leading to an expectation of a relatively low risk of HBV reactivation. Conversely, however, they can trigger severe acute exacerbation of hepatitis by over-activating the immune response against HBV. Therefore, it is necessary to suppress HBV replication with antiviral treatment before initiating ICI therapy.[422] In the phase 3 IMbrave150 study, HBV reactivation occurred in 2% of patients receiving the combination of atezolizumab and bevacizumab.[509] Furthermore, a meta-analysis of HCC patients receiving ICIs showed HBV reactivation in 7.8% of cases, with the majority of these events occurring in patients who were not taking antiviral agents.[478] Similarly, a Korean retrospective study of 398 patients with HBV-related HCC receiving ICIs and antiviral prophylaxis found that HBV reactivation occurred in only two patients (0.5%), both of whom had poor adherence to their antiviral medications.[462] Other retrospective studies have reported that antiviral prophylaxis lowers the risk of HBV reactivation regardless of the baseline HBV DNA level, supporting the recommendation for antiviral prophylaxis in HCC patients receiving ICIs.[510,511] In cases where antiviral prophylaxis is not administered, close monitoring for HBV reactivation at 1- to 3-month intervals is required. Meanwhile, HBV reactivation was diagnosed in approximately 6.6% of patients with advanced HBV-related HCC undergoing sorafenib or lenvatinib treatment without antiviral therapy.[512] According to domestic and international retrospective studies, a baseline HBV DNA level exceeding 2,000 IU/mL is associated with a poor prognosis during sorafenib treatment, whereas the use of antiviral agents is significantly associated with improved overall survival.[513,514]

[Recommendation]
1. In patients with HBV-related HCC, antiviral therapy

should be initiated if serum HBV DNA is detected, regardless of the cancer treatment status. (A1).
2. For HBsAg-positive patients, prophylactic antiviral therapy should be considered even if serum HBV DNA is undetectable, as there is a potential risk of HBV reactivation during HCC treatment. (B1)
3. In patients with resolved HBV infection (HBsAg-negative, anti-HBc-positive, and undetectable HBV DNA) undergoing HCC treatments including TACE, HBV reactivation should be closely monitored, and antiviral therapy should be initiated upon the occurrence of reactivation. (B1)

PATIENTS WITH EXTRAHEPATIC MANIFESTATIONS

HBV infection can lead to a variety of extrahepatic manifestations, including mixed cryoglobulinemia vasculitis, serum sickness-like syndrome, non-RA, RA, polyarteritis nodosa, glomerular disease, and non-Hodgkin lymphoma. These conditions may adversely affect patient morbidity, quality of life, and mortality.[515-518] However, the frequency of extrahepatic manifestations in HBV infection is known to be relatively lower than in HCV infection.

The goal of antiviral therapy is to suppress HBV replication and thereby improve these extrahepatic manifestations. However, there is no clearly established threshold of HBV virologic markers that can predict improvement in extrahepatic symptoms, and the evidence remains limited regarding whether antiviral therapy alone can lead to complete resolution of these conditions.

Therefore, in cases accompanied by major renal, neurological, or hematologic complications, treatment with immunomodulatory or immunosuppressive agents—such as high-dose intravenous immunoglobulin, rituximab, high-dose corticosteroids, or plasmapheresis—may be required. In such situations, antiviral therapy must be administered concomitantly. The use of antiviral agents is essential in the management of HBV-related extrahepatic manifestations, and particularly when immunosuppressive therapy is used, antiviral treatment is recommended for controlling extrahepatic disease and preventing HBV reactivation.

LIVER AND OTHER SOLID ORGAN TRANSPLANT RECIPIENTS

HBsAg-positive recipients undergoing liver or other solid organ transplantation

HBsAg-positive patients undergoing liver transplantation

In patients with HBV undergoing liver transplantation, prophylactic therapy to prevent post-transplant HBV recurrence is essential. HBV recurrence is defined by the reappearance of HBsAg or HBV DNA, and, if untreated, is associated with graft loss and mortality.[519,520] The current standard treatment is a combination of NA and HBIG, which reduces the posttransplant HBV reinfection rate to <5%.[521-523] HBIG should be initiated at the time of transplantation and maintained thereafter to achieve target anti-HBs titers ≥50–100 mIU/mL.[524] NA therapy should be individualized based on prior antiviral treatment history, drug resistance profile, and comorbidities. Potent agents, including TAF, ETV, and TDF, achieve robust viral suppression and can reduce the risk of HBV recurrence to near zero.[522,525,526] Given that liver transplant recipients are at increased risk of renal dysfunction and bone disease due to concomitant use of calcineurin inhibitors and corticosteroids, TAF or ETV may be preferred.[27]

With the advent of NA with high potency, a risk-adapted approach to prophylaxis has recently been proposed. The use and duration of HBIG may be individualized based on the patient's risk of HBV recurrence at the time of liver transplantation. In patients at low risk of recurrence (undetectable HBV DNA at transplantation and good adherence to antiviral therapy), discontinuation of HBIG after a short course or HBIG-free regimen may be considered, while maintaining long-term NA therapy. Recent studies have evaluated the efficacy of HBIG-free regimens using potent NA monotherapy.[527-531] In an analysis of 265 patients who received ETV monotherapy, sustained HBsAg seroclearance was maintained in 92% of patients over 8 years. HBV DNA remained undetectable in all patients, and the 9-year overall survival rate was 85%, indicating excellent long-term outcomes.[527] In another study including 362 patients with a median follow-up of 53 months (lamivudine 49%, ETV 39%, and other NA combination therapy 12%), the rates of HBsAg negativity and HBV DNA negativity at 8 years were

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88% and 98%, respectively, with favorable overall survival. However, patients treated with lamivudine showed a relatively higher rate of recurrence, underscoring the importance of using NA with a high genetic barrier to resistance.[528] In HBV-related liver transplant recipients with stage ≥2 chronic kidney disease receiving TDF, a comparative study (n=51) showed no HBV reactivation in either the TAF switch group (n=26) or the TDF continuation group (n=25). Improvement in GFR was greater in the TAF group, although not significant, whereas BMD at the hip and spine was significantly increased compared to the TDF group. Therefore, TAF may be considered a safer and effective therapeutic option than TDF in liver transplant recipients at high risk of renal dysfunction and bone loss.[532] Regarding the optimal timing for discontinuation of HBIG, available evidence varies. In most studies, HBIG was discontinued at 12 months post-transplantation, whereas some studies demonstrated that early discontinuation between 1 week and 3 months after transplantation is also safe and effective. When HBIG is discontinued, regular monitoring of HBsAg and HBV DNA is essential for early detection of HBV recurrence. Monitoring is generally recommended every 4–8 weeks in the early phase, every 3 months during the first-year post-transplantation, and every 6 months thereafter.[27]

In contrast, patients with a high risk of HBV recurrence (HBV DNA positive at liver transplantation, HDV or HIV coinfection, coexistence of HCC, or poor adherence to NA therapy) require lifelong or prolonged combination of NA and HBIG.[524,533,534] In patients receiving combination therapy with NA and HBIG, HBIG may be discontinued if HBsAg reappears but HBV DNA remains undetectable; in such cases, NA should be maintained with HBV DNA monitoring every 3 months. If HBV DNA increases during NA monotherapy or combination therapy with HBIG, poor adherence or antiviral resistance should be suspected; resistance testing is recommended in patients with confirmed good adherence.[27]

HBsAg-positive patients undergoing other solid organ transplantation

All recipients of non-hepatic solid organ transplantation should be evaluated for hepatitis B serologic markers, including HBsAg, anti-HBc, and anti-HBs. Patients who are HBsAg-positive should undergo assessment of ALT and HBV DNA levels, and evaluation of liver fibrosis and the presence of cirrhosis. HBsAg-positive kidney transplant recipients are at high risk of persistent viral activity or reactivation and have significantly higher mortality due to liver-related complications such as cirrhosis and HCC.[535,536] Recent reports indicate that NA therapy significantly decreased the HBV reactivation rate and increased the survival of HBsAg-positive kidney transplant recipients.[537,538]

Therefore, all HBsAg-positive organ transplant recipients undergoing non-hepatic solid organ transplantation, NA therapy should be initiated prior to or at the time of transplantation. Potent agents with a high genetic barrier to resistance, such as TAF, ETV, or TDF, are recommended; in kidney transplant recipients or those at risk of renal dysfunction, TAF or ETV are preferred. With the introduction of effective NA therapy, solid organ transplantation has become feasible in patients with CHB, including those with compensated cirrhosis without portal hypertension. In particular, kidney transplantation in patients with compensated cirrhosis has demonstrated comparable outcomes to those without liver disease in terms of survival, rejection rates, and length of hospitalization.[539,540] However, in patients with advanced or decompensated cirrhosis who are at risk of liver failure, simultaneous transplantation of the liver and other organs, such as kidneys, heart, and lungs, should be considered.

[Recommendation]

1. In the recipients of HBV-related liver transplant, prophylactic combination of NA (TAF, ETV, or TDF) and HBIG posttransplantation is recommended for the prevention of HBV recurrence (A1). Patients with a low risk of recurrence (HBV DNA negative at liver transplantation, and good medication adherence) can receive a short course or HBIG free regimens but need continued monoprophylaxis with a potent NA. (B1)
2. All HBsAg-positive or HBV DNA-positive solid organ transplant recipients should initiate prophylactic NA therapy at the time of transplantation, with antiviral agent selection based on renal function and overall clinical status. (A1)

HBsAg-negative recipients undergoing liver or other solid organ transplantation

In HBsAg-negative individuals, the risk of HBV infection or reactivation persists if either the recipient or donor is anti-HBc-positive. Prior to transplantation, immunization status against HBV of recipient and donor, as well as the type of transplanted organ (liver vs. non-hepatic solid organ), should be assessed to guide risk-stratified antiviral therapy or monitoring strategies to prevent HBV infection or reactivation.

HBsAg-negative patients undergoing liver transplantation

HBV infection after transplantation of an anti-HBc-positive donor liver into an HBsAg-negative recipient

HBsAg-negative/anti-HBc-positive donor livers indicate occult HBV infection and carry a risk of post-transplant transmission or reactivation; therefore, such grafts are preferably allocated to HBsAg-positive recipients. In HBsAg-negative recipients receiving anti-HBc-positive donor livers, the incidence of de novo HBV infection varies widely (10–80%) depending on the recipient's immunization status against HBV.[541] The risk is the highest in recipients without HBV immunity (anti-HBs–negative/anti-HBc-negative, 47.8%) and lowest in those with anti-HBs and anti-HBc positivity (1.4%).[542] Intermediate risks have been reported in recipients with anti-HBs–negative/anti-HBc-positive (13.1%) and anti-HBs–positive/anti-HBc-negative status (9.7%). In HBsAg-negative recipients receiving livers from anti-HBc-positive donors, prophylactic antiviral therapy significantly reduces the incidence of HBV infection. Specifically, the incidence decreased from 47.8% to 12% in recipients without HBV immunity (anti-HBs–negative/anti-HBc-negative), from 15.2% to 3.4% in anti-HBc-positive recipients, and from 9.7 to 0% in recipients with vaccine-induced immunity (anti-HBs–positive/anti-HBc-negative).[541] Accordingly, management strategies should be tailored to the recipient's immunization status against HBV. Prophylactic NA therapy is recommended in recipients who are anti-HBs–negative/anti-HBc-negative, anti-HBs–positive/anti-HBc-negative, or anti-HBs–negative/anti-HBc-positive. In recipients who are anti-HBs–positive/anti-HBc-positive, routine prophylaxis is not mandatory; however, regular monitoring of HBsAg and HBV DNA is required, and NA therapy should be initiated promptly upon detection of HBsAg or HBV DNA positivity. If close monitoring is not feasible, prophylactic NA therapy is recommended (Fig. 5). NA therapy should be initiated as early as possible after transplantation, preferably using potent agents with a high genetic barrier to resistance, such as TAF, ETV, or TDF. The optimal duration of NA therapy remains uncertain; however, discontinuation may be considered in selected patients who achieve and maintain anti-HBs levels >100 mIU/mL after vaccination, with strict monitoring (every 3 months during the first year and every 3–6 months thereafter).

Meanwhile, in a cohort of 117 HBsAg-negative recipients who received liver from anti-HBc-positive donors, HBIG monotherapy was associated with a low incidence of HBV infection (0.9%).[543] Higher anti-HBs titers are associated with greater protection against HBV reactivation; therefore, HBV vaccination or revaccination is recommended prior to transplantation in recipients without adequate immunity.[27,29]

HBV reactivation after liver transplantation in HBsAg-negative, anti-HBc-positive recipients

In HBsAg-negative/anti-HBc-positive recipients receiving livers from anti-HBc-negative donors, HBV reactivation may occur due to latent virus in extrahepatic reservoirs (peripheral blood or lymphoid tissue) despite removal of the native liver under immunosuppressive therapy; however, the reported incidence is low (0–1.5%).[544-547] Therefore, regular monitoring of HBsAg and HBV DNA is recommended in this setting, and NA therapy (TAF, ETV, or TDF) should be considered upon detection of HBsAg or HBV DNA positivity.

HBsAg-negative patients undergoing other solid organ transplantation

HBV infection after transplantation of anti-HBc-positive non-hepatic solid organs into HBsAg-negative recipients

In HBsAg-negative recipients receiving non-hepatic solid organs (kidney, lung, or heart) from anti-HBc-positive donors, the risk of HBV reactivation is low because transplanted organs do not contain intrahepatic cccDNA. However, caution is required as HBV transmission may occur if HBV DNA is present in the donor's blood. In a systematic review of 1,385 recipients who received kidneys from HBsAg-negative/anti-HBc-positive donors, the rates of HBsAg seroconversion and anti-HBc seroconversion were 0.3% and 2.3%, respectively, indicating a relatively low risk of HBV transmission.[548] Therefore, in HBsAg-negative recipi-

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ents of anti-HBc-positive non-hepatic solid organs, regular post-transplant monitoring is recommended to detect HBV infection or reactivation, including HBsAg and HBV DNA testing every 3 months during the first year and every 6 months thereafter. NA therapy (TAF, ETV, or TDF) should be initiated upon detection of HBsAg or HBV DNA positivity.[27] In addition, acquisition of anti-HBs through HBV vaccination further reduces the risk of donor-derived HBV transmission; therefore, recipients without immunity to HBV should receive HBV vaccination or revaccination prior to transplantation.[549,550]

HBV reactivation after non-hepatic solid organ transplantation in HBsAg-negative, anti-HBc-positive recipients

In HBsAg-negative/anti-HBc-positive recipients undergoing non-hepatic solid organ transplantation, intrahepatic HBV cccDNA may persist, and the risk of HBV reactivation may vary depending on the intensity of post-transplant immunosuppression and the recipient's immunization status against HBV, regardless of the donor's anti-HBc status. The reported incidence of HBV reactivation after transplantation ranges from 0 to 12%,[551-557] with higher rates observed in anti-HBs–negative/anti-HBc-positive recipients (5.6–12.0%) compared to those who are anti-HBs–positive/anti-HBc-positive (1.1–2.7%).[551,556,557] In a recent systematic review, the overall HBV reactivation rate in anti-HBc-positive recipients was approximately 2.5%, but increased to 7–8% in anti-HBs–negative individuals; among those with reactivation, the risks of liver failure and mortality were both reported at 11%.[558] Therefore, in anti-HBs–negative/anti-HBc-positive recipients, regular post-transplant monitoring is recommended to detect HBV reactivation, including HBsAg and HBV DNA testing every 3 months during the first year and every 6 months thereafter. NA therapy (TAF, ETV, or TDF) should be initiated upon detection of HBsAg or HBV DNA positivity. In addition, HBV vaccination or revaccination prior to transplantation is recommended.[27]

[Recommendation]

1. All the recipients of non-liver solid organ transplantation should be tested for HBsAg, anti-HBc, and anti-HBs before transplantation. (A1)
2. HBsAg-negative patients receiving anti-HBc-positive liver grafts show variation in HBV reactivation rate depending on the recipient's immunization status against HBV and should receive NA therapy accordingly. (B1)
3. HBsAg-negative recipients receiving non-hepatic solid organ transplants from anti-HBc-positive do

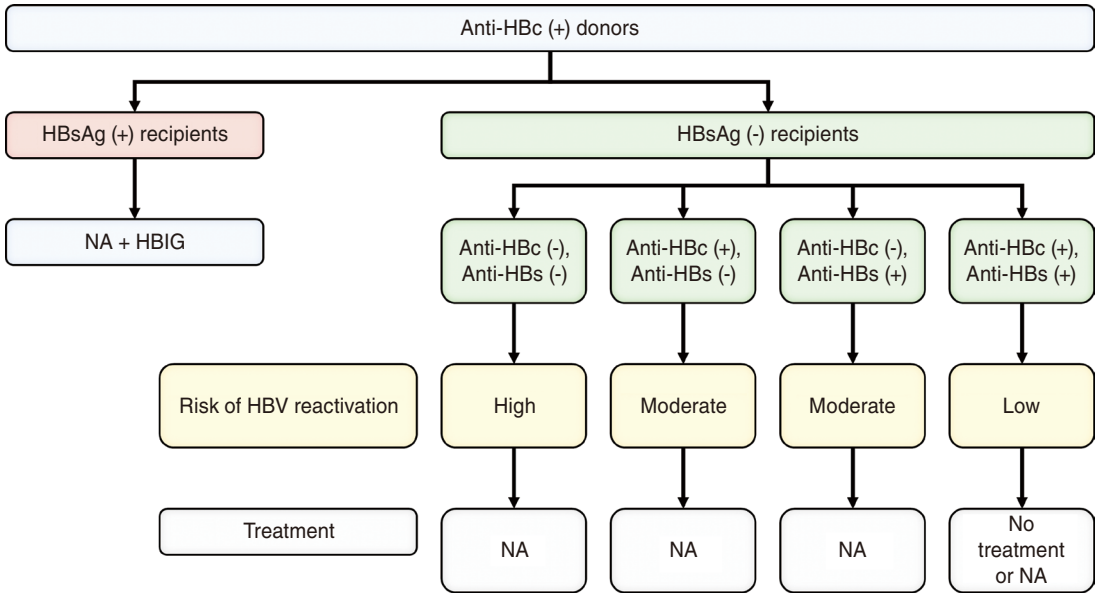

Figure 5. Management strategies after liver transplantation in patients receiving anti-HBc-positive liver graft. anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue.

nors, or HBsAg-negative/anti-HBc-positive recipients undergoing non-hepatic solid organ transplantation, should be monitored for HBV reactivation after transplantation with HBsAg and HBV DNA; NA therapy (TAF, ETV, or TDF) should be initiated if either becomes positive. (B1)

Recipients undergoing liver or other solid organ transplantation from HBsAg-positive donors

Liver transplantation from HBsAg-positive donors

Liver transplantation from HBsAg-positive donors may be considered in selected cases to expand the donor pool, particularly in HBsAg-positive recipients.[559,560] Careful patient selection, thorough risk–benefit assessment, and informed consent regarding the potential risk of HCC are required.[524] Transplantation from HBsAg-positive donors should not be performed in patients with HDV infection, given the high likelihood of HDV reinfection or recurrence and poor clinical outcomes. Recipients of HBsAg-positive donor livers should receive lifelong NA therapy (TAF, ETV, or TDF). HBIG is generally not required, because the graft is already infected with HBV.

Other solid organ transplantation from HBsAg-positive donors

Transplantation of non-hepatic solid organs from HBsAg-positive donors may be considered in HBsAg-positive recipients or in carefully selected HBsAg-negative recipients, as it may expand the donor pool and provide clinical benefit. However, HBsAg-negative recipients are at risk of de novo HBV infection; therefore, active and passive immunization, along with NA therapy, is recommended. In particular, when non-hepatic solid organs are transplanted from HBsAg-positive donors, combination prophylaxis with NA and HBIG is recommended in recipients who do not have protective threshold of anti-HBs titers (>100 mIU/mL).[27,524] The optimal duration of HBIG therapy has not been clearly established; however, limited data suggest that a short course (approximately 3 months) may be sufficient.[549,561,562] All recipients of organs from HBsAg-positive donors should undergo long-term prophylaxis with potent NAs (TAF, ETV, or TDF). The optimal duration of NA prophylaxis remains uncertain; however, discontinuation may be considered in selected patients who achieve a stable anti-HBs response (>100 mIU/mL) after HBV vaccination, with close monitoring of HBsAg and HBV DNA.

[Recommendation]

1. Recipients of liver transplants from HBsAg-positive donors should receive NA (TAF, ETV, or TDF) therapy. (B1)
2. Recipients of non-hepatic solid organ transplants from HBsAg-positive donors with anti-HBs levels below the protective threshold (<100 mIU/mL) should be considered for combination prophylaxis with NA (TAF, ETV, or TDF) and HBIG. (C1)

ACUTE HEPATITIS B

In the majority of immunocompetent adults, AHB is a self-limiting condition, with over 95% of patients achieving spontaneous recovery and HBsAg seroclearance without the antiviral intervention. However, in regions where CHB is endemic, distinguishing a primary AHB infection from an acute exacerbation of underlying CHB remains a significant diagnostic challenge due to their overlapping symptomatic and serological profiles.[563,564] Accurate differentiation is essential, as the therapeutic strategies and long-term prognoses for these two conditions differ fundamentally. Although IgM anti-HBc has served as the hallmark diagnostic marker for AHB, its specificity is limited by the fact that nearly 25% of patients with acute exacerbation of CHB also exhibit IgM anti-HBc positivity. Quantification of IgM anti-HBc can provide additional diagnostic clarity, as significantly higher titers are more indicative of AHB.[134] Furthermore, a detailed review of the patient's medical history—including previous HBV status and family history—is critical for an accurate diagnosis.

The necessity of antiviral therapy for AHB remains controversial. Some data suggest that early antiviral intervention might interfere with the host's natural immune response and suppress the production of virus-specific neutralizing antibodies, potentially increasing the risk of progression to chronicity.[565,566] In a meta-analysis involving 597 patients across seven studies, those treated with lamivudine had a higher risk of developing chronic infection compared to the placebo group.[567]

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However, a subset of patients may progress to severe hepatitis or acute liver failure, which can lead to mortality or necessitate urgent liver transplantation. Severe AHB is clinically defined by the presence of coagulopathy (INR >1.5), profound jaundice, or signs of hepatic encephalopathy.[568] In patients patients who progress to severe hepatitis or acute liver failure, antiviral therapy has been shown to significantly reduce mortality rates and the need for liver transplantation.[569,570] Although RCTs evaluating the overall clinical benefit of early treatment are limited, cohort data suggest that the early administration of potent NAs—such as TAF, TDF, or ETV—can prevent the onset of acute liver failure, lower transplantation rates, and enhance survival. Additionally, one prospective multicenter cohort study observed that initiating antiviral therapy within 8 weeks of symptom onset was associated with lower rates of chronicity compared to delayed initiation beyond 8 weeks.[571,572]

Clinicians should closely monitor the liver function of all symptomatic patients with AHB. If the clinical course shows signs of progression toward severe hepatitis, immediate pharmacological and surgical considerations are warranted.

[Recommendation]

1. For AHB patients who exhibit a severe clinical course—characterized by coagulopathy, severe jaundice, or signs of liver failure—antiviral therapy should be initiated immediately, and liver transplantation may be considered. (B1)

PATIENTS WITH VIRAL COINFECTION

HBV/HCV coinfection

In South Korea, the prevalence of HBV and HCV coinfection among HBsAg-positive individuals is estimated to be approximately 1.5 to 2.4%.[573,574] Clinically, coinfected patients often present with more severe necroinflammatory activity and hepatic fibrosis, and face a substantially higher risk of developing cirrhosis, hepatic decompensation, and HCC compared to those with monoinfection.[575-579] Before initiating any antiviral therapy, a comprehensive virological assessment is mandatory. Clinicians should quantify serum HBV DNA and HCV RNA levels to determine the replicative activity of each virus. If HCV RNA is detectable, antiviral therapy using HCV-specific DAAs should be initiated. If the patient meets the established treatment criteria for CHB, HBV therapy should be administered concurrently or sequentially, following the same therapeutic principles as HBV monoinfection (Fig. 2).

A critical clinical challenge in coinfected patients is the potential for HBV reactivation during or after the clearance of HCV with DAA therapy. As HCV is eradicated, the suppressive effect it may have exerted on HBV replication is lifted, which can lead to a significant rise in HBV DNA levels and subsequent ALT flares. Meta-analyses have shown that approximately 12% to 14.1% of coinfected patients experience a significant rise in HBV DNA, with biochemical flares occurring in 12.2% of them.[580,581] In patients with resolved HBV infection (HBsAg-negative and anti-HBc-positive), the risk of reactivation is approximately 0.4%. For patients with a history of cirrhosis or HCC, prophylactic HBV therapy should be considered alongside DAA treatment to mitigate the risk of severe liver failure induced by HBV reactivation.[582,583]

Potent NAs such as TAF, TDF, or ETV are the preferred, and have revealed no significant drug-drug interactions with current HCV DAAs. However, in cases of triple infection (HBV/HCV/HIV), an appropriate antiviral regimen should be selected cautiously to avoid potential drug-drug interactions.[584,585]

Continuous monitoring of serum ALT and HBV DNA levels is essential throughout the duration of HCV treatment and after its completion to detect HBV reactivation.

[Recommendation]

1. Patients with HBV/HCV coinfection with detectable HCV RNA should be treated with appropriate HCV-specific DAA regimens. (A1)
2. Patients with HBV/HCV coinfection who meet the standard treatment criteria for CHB should receive HBV antiviral therapy as per current guidelines. (A1)
3. Regular monitoring of ALT and HBV DNA is required during and after DAA therapy for all HBsAg-positive patients to identify HBV reactivation promptly. (B1)
4. In HBsAg-negative/anti-HBc-positive patients undergoing DAA therapy, HBsAg and HBV DNA testing

should be performed immediately if ALT elevation occurs to exclude HBV reactivation. (B1)

HBV/HIV coinfection

The prevalence of HBV coinfection among patients with HIV is estimated to be approximately 8.4% globally and about 5% in South Korea.[586,587] Coinfected patients face a significantly higher risk of rapid fibrosis progression and HCC compared to those with HBV monoinfection. Furthermore, mortality rates are markedly increased in this population, particularly among individuals with lower CD4+ T-cell counts.[588,589]

In alignment with current HIV guidelines, antiretroviral therapy (ART) is recommended for all HIV/HBV coinfected individuals, regardless of their CD4+ T-cell count. The ART regimen must include tenofovir (either TAF or TDF) as a core component, as these agents provide potent, long-term suppression of both viruses.[590] If a modification to the ART regimen becomes necessary, clinicians must ensure that HBV-active agents are continuously maintained to mitigate the risk of HBV reactivation or severe biochemical relapse. If tenofovir-containing regimens are not feasible, ETV may be utilized to manage the HBV infection; however, the potential for resistance must be carefully evaluated, particularly in patients with a history of prior NA exposure.

Clinicians should be vigilant during the initial phase of treatment for the development of immune reconstitution inflammatory syndrome, which can manifest as paradoxical elevations in liver enzymes.

[Recommendation]

1. For HBV/HIV coinfected patients, ART regimen including tenofovir (TAF or TDF) must be initiated. (A1)

HBV/HDV coinfection

HDV is characterized as a defective RNA virus that is unable to produce its own envelope protein, thus requiring the presence of HBsAg to enter hepatocytes, replicate its genome, and express its antigens.[591] It occurs either as a simultaneous coinfection with HBV or as a superinfection in individuals already infected with HBV, and it is recognized as the most aggressive form of viral hepatitis, carrying approximately a three-fold higher risk of progression to cirrhosis and HCC compared to HBV monoinfection.[533]

Accurate diagnosis relies on detecting serum HDV RNA or identifying the HDV antigen in liver tissue via immunohistochemistry, as the initial anti-HDV antibody screening only indicates exposure rather than current active replication.[23] Clinicians should exercise caution as HDV RNA can be transiently undetectable; therefore, rather than relying on a single test, repeated testing at three to six-month intervals is recommended. Regardless of the viral load, all coinfected patients must undergo a baseline assessment of liver fibrosis.

For patients with HBV/HDV coinfection who meet the standard treatment criteria for CHB, NAs should be administered to prevent disease progression. Since NAs do not directly inhibit HDV replication, Peg-IFNα could be considered to suppress both viruses in patients with compensated liver disease.

The primary clinical objectives for patients with detectable HDV RNA—who are all candidates for therapy regardless of disease severity—are the suppression of HDV replication, normalization of ALT levels, and histological improvement. The traditional standard of treatment involves the subcutaneous administration of 180 μg of Peg-IFNα weekly for 48 weeks, though long-term follow-up indicates that SVR rates remain low, approximately 12%, due to frequent post-treatment relapses.[592-594] The achievement of a sustained virological response can be predicted by measuring serum HDV RNA at 24 weeks after the start of Peg-IFNα.[595]

Therapeutic advances have introduced bulevirtide, a synthetic lipopeptide entry inhibitor that competitively targets the sodium taurocholate cotransporting polypeptide (NTCP) receptor shared by HBV and HDV.[596] Clinical trials have demonstrated that bulevirtide yields significant virological and biochemical responses, leading to its conditional approval by the European Medicines Agency for patients with compensated liver disease.[597,598] Additionally, combination therapy involving bulevirtide and Peg-IFNα has shown potential for enhancing SVR rates compared to monotherapy.[599]

Emerging therapeutic agents, including the siRNA elebsiran and the monoclonal antibody tobevibart, are currently being evaluated and have demonstrated high rates of viro-

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logical response and significant HBsAg reduction in recent phase II trials.[600] For patients with decompensated liver disease, liver transplantation remains the primary management consideration.

[Recommendation]

1. In patients with CHB who exhibit elevated ALT levels despite low serum HBV DNA concentrations—and where no other identifiable causes for liver enzyme elevation are present—screening for HDV coinfection through anti-HDV or HDV RNA testing should be performed. (B1)
2. For patients with HBV/HDV coinfection who meet the established criteria for CHB treatment or those presenting with decompensated cirrhosis, NAs should be administered to prevent liver disease progression. (A1)
3. In HDV-coinfected patients with compensated liver disease, treatment with Peg-IFNα or bulevirtide should be considered. (A2)

PREGNANT OR BREASTFEEDING WOMEN AND THOSE PLANNING PREGNANCY

In general, during pregnancy, many women with CHB are in the immune-tolerant phase either because of hormonal changes or because this period corresponds to the early stage of the natural disease course, and changes in the maternal immune system, with a shift of the Th1-Th2 balance toward Th2 responses, lead to an increase in serum HBV DNA and a decrease in ALT levels.[601,602] However, in late pregnancy and the postpartum period, these immune changes revert, which may result in a decrease in serum HBV DNA and an increase in ALT levels; therefore, careful monitoring is required during this period.[603,604]

When initiating antiviral therapy in women who are planning pregnancy or who are pregnant, treatment decisions should be based on general treatment principles. During pregnancy, antiviral agents should be selected with careful consideration of safety for both the fetus and the mother. Tenofovir (TDF or TAF) and telbivudine have shown no fetal adverse effects in animal studies, and although controlled human studies are limited, multiple clinical studies and pregnancy registry data have demonstrated that these agents can be used safely without an increased risk of congenital malformations.[605-611] Several recent clinical studies from China have demonstrated the safety and efficacy of TAF when used during pregnancy. In a national retrospective cohort study that analyzed 71 pregnant women who received TAF during the second to third trimester and 73 infants (including two pairs of twins), no congenital anomalies or malformations were observed, the infants' growth and development were within normal ranges, and no serious adverse events were reported in either mothers or infants.[609] In a multicenter prospective observational study comparing TAF (n=116) with TDF (n=116), the rate of vertical transmission was 0% in both groups, and physical and neurodevelopmental outcomes were comparable or better in the TAF group. Notably, compared with the TDF group, the TAF group did not show elevations in urine retinol-binding protein and β2-microglobulin, suggesting better renal safety, and drug concentrations were undetectable in breast milk, supporting the safety of use during breastfeeding.[608] In an RCT of pregnant women with high viral loads (HBV DNA ≥6 $\log_{10}$ IU/mL), both TAF and TDF achieved 100% prevention of vertical transmission, and no congenital malformations were reported.[611] Although fetal adverse effects have been reported for lamivudine in animal studies, sufficient safety data from clinical trials and large pregnancy registries have accumulated, and an increased rate of congenital malformations has not been reported even when lamivudine is administered during the first trimester.[605] In contrast, ETV and adefovir are not recommended during pregnancy because their safety has not been clearly established and adverse effects have been reported in animal studies. Therefore, when antiviral therapy is required during pregnancy, tenofovir (TDF or TAF) is recommended as the first-line agent.

In women who become pregnant while already receiving oral antiviral therapy before pregnancy, continuation of antiviral treatment during pregnancy is recommended. In women who are planning pregnancy or who become aware of their pregnancy while receiving antiviral agents other than tenofovir (TDF or TAF), switching to tenofovir (TDF or TAF) is recommended to continue treatment.

In HBsAg-positive mothers who are not receiving antiviral therapy, accumulating evidence indicates that breastfeeding itself does not increase the risk of vertical transmission

if appropriate immunoprophylaxis (administration of HBIG and vaccine immediately after birth) is provided. In a retrospective study from China that followed 546 infants born to HBsAg-positive mothers for a mean of 4.7 years, there was no significant difference in the rate of HBsAg positivity between the breastfeeding and formula-feeding groups.[612] Similarly, in a prospective cohort of 435 HBeAg-positive mothers, the rate of HBsAg positivity in infants at 8–12 months was 8.3% in the breastfeeding group and 9.2% in the formula-feeding group, with no statistically significant difference, supporting the notion that breastfeeding does not increase the risk of infection.[613]

Although evidence regarding the safety of breastfeeding during antiviral therapy is limited, important information has been provided from studies on prevention of mother-to-child transmission using TDF and TAF. In the aforementioned RCT of pregnant women with high viral loads (HBV DNA ≥6 $\log_{10}$ IU/mL), drug concentrations were undetectable in cord blood and breast milk in the TAF group, whereas low concentrations were detected in breast milk in the TDF group; nonetheless, all infants showed negative HBV DNA and HBsAg results, and no significant issues in their growth or short-term safety were observed.[611] In addition, in a retrospective cohort study of 210 pregnant women with high viral loads, the group that continued TDF therapy and breastfeeding after delivery had a lower rate of vertical transmission than the group that discontinued treatment, and although low drug concentrations were detected in breast milk, drug was undetectable in infant plasma and no statistically significant differences in infant growth or safety outcomes were observed.[614] These findings suggest that, although tenofovir is excreted into breast milk, its concentration is very low and clinically significant drug exposure or absorption in infants is unlikely. Furthermore, studies of pre-exposure prophylaxis and ART in regions with a high prevalence of HIV have consistently shown that TDF-based regimens are effective for preventing vertical HIV transmission during pregnancy and breastfeeding, with low drug concentrations in breast milk and no major abnormalities in infant growth or bone development.[615-618] However, the evidence is still insufficient to draw definitive conclusions regarding the safety of breastfeeding while taking TAF, and more systematic studies are needed.

In HBsAg-positive pregnant women, when serum HBV DNA levels exceed 6–8 $\log_{10}$ IU/mL, the rate of vertical transmission can reach 30%, and this can occur even when appropriate immunoprophylaxis is provided to the newborn.[619,620] Therefore, the key to preventing vertical transmission is to reduce maternal serum HBV DNA levels to below 200,000 IU/mL as early as possible during pregnancy through antiviral therapy.

Tenofovir (TDF or TAF) is recommended for antiviral therapy to prevent vertical transmission. A recent systematic review and meta-analysis including 31 studies (2,588 women treated with TDF, 280 treated with TAF, and 1,600 untreated controls) confirmed that both TDF and TAF are effective in preventing vertical transmission and are safe for both mothers and infants.[610]

Antiviral therapy to prevent vertical transmission is ideally started before 28 weeks of gestation and is recommended to begin between 24 and 32 weeks. However, recent data suggest flexibility in the timing of treatment initiation. Although most previous studies initiated antiviral therapy between 28 and 32 weeks of gestation, a recent multicenter RCT from China reported that starting TAF at 33 weeks of gestation and continuing treatment for 8 weeks allowed 97% of pregnant women to achieve HBV DNA <200,000 IU/mL by the time of delivery.[621] A modeling study based on real-world clinical data suggested that pregnant women with serum HBV DNA levels >8 $\log_{10}$ IU/mL should begin antiviral therapy before 25 weeks of gestation.[622] In a recent RCT of pregnant women with serum HBV DNA >200,000 IU/mL, the effectiveness of preventing vertical transmission was comparable between a group that received TDF from 16 weeks of gestation with vaccination alone for newborns and a group that started TDF at 28 weeks with a combination of vaccination and HBIG for newborns.[623] These findings indicate that early initiation of antiviral therapy is effective in preventing vertical transmission and suggest that starting treatment as early as 16 weeks of gestation may be a viable alternative in resource-limited settings where the use of HBIG is constrained.[623] In clinical practice, antiviral therapy during pregnancy can therefore be started as early as possible (including the first trimester), but should be initiated no later than 28 weeks of gestation, and the timing of initiation should be individualized based on maternal serum HBV DNA levels, pregnancy plans, and other clinical factors.

Antiviral therapy for the sole purpose of preventing vertical transmission should in principle be continued until the

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time of delivery, and extension of treatment for 2–12 weeks postpartum is recommended. However, the decision to discontinue therapy after delivery and the timing of discontinuation should be made after considering future pregnancy plans, the presence or absence of conventional treatment indications, and the patient's preference for ongoing therapy. Systematic reviews and prospective studies have shown no significant differences in the rates of vertical transmission or virologic relapse between women who discontinued antiviral therapy at the time of delivery and those who continued therapy for several weeks postpartum, and no long-term benefit of prolonged therapy has been demonstrated.[610,624,625] Although transient ALT flares after discontinuation of antiviral therapy have been reported, meta-analyses indicate no difference in the incidence of acute ALT flares between discontinuation at delivery and discontinuation several weeks later.[610,624] Therefore, in women who receive antiviral therapy solely for the purpose of preventing vertical transmission, treatment can be stopped at the time of delivery; however, careful follow-up of liver function and virologic response is essential for a certain period after treatment cessation.

[Recommendation]

1. In pregnant women or women with CHB who are planning pregnancy, the decision to initiate oral antiviral therapy should be based on general treatment principles, and TDF or TAF is recommended as the first-line agent. (A1)
2. In patients who are planning pregnancy or who become aware of pregnancy while receiving oral antiviral agents other than TDF or TAF, switching to TDF or TAF, which are relatively safe for both the mother and fetus, is recommended. (A1)
3. In pregnant women with CHB who are not receiving antiviral therapy, breastfeeding should not be restricted after delivery. (B1)
4. In pregnant women with serum HBV DNA levels ≥200,000 IU/mL, antiviral therapy during pregnancy should be initiated to prevent vertical transmission. (A1) For the purpose of preventing vertical transmission, antiviral therapy is ideally started before 28 weeks of gestation and is recommended to begin between 24 and 32 weeks, with continuation until 2–12 weeks postpartum. (B1)

PEDIATRIC AND ADOLESCENT PATIENTS

Hepatitis B immunoglobulin injection and vaccination within 12 hours of birth can reduce perinatal hepatitis B infection by up to 90–95%.[626,627] However, approximately 90% of infants who acquire HBV perinatally progress to chronic infection. These patients typically remain in the immune-tolerant phase—characterized by HBeAg positivity and very high HBV DNA levels—throughout late childhood or adolescence, although a subset eventually transitions to the immune-active phase (Supplementary Fig. 1). In South Korean pediatric cohorts, the estimated transition rates from the immune-tolerant to the immune-active phase are 4.6% in children under 6 years, 7.1% between 6–12 years, and 28% in those aged 12–18 years.[628] Longitudinal data from Taiwan indicate that the annual rate of spontaneous HBeAg seroconversion is approximately 2% in children under 3 years and 4–5% thereafter.[629] Although the immune-active phase is associated with elevated ALT levels and histological evidence of necroinflammation and fibrosis, pediatric patients are often asymptomatic. Persistent ALT elevation in this population necessitates serum HBV DNA test to assess the level of viral replication. A long-term study following 104 pediatric patients for a median of 23.7 years observed that ALT levels exceeding 60 IU/L were predictive of spontaneous HBeAg seroconversion.[630]

The decision to initiate antiviral therapy in children and adolescents requires a careful risk-benefit analysis, balancing the risk of disease progression to cirrhosis and HCC against the challenges of potential long-term treatment, drug side effects, and the emergence of viral resistance.[631,632] The primary therapeutic objectives are to suppress viral replication, alleviate hepatic inflammation, and improve fibrosis to prevent long-term complications. Although data on treating immune-tolerant pediatric patients are limited, a small RCT in China reported that 72 weeks of interferon monotherapy or sequential lamivudine therapy resulted in a 32.6% HBeAg seroconversion rate and 21.7% HBsAg loss at 24 weeks post-treatment.[633] Subsequent retrospective studies suggested that earlier treatment initiation is associated with significantly higher rates of HBeAg and HBsAg clearance. Notably, patients starting therapy before 7-years old achieved HBsAg loss rates of 50.8–52.8%, compared to only 12.3–12.9% in those starting after 7-years old. Furthermore, early intervention was associated

Table 8. Approved antiviral drugs in children and adolescents

Drugs	Age (years)	Dose
ETV	≥2 (and weighing at least 10 kg)	10–30 kg: 0.015 mg/kg daily (maximum 0.5 mg) >30 kg: 0.5 mg daily
TDF	≥2 (and weighing at least 10 kg)	10–35 kg: 8 mg/kg daily (maximum 300 mg) >35 kg: 300 mg daily
TAF	≥6 (and weighing at least 25 kg)	25 mg daily
Peg-IFNα	≥3	180 μg/1.73 m^2 once a week

BSV, besifovir dipivoxil maleate; ETV, entecavir; Peg-IFNα, pegylated interferon-alpha; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

with more rapid improvements in liver stiffness.[634,635] However, in children and adolescents, ALT fluctuations caused by factors other than HBV are common, making differential diagnosis important, and treatment decisions must be made cautiously to avoid interfering with natural HBeAg seroconversion. Based on these data, current consensus proposes initiating treatment if serum HBV DNA is ≥2,000 IU/mL accompanied by persistently elevated ALT levels for more than 6 months or evidence of significant liver fibrosis.[33,636,637] In patients with compensated or decompensated cirrhosis or HCC, antiviral therapy should be initiated immediately if HBV DNA is detectable, regardless of ALT levels.[635]

Although liver biopsy remains a definitive tool for fibrosis evaluation, there is an increasing clinical interest in NITs to assess fibrosis in children. However, the accuracy of NITs may vary significantly by age and sex.[160] A prospective study in China involving 157 pediatric patients (aged 0–6 years) found that VCTE provided the highest diagnostic accuracy compared to APRI or FIB-4. The established cut-off values for this population were 5.6 kPa for significant fibrosis and 6.9 kPa for advanced fibrosis.[638]

Antiviral agents approved for use in the pediatric population include Peg-IFNα, TAF, TDF and ETV (Table 8). Lamivudine and adefovir disoproxil are no longer recommended due to high resistance rates and limited efficacy. Treatment with ETV or TDF for 72–96 weeks has yielded virological response rates ranging from 70% to 90%, with HBeAg loss reported in 30–40% of cases.[639,640] The criteria for discontinuation of NAs aligns with those established for adult patients.

Peg-IFNα offers the advantage of a finite treatment duration and the absence of drug resistance, making it a viable therapeutic alternative for patients in whom long-term administration of NAs is challenging. In a phase III RCT evaluating a 48-week course of Peg-IFNα, the rate of HBeAg seroconversion at 24 weeks post-treatment was 25.7% in the treatment arm—significantly superior to the 6% in the control group. Furthermore, this regimen yielded markedly higher rates of HBsAg loss, virological response, and ALT normalization.[641]

[Recommendation]

1. Antiviral therapy could be considered in pediatric and adolescent patients who exhibit serum HBV DNA levels ≥2,000 IU/mL and either persistently elevated ALT levels for ≥6 months or evidence of significant liver fibrosis. (B2)
2. In pediatric and adolescent patients with cirrhosis and detectable serum HBV DNA, immediate antiviral therapy is recommended. (B1) Preferred initial therapeutic options include TAF, TDF, ETV, or Peg-IFNα. (A1)
3. If viral resistance emerges during treatment, rescue therapy should be managed in accordance with the established guidelines for adults. (B1)

Authors' contributions

List of author contributions is available at the official website of Clinical and Molecular Hepatology (Appendix 1, https://doi.org/10.3350/cmh.2026.0579).

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Conflicts of Interest

A conflict of interest statement is available at the official website of Clinical and Molecular Hepatology (Appendix 2, https://doi.org/10.3350/cmh.2026.0579).

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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