



APASL clinical practice guidelines on the management of chronic hepatitis B infection: a 2026 update

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Abstract

Globally, especially in the Asia Pacific region, chronic hepatitis B infection has led to an undesirable escalating morbidity and mortality with acute-on chronic liver failure, end-staged liver cirrhosis, and hepatocellular carcinoma. This has happened despite the past four decades of major scientific advances made in screening methods, vaccination strategies, highly effective low-cost anti-viral therapies, and surveillance strategies for early detection of hepatocellular carcinoma. To address this health threat, APASL has formed a Viral Elimination Taskforce to unite key opinion leaders from its member countries and regions. The ongoing shifts in hepatitis B epidemiology, socioeconomic changes, and advancements in technology are taken into consideration. With the conjoint efforts of all the members of the APASL Viral Elimination Taskforce, these clinical practice guidelines have been formulated aiming to facilitate healthcare professionals, policy-makers, and patients in making practical and cost-effective management decisions for chronic hepatitis B infection. Altogether, it provides recommendations in 13 major areas related to screening, vaccination, treatment, and HCC surveillance. The implementation of these clinical practice guidelines represents major APASL effort toward elimination of the disease burden due to chronic hepatitis B infection in Asia Pacific region.

Keywords Chronic hepatitis B · Prevention · Treatment · Hepatocellular carcinoma · Treat all · Guideline

Abbreviations

AI	Artificial intelligence
ALT	Alanine aminotransferase
AP	Asia Pacific
ALD	Alcohol-associated liver disease
CHB	Chronic hepatitis B
CPGs	Clinical Practice Guidelines
APASL	Asian Pacific Association for the Study of the Liver

AASLD	American Association for the Study of Liver Diseases
EASL	European Association for the Study of the Liver
DAA	Direct-acting antiviral
ETV	Entecavir
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBVr	HBV reactivation
HCC	Hepatocellular carcinoma
HCP	Healthcare professionals
HIV	Human immunodeficiency virus
MAFLD	Metabolic dysfunction-associated fatty liver disease

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MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MTCT	Mother-to-child transmission
NITs	Non-invasive tests
NUCs	Nucleos(t)ide analogs
Peg-IFN- α	Pegylated interferon alpha
qHBsAg	Quantitative HBsAg
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
VCTE	Vibration-controlled transient elastography
WHO	The World Health Organization

Introduction

Burden of diseases in Asia Pacific region

Hepatitis B virus (HBV) infection remains a major public health challenge in the Asia Pacific (AP) region, home to over two-thirds of the world's 260 million people with chronic HBV (CHB) infection [1]. Eight countries, i.e., China, India, Indonesia, Bangladesh, Vietnam, the Philippines, Pakistan, and Myanmar, collectively account for nearly 90% of HBV cases and related deaths in the AP region (Table 1). HBV prevalence among children under five in the AP region is lower than the global average, but the region's large pediatric population means an estimated 1.6–2.6 million being HBsAg-positive, representing 26–34% of the global burden in this age group [1]. The success of HBV control efforts in these countries will therefore largely determine the trajectory of disease burden reduction globally.

Despite the availability of universal vaccination, reliable diagnostics, and effective antiviral therapy, CHB diagnosis and treatment rates remain low in the AP region, often below 15% [2], severely hampering progress toward global elimination targets. Persistent barriers, such as insufficient linkage to care, unaffordable CHB treatment [3], constrained health budgets, low prioritization of HBV programs, stigma, fragmented health services, and weak integration of HBV care into primary health systems, continue to impede progress.

Evolving understanding of chronic hepatitis B natural history

Recent advances in HBV virology and immunopathology have reshaped our understanding of chronic hepatitis B (CHB). The traditionally defined “immune-tolerant” phase is now recognized as potentially progressive, with ongoing hepatic inflammation and hepatocellular carcinoma (HCC) risk even when alanine aminotransferase (ALT) levels are within so-called “reference range” [4, 5]. Non-invasive

fibrosis assessment and novel quantitative biomarkers, including quantitative HBsAg (qHBsAg), HBV RNA, and hepatitis B core-related antigen (HBcrAg), have transformed disease monitoring, risk stratification, and treatment decision-making [6].

In the AP region, most adults with CHB are now HBeAg-negative, while younger patients often present in the immune-tolerant phase with high viral loads but minimal biochemical abnormalities [7]. These evolving patterns underscore the need for earlier risk assessments and individualized treatment strategies.

Rationale for updated guidelines

Clinical practice guideline (CPG) development for CHB by regional professional associations, including Asian Pacific Association for the Study of the Liver (APASL) [10], American Association for the Study of Liver Diseases (AASLD) [8], and European Association for the Study of the Liver (EASL) [9], began more than two decades ago. These earlier CPGs by APASL were developed when many of today's diagnostic tools and treatment options were unavailable [10–12]. Eligibility criteria for antiviral therapy were based on studies conducted before the advance of novel biomarkers, such as qHBsAg, HBcrAg, HBV RNA, more precise HBV DNA quantification, and non-invasive fibrosis assessment technologies [10, 11, 13–17].

In recent years, the therapeutic landscape for CHB has evolved substantially. The reduced cost of established first-line antivirals with high-resistance barrier nucleos(t)ide analogs (NUCs) such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and pegylated interferon- α has been proven to have long-term safety [18]. This together with emerging evidence supporting combination therapy [19, 20], early treatment initiation to reduce the risk of cirrhosis and liver cancer, and perhaps the development of new agents aiming for functional cure, are rapidly reshaping clinical management of CHB. Hence, simplified clinical algorithms are increasingly needed to improve diagnosis and treatment uptake amid persistently high HBV-related morbidity and mortality.

The rising prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD, as defined and endorsed by APASL [21]) and alcohol-associated liver disease (ALD), further complicates CHB management. While the term metabolic dysfunction-associated steatotic liver disease (MASLD) has been proposed and adopted in some international consensus statements, MAFLD remains the recommended terminology within APASL guidelines and is widely used across the Asia Pacific region. In this guideline, MAFLD is therefore adopted in accordance with APASL recommendations, while MASLD is acknowledged when

Table 1 (continued)

	Polaris 2024				GBD 2021			
	All ages		Age ≤ 5		All ages		Age 0–4	
	Population	HBV Prevalence	Annual Deaths	HBV Prevalence	Population	HBV Prevalence	Population	HBV Prevalence
Rate, per 100,000		6,173	30	1,000		6,590		6,590
Philippines								
Number	115,843,670	5,513,070	19,484	11,376,927	113,249,536	6,979,990	11,213,381	330,224
Rate, per 100,000		4,759	17	800		6,163		6,163
Pakistan								
Number	251,269,164	3,852,085	10,723	38,148,254	235,553,608	5,930,561	29,725,996	187,065
Rate, per 100,000		1,533	4	200		2,518		2,518
Myanmar								
Number	54,500,091	2,515,831	9,756	5,291,923	56,419,670	977,626	5,226,411	57,035
Rate, per 100,000		4,616	18	1,200		1,733		1,733

referring to international literature and broader consensus frameworks.

In addition, the rapid integration of artificial intelligence (AI) and big data analytics into clinical decision-making is anticipated to transform CHB management in future. Therefore, the updated APASL clinical practice guidelines are needed to provide evidence-based recommendations that reflect the evolving science, improve cost-effectiveness, and optimize care for CHB patients across the Asia Pacific region.

Methodology

The development of the current CPGs was initiated by the APASL Viral Elimination Taskforce established in 2022 as part of its mission to break the barriers to alleviate disease burden related to viral hepatitis in the AP region. The guideline development followed a rigorous, systematic, and evidence-based process to ensure validity, reliability, and clinical applicability of the recommendations. A panel comprising key opinion leaders from about 20 countries or special administrative regions across the AP region was convened to formulate the CPGs. The panel operated under the chairmanship of Drs. George Lau, Shiv Kumar Sarin, and Masao Omata. All members were selected based on their significant clinical experience and research contributions in the field of HBV infection and were required to comply with the APASL conflict of interest policy with full disclosure. Individuals whose research activities or publications were primarily sponsored by pharmaceutical companies were excluded to ensure unbiased recommendations and to uphold the best interests of patients and the public. The first face-to-face meeting was held during the 34th APASL Annual Meeting in Beijing, China, on 29th March 2025, where the workflow of the CPGs was discussed and agreed upon. The process began with the identification of key clinical questions related to the management of CHB, categorized according to clinical practice needs. Each panel member was assigned to address one or two questions, typically within their respective areas of expertise. A rigorous methodology was adopted, encompassing systematic literature reviews, evidence appraisal, consideration of patient values and preferences, cost-effectiveness, and feasibility. Comprehensive reviews of clinical trials, systematic reviews, meta-analyses, and other relevant studies were conducted by the panel members to inform the final recommendations. The quality of evidence and the strength of each recommendation were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Table 2). On 20 September 2025, a hybrid meeting was conducted in Hong Kong SAR, China with 13 areas of recommendations presented by expert members and thoroughly

Table 2 GRADE system

Category	Grade / Symbol	Definition & Meaning	Typical Wording in Guidelines
Quality of Evidence	High (A)	We are very confident that the true effect lies close to the estimate of the effect. Further research is very unlikely to change our confidence in the estimate	"The evidence is of high quality..."
	Moderate (B)	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate, but there is a possibility that it is substantially different. Further research may have an important impact	"The evidence is of moderate quality..."
	Low (C)	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate. Further research is very likely to have an important impact	"The evidence is of low quality..."
	Very Low (D)	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate. Any estimate is very uncertain	"The evidence is of very low quality..."
Strength of Recommendation	Strong (1)	The desirable effects of the intervention (benefits) clearly outweigh the undesirable effects (harms and burdens), or vice versa. Most informed patients would choose the recommended course of action	"We recommend..."
	Weak / Conditional (2)	The trade-offs are less certain: either the evidence is lower quality, or the benefits and harms are closely balanced. Different choices will be appropriate for different patients; shared decision-making is needed	"We suggest..." or "Conditionally recommend..."

discussed. Consensus on the final recommendations was achieved through structured discussions among the panel members with further multiple rounds of online and in-person meetings. The manuscript was subsequently drafted and received final approval from the APASL Steering Committee on 8 November 2025 at Washington DC, USA during the AASLD The Liver Meeting 2025.

Recommendations

The CHB CPG addresses key clinical questions in 13 areas, each accompanied by evidence-based recommendations (Table 3). The following sections present these recommendations along with their underlying clinical rationale.

I. Vaccination, screening, and testing

Vaccination

Hepatitis B vaccines, first developed as plasma-derived formulations in early 1980s and later as recombinant DNA

vaccines, have dramatically reduced HBV transmission and liver disease burden worldwide. Universal immunization has led to marked declines in infection, chronic virus carriage, cirrhosis, and HCC [22]. A timely birth dose remains essential to prevent perinatal transmission [23]. For individuals who missed birth dose or childhood vaccination, catch-up and targeted vaccination remain essential particularly for high-risk populations, including immunocompromised individuals, patients at increased risk of severe hepatitis B, and those with a higher likelihood of occupational and non-occupational exposure [24].

In newborns, what is the optimal timing of the first dose of the hepatitis B vaccine to prevent perinatal transmission of HBV?

Timely administration of the hepatitis B birth dose is a highly effective intervention to prevent perinatal HBV transmission. Evidence demonstrates that vaccination within 24 h of birth provides substantial protection against infection, while delays significantly reduce effectiveness [25]. For infants born to HBsAg-positive mothers, early

Table 3 Summary of the CHB CPG

1	Vaccination
	In newborns, what is the optimal timing of the first dose of the hepatitis B vaccine to prevent perinatal transmission of HBV?
	In vaccinated individuals, is post-vaccination serologic testing necessary to confirm immunity?
	Should hepatitis B vaccination booster doses be given to individuals who have completed the primary vaccination series?
2	Screening
	Who should be screened for HBV infection?
	How to screen HBV infection?
3	Assessment of liver fibrosis
	How to assess liver fibrosis?
	How should liver fibrosis be assessed in resource-limited settings and what is the role of non-invasive tests?
	How to identify predominant driver of liver injury in patients with concurrent CHB and MAFLD non-invasively?
4	Treatment goals
	What are the goals of CHB therapy, and what are the surrogate endpoints for the treatment goals?
5	Treatment Strategies
	How effective are current therapies?
	What biomarkers should guide treatment?
	How should treatment decisions be guided by cost-effectiveness, long-term safety, and patient preferences?
	Should treatment be initiated in CHB patients at earlier fibrosis stages or specific groups that do not meet traditional treatment initiation criteria?
	Under what conditions can antiviral therapy be safely stopped, and how should relapse be monitored post-cessation?
6	Special populations
	How to manage HBV in pregnant women?
	How to manage HBV in population with metabolic comorbidities?
	How to manage HBV in patients with coinfections (HDV/HCV/HIV)?
	How to manage HBV in patients with alcohol-associated liver diseases?
	How to manage HBV in those with end-stage liver disease?
7	Prevention of HBV reactivation related to the use of immunosuppressive therapy
8	HCC risk prediction
	How do risk prediction models best guide HCC surveillance?
9	HCC surveillance strategies
	What surveillance strategies are needed for those with mPAGE-B ≥ 9 ?
	What surveillance strategies are needed for those with post-HBsAg clearance?
10	Prevention of MTCT
	In infants born to HBV-infected mothers, when should HBV testing be performed?
11	Prevention of transmission in other populations
	Should NUCs be used prophylactically to prevent HBV transmission in general populations and in HBV-infected healthcare professionals (HCP) performing exposure-prone procedures?
	In households or sexual contacts of individuals with chronic HBV infection, should family-based screening be implemented to identify undiagnosed infection and guide vaccination of susceptible persons?
12	Service delivery models
	How can stigma in occupational settings be addressed?
	What are optimal models of care to enhance access to screening and linkage to treatment?
13	Functional cure
	What is the role of functional cure as a therapeutic endpoint in the management of chronic hepatitis B?

vaccination within 12 h, in combination with hepatitis B immune globulin (HBIG), further reduces the risk of mother-to-child transmission to less than 5% [25]. Completion of the full hepatitis B vaccine series is recommended according to the standard schedule. For the conventional 3-dose regimen, vaccines should be administered

at 0, 1, and 6 months, with the full series ideally completed within 6 months. When alternative accelerated schedules are used, doses should be given according to the approved product labeling. Completion of the full vaccine series ensures durable immunity and long-term protection.

Recommendations

1. The first dose of the hepatitis B vaccine should be administered to all clinically stable newborns within 24 h of birth. **(A1)**
2. For infants born to HBsAg-positive mothers, the vaccine should be administered within 12 h of birth, preferably together with hepatitis B immune globulin (HBIG). **(A1)**
3. Completion of the full vaccine series according to the standard schedule is necessary to ensure long-term protection. **(A1)**

In vaccinated individuals, is post-vaccination serologic testing necessary to confirm immunity?

Over 90% of healthy adults and over 95% of vaccinated infants achieve protective anti-HBs levels (≥ 10 mIU/mL) after the standard three-dose hepatitis B vaccination series [26]. Immune memory persists even as antibody levels decline, allowing rapid protection upon exposure [27]; thus, routine post-vaccination testing is clinically unnecessary and not cost-effective [28].

Testing is recommended only for high-risk groups. Early identification of non-responders through post-vaccination testing guides revaccination with higher or adjuvanted doses, optimizing individual and public health protection [29]. In immunocompromised populations, response rates are lower or wane faster [30]. Among individuals living with HIV, the response to vaccination is inversely correlated with CD4 count and HIV viral load control [31]. For healthcare workers, post-vaccination testing also serves as documentation for occupational safety [32]. Infants of HBsAg-positive mothers should be tested at 9–12 months as 5–10% may fail prophylaxis despite timely vaccination and HBIG [33]. Household contacts and sexual partners should complete vaccination and undergo post-vaccination serologic testing 1–2 months after the final dose to confirm protective immunity (anti-HBs ≥ 10 mIU/mL). These targeted approaches optimize individual and public health protection while avoiding unnecessary interventions in the general population.

For infants born to mothers who present in late pregnancy with high viral loads and have not had adequate maternal prophylaxis, administration of HBIG together with first dose of hepatitis B vaccine within 24 h of birth, followed by doses at 1 and 6 months, effectively prevents MTCT [34]. Maternal HBsAg may persist in infants for up to 7 months, potentially causing false-positive results, so testing should be delayed until after this period [35, 36]. Anti-HBs ≥ 10 mIU/mL indicates protective immunity, while < 10 mIU/mL requires a booster dose and retesting. Despite standard immunoprophylaxis, 5–10% of infants born to HBeAg-positive mothers with high HBV DNA ($\geq 10^6$ IU/mL) may still acquire HBV

[37]. In such cases, early testing of HBsAg and HBV DNA 1–2 months after the second vaccine dose is recommended where feasible. Persistent dual positivity with rising HBV DNA confirms infection and warrants prompt referral for evaluation and management.

Recommendations

1. Routine post-vaccination serologic testing is *not* recommended for healthy individuals following hepatitis B or other standard vaccinations, given the high immunogenicity of current vaccines. **(A1)**
2. Testing is recommended for populations at risk of inadequate vaccine response or clinical consequences if unprotected:
 - a. Immunocompromised patients: Test anti-HBs 1–2 months post-vaccination; repeat vaccination if < 10 mIU/mL. **(A1)**
 - b. Healthcare workers: Test anti-HBs 1–2 months post-vaccination; repeat vaccination if < 10 mIU/mL, test HBsAg if persistently non-responsive. **(A1)**
 - c. Infants of HBsAg-positive mothers: Combined testing of HBsAg and anti-HBs should be performed 1–2 months after completion of the full three-dose hepatitis B vaccine series (i.e., at 9–12 months of age) to assess the effectiveness of immunoprophylaxis. **(A1)**
 - d. Household and sexual contacts of HBsAg-positive individuals: Test anti-HBs 1–2 months post-vaccination; repeat vaccination if < 10 mIU/mL. **(A2)**

Should hepatitis B vaccination booster doses be given to individuals who have completed the primary vaccination series?

Hepatitis B vaccination induces robust immune memory, providing long-lasting protection of at least 20 years in immunocompetent individuals, even as anti-HBs antibody levels decline [38]. Long-term follow-up studies show breakthrough infections and clinical disease are rare, supporting the recommendation against routine boosters in the general population. However, healthcare workers with ongoing exposures may be at increased risk, and immunocompromised individuals, such as dialysis patients or healthcare workers with ongoing exposure, may have weaker or waning immunity. In these groups, periodic anti-HBs monitoring can identify those who would benefit from a booster, ensuring targeted protection without unnecessary vaccination for most individuals. When anti-HBs concentration falls below 10 mIU/mL in high-risk or immunocompromised persons, booster dose may be considered.

Recommendations

1. Routine booster doses are *not* recommended for immunocompetent individuals who have completed the primary hepatitis B vaccination series and demonstrated an adequate immune response. **(A1)**.
2. Booster doses should be considered for high-risk or immunocompromised individuals when anti-HBs concentration falls below 10 mIU/mL. In such individuals, post-vaccination serologic testing can guide the need for a booster dose. **(A1)**.

Screening

Core principles of HBV screening

The World Health Organization (WHO) underscores the critical role of widespread screening, simplified diagnostic pathways, and vaccination in achieving global HBV elimination targets [2]. The HBV diagnosis rate remains low in the AP region. Undiagnosed infections perpetuate transmission and delay treatment, leading to advanced liver disease and death. Effective screening should combine universal and targeted strategies while ensuring equitable, patient-centered access to testing.

Who should be screened and tested for HBV infection?

Universal screening is highly cost-effective [39, 40], even at low prevalence ($>0.3\%$) [41]. In the AP region, where prevalence commonly exceeds 2%, universal one-time screening of adults is essential toward WHO's HBV elimination goals. Risk-based screening alone misses up to two-thirds of infections [42] because many individuals are asymptomatic or unaware of their exposure risk. In contrast, universal testing reduces undiagnosed cases, enables earlier intervention, and lowers morbidity, mortality, and transmission rates. Apart from clinical benefits, universal screening also helps to normalize testing, mitigate stigma, and ensure equitable access to care [43].

In addition to universal testing, targeted screening remains vital for specific high-risk groups. Individuals undergoing immunosuppressive or immunomodulatory therapy, such as tumor necrosis factor- α inhibitors, anti-CD20 agents, immune checkpoint inhibitors, tyrosine kinase inhibitors, CAR T cell therapy, or organ/bone marrow transplantation, are at elevated risk for HBV reactivation (HBVr) [44]. Screening before therapy is essential to identify those who should receive prophylactic antiviral treatment. Other priority populations include individuals with coinfections (e.g., HBV/HCV, HBV/HDV, HBV/HIV), existing other liver diseases, people who inject drugs, incarcerated individuals, and those with high-risk sexual, occupational and non-occupational exposures [45]. Early identification in

these groups reduces the risk of transmission, reactivation, and severe liver outcomes. Universal maternal screening, ideally during the first trimester, is crucial to preventing mother-to-child transmission (MTCT). Timely initiation of antiviral therapy for mothers where indicated (referred to Sect. "[Prevention of mother-to-child transmission](#)") and appropriate newborn prophylaxis, hepatitis B vaccination with or without HBIG, are highly effective in blocking vertical transmission [46].

Screening strategies should be prioritized based on cost-effectiveness, integrating both universal and targeted approaches while optimizing factors, such as test cost, linkage to care, and timely implementation to maximize public health impact.

Recommendations

1. Universal HBV screening should be offered at population level at least once in adulthood in endemic regions ($\geq 2\%$ prevalence). **(B1)**
2. Risk-based screening should be performed in individuals at increased risk of HBV infection*, regardless of age or country of origins. **(B1)**

*Include: Persons with liver disease or with elevated ALT or levels of unknown origin; Individuals receiving immunosuppressive or immunomodulatory therapies, including cancer chemotherapy, immune checkpoint inhibitors, CAR T cell therapy, or organ/bone marrow transplantation; History or current Injection drug users (IDU); Inmates of correctional facilities; Recipients of unsafe injections; Men who have sex with men (MSM) or individuals with multiple sexual partners or a history of sexually transmitted infections; Family members, household contacts, and sexual partners of individuals with HBV; Patients on dialysis; Individuals with HBV-related extrahepatic manifestations; Persons co-infected with HCV or HIV; Pregnant women and infants born to HBV-infected mothers; Blood or organ donors; Healthcare workers; in low prevalence countries ($<2\%$), recommend screening in people who were born in higher prevalence countries ($>2\%$)

How to screen HBV infection?

HBsAg is the gold standard for diagnosing acute or chronic HBV infection. Standard immunoassays detect levels <0.05 IU/mL, while ultrasensitive assays (<0.005 IU/mL) may be needed for early infection, vaccine-escape mutants, or when HBV DNA testing is unavailable. In such cases, confirmatory HBV DNA or anti-HBc testing ensures diagnostic accuracy [47]. Anti-HBc antibodies indicate current or past infection and aid in staging and risk assessment [48]. IgM anti-HBc reflects acute or reactivated infection,

whereas IgG anti-HBc suggests chronic or resolved infection. Anti-HBs testing complements this by confirming immunity, vaccination status, or risk of relapse during immunosuppression. HBeAg, anti-HBe, ALT, and HBV DNA together help assess disease activity and treatment response.

HBV DNA quantification measures viral replication and guides treatment eligibility. Limited access remains a barrier; implementing reflex HBV DNA testing for HBsAg-positive samples can accelerate care and support elimination goals.

Recommendations

1. Initial HBV screening should include at least a screen panel comprising HBsAg and total anti-HBc. **(A1)**
2. Reflex testing, automatically initiating HBV DNA testing on HBsAg-positive specimens, may serve as an additional strategy to promote linkage-to-care and treatment. **(B2)**

Assessment of liver fibrosis

How to assess liver fibrosis?

Liver biopsy remains the gold standard for assessing inflammation, fibrosis, and concomitant conditions such as steatosis or iron overload in patients with CHB [49]. It accurately identifies disease phases and provides prognostic information, but its cost, invasiveness, risk, and sampling variability limit routine use. Importantly, advance fibrosis can occur even with normal ALT or low HBV DNA [50].

Non-invasive tests (NITs), including serum biomarkers and imaging techniques, are practical, safe, and reliable for detecting advanced fibrosis and cirrhosis, while allowing repeated monitoring of disease progression and treatment response. They are preferred as first-line assessment in most patients. Biopsy is reserved for selected situations, such as uncertain etiology, discordant NITs results, or concomitant conditions like MAFLD or HDV, where histology can clarify diagnosis, detect steatohepatitis, guide therapy, and refine prognosis.

Recommendations

1. Liver biopsy is the gold standard for diagnosing the extent and severity of inflammation and fibrosis in patients with CHB. **(A1)**
2. Non-invasive tests are preferred as first-line assessment for detection of severity of fibrosis in patients with CHB. **(B1)**
3. Liver biopsy should be individualized for patients with discordant non-invasive test results, or concomitant etiologies and/or metabolic comorbidities where the diagnosis may alter treatment decisions and prognosis. **(C2)**

4. Non-invasive tests using a combination of blood tests and imaging techniques are recommended over liver biopsy for determination of advance fibrosis and monitoring disease progression. **(B1)**

How should liver fibrosis be assessed in resource-limited settings and what is the role of non-invasive tests?

Simple blood-based scores like FIB-4 (age, AST, ALT, platelet count) and APRI (AST, platelet count) are inexpensive and widely validated. FIB-4 values > 1.3 indicate a higher probability of significant fibrosis ($\geq F2$), while > 2.67 strongly predicts advanced fibrosis or cirrhosis (F3–F4). For adults aged ≥ 65 years, age-adjusted thresholds (> 2.0 for significant fibrosis and > 3.25 for cirrhosis) improve accuracy. APRI cutoffs of 0.3–0.7 predict significant fibrosis ($\geq F2$) with 73% sensitivity and 65% specificity, while 0.8–1.2 predicts cirrhosis (F4) with 59% sensitivity and 74% specificity [51]. The WHO 2024 guidelines recommend initiating antiviral therapy in CHB patients with APRI > 0.5 or > 1 as indicative of significant fibrosis or cirrhosis respectively, regardless of HBV DNA or ALT levels [43].

Vibration-controlled transient elastography (VCTE) offers more accurate fibrosis assessment, with an optimal cutoff of 7.7 kPa for significant fibrosis (64% sensitivity, 83% specificity, HSROC 0.81) [52]. However, cost and infrastructure limit its availability, making serum-based tests the first-line approach, with VCTE as a supplementary tool when accessible.

Recommendations

1. Blood-based non-invasive tests (FIB-4 or APRI), should be used as the primary tools for liver fibrosis assessment in CHB patients in resource-limited settings. **(B1)**
2. Vibration-controlled transient elastography (VCTE) should be used as a complementary tool to improve diagnostic precision, particularly when treatment decisions remain uncertain after blood-based non-invasive assessment. **(B2).**

How to identify predominant driver of liver injury in patients with concurrent CHB and MAFLD non-invasively?

With population aging, more CHB patients present with cardiometabolic risk factors, such as obesity, diabetes, hypertension, and dyslipidemia [53]. Over one-third (35%) of CHB patients have hepatic steatosis [54], often linked to obesity, diabetes, hypertension, and lower HBV DNA levels [55]. Coexisting MAFLD increases the risks of cirrhosis, HCC [56], and liver-related mortality, in a dose-dependent manner

[57], while high BMI, and diabetes reduce the likelihood of cirrhosis regression during antiviral therapy [58].

In CHB patients, MAFLD contributes independently and synergistically to liver fibrosis, hepatocarcinogenesis, and mortality [59]. Even when viral replication is suppressed, metabolic liver injury persists, making metabolic risk assessment and intervention critical in comprehensive CHB management [60, 61].

In clinical practice, distinguishing HBV- from MAFLD-related liver injury can be challenging, as ALT elevations may reflect either condition or metabolic treatments. In phase 3 trials of metabolic dysfunction-associated steatohepatitis (MASH), mean baseline ALT typically ranges from 40 to 70 U/L and rarely exceeds 200 U/L [62–65], whereas CHB patients in the “indeterminate phase” exhibit higher fibrosis stages and greater HCC risk than those with low viraemic activity [66]. Antiviral therapy reduces the risk of HCC [67], decompensation, transplantation, and mortality in patients with moderate HBV DNA and ALT elevation, but benefits are less clear when ALT is elevated due to MAFLD or alcohol [68].

NITs including APRI, FIB-4, enhanced liver fibrosis, and VCTE remain useful [69–71] but may be influenced by inflammation, obesity, or necroinflammation [72, 73]. Although the underlying etiology may influence measurement thresholds, these tools cannot reliably distinguish HBV- from MAFLD-related injury. Emerging machine learning models and novel biomarkers show promise for differentiating disease activity, but further validation is required [74].

Recommendation

1. All CHB patients should be routinely evaluated for MAFLD, its components (obesity, diabetes, dyslipidemia, and hypertension), and the degree of hepatic fibrosis using non-invasive fibrosis assessment tools. **(B2)**
2. Patients with concurrent CHB and MAFLD should be monitored for liver disease progression and liver-related events, regardless of whether antiviral therapy has been started. **(B2)**
3. In patients with concurrent CHB and MAFLD, biomarkers of hepatic steatosis and fibrosis cannot be used to attribute the primary cause of liver injury to either HBV or MAFLD or both. **(C2)**

II. Treatment

Treatment goals

What are the goals of CHB therapy, and what are the surrogate endpoints for the treatment goals?

The overarching goal of CHB management is to reduce the global HBV disease burden through integrated strategies including vaccination, screening, anti-viral therapy, surveillance and prevention of transmission. At the individual level, therapy aims to prevent progression to cirrhosis, hepatic decompensation, and HCC, thereby improving long-term survival and quality of life (Fig. 1) [75].

CHB management follows a time-based, response-guided approach using validated markers, including HBV DNA, ALT, HBeAg status, and HBsAg level (qHBsAg), to guide treatment initiation, monitor response, and stratify risk. The choice of antiviral regimen, e.g., high-resistant barrier NUCs (long-term) or Pegylated interferon alpha (Peg-IFN- α) (finite), should be individualized according to the viral profile, fibrosis stage, comorbidities, adherence and patient preferences. Immune-modulatory therapy may be appropriate for selected patients depending on immune status and disease phase.

Sustained suppression of HBV DNA and ALT normalization, achievable with NUCs, is strongly associated with reduced risk of cirrhosis, HCC, and other liver-related complications [76]. Early ALT normalization within the first year of antiviral treatment further improves outcomes [77, 78]. In HBeAg-positive patients, anti-HBe seroconversion indicates effective viral control [79, 80], while in HBeAg-negative patients, maintaining low-level replication (HBV DNA < 2,000 IU/mL) and HBsAg < 1,000 IU/mL reduces HCC risk [81, 82].

The long-term goal is a functional cure defined as sustained HBsAg loss with undetectable HBV DNA after finite therapy [83]. Although uncommon with current therapies [84, 85], HBsAg loss remains the best surrogate marker of cure and is more likely in patients with low baseline HBsAg levels. A partial cure, defined as persistently low HBsAg (< 100 IU/mL) and normal ALT in non-cirrhotic, HBeAg-negative patients after finite therapy, is a practical surrogate associated with minimal HCC risk [86].

Recommendations Short-term goals

1. In both HBeAg-positive and HBeAg-negative patients receiving antiviral therapy, the primary short-term goal is to achieve sustained undetectable HBV DNA and normalization of ALT. **(A1)**

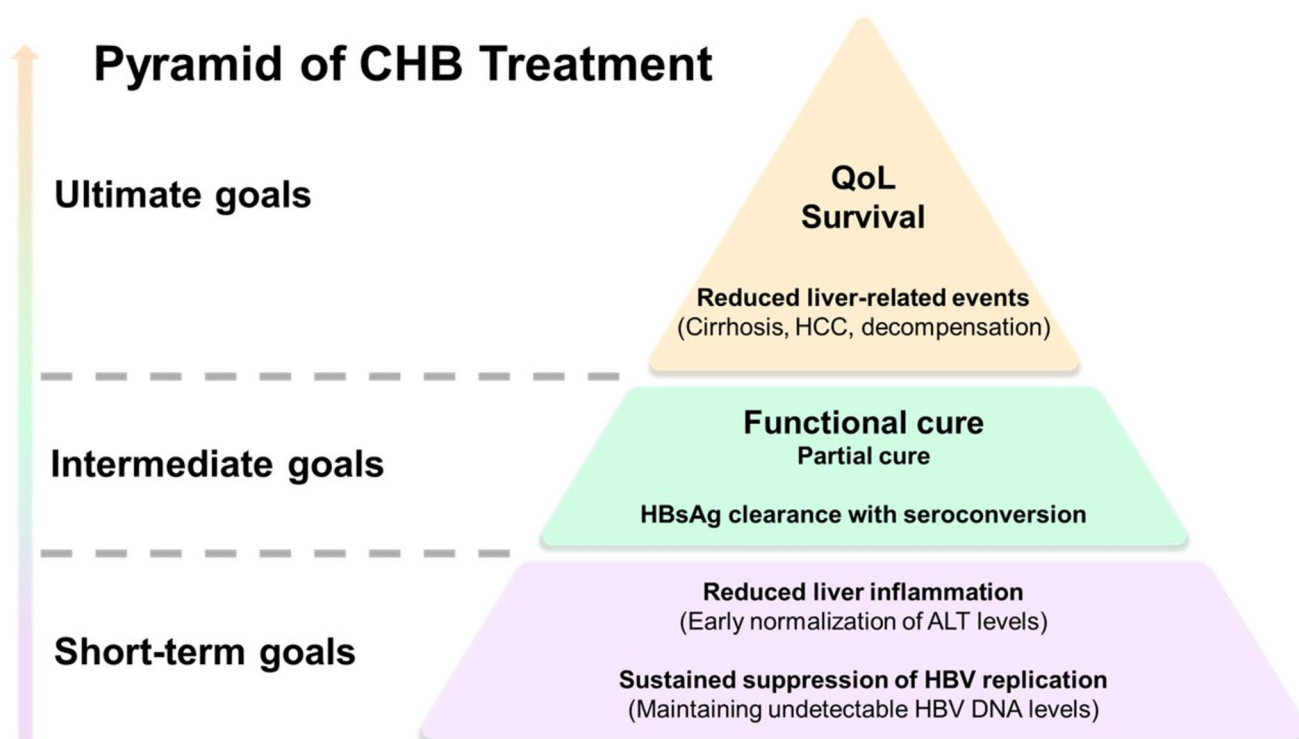


Fig. 1 Pyramid of CHB treatment

2. In HBeAg-positive patients, it is desirable to obtain HBeAg seroconversion as this reflects a favorable therapeutic response. (A1)
3. In HBeAg-negative patients, therapy should aim to maintain virologic suppression and persistently normal ALT. (A1)

Intermediate goals

1. Therapy should maintain virologic suppression and biochemical remission, which are validated surrogate markers of antiviral efficacy. (A1)
2. Where feasible, therapy may aim for functional cure, defined as sustained (≥ 6 months) HBsAg loss with undetectable HBV DNA after completion of therapy. (A1)
3. When functional cure is unlikely, achieving a substantial decline in HBsAg levels (e.g., < 100 IU/mL) may be considered a partial cure and an appropriate therapeutic target. (B1)

Ultimate goals

1. Public health efforts should aim to reduce the global HBV burden through vaccination, screening, timely antiviral treatment, and prevention of transmission. (A1)

2. Treatment should prevent liver-related complications and ultimately improve survival and quality of life. (A1)

Treatment strategies

The treatment strategies (Fig. 2) prioritize potent first-line NUCs (TAF, TDF, TMF, ETV) for their efficacy and safety, and protection against cirrhosis and HCC. Peg-IFN- α can serve as an alternative first-line option or as finite add-on therapy in NUC-suppressed patients with low HBsAg to pursue functional cure. Quantitative HBsAg and HBV DNA guide treatment initiation and decisions on finite Peg-IFN- α or NUCs discontinuation in non-cirrhotic patients. The approach incorporates cost-effectiveness, long-term safety, and patient preferences, supporting broader “treat-all” coverage, including early-stage and low-viremia groups. Treatment cessation is limited to non-cirrhotic patients achieving sustained HBsAg seroclearance or long-term suppression, with close monitoring, while cirrhotic patients should continue lifelong NUCs. Patient education and adherence support remain essential throughout care.

How effective are current therapies?

NUCs, including ETV, TDF and TAF, effectively suppress HBV DNA replication, resolve hepatic inflammation, and

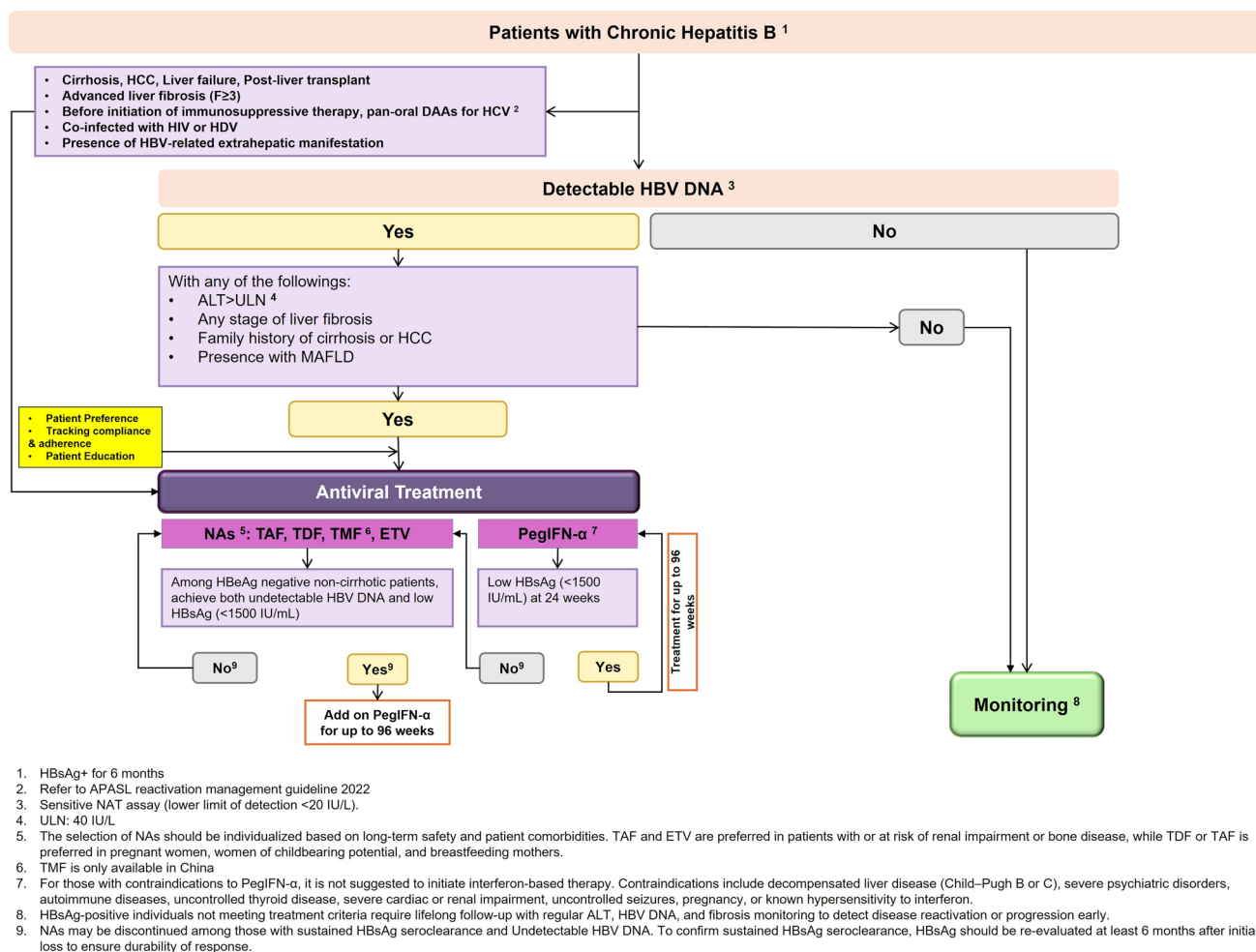


Fig. 2 CHB treatment algorithm

prevent progression to cirrhosis, hepatic decompensation, and HCC (Table 4) [58, 67, 87–100]. Long-term NUCs therapy achieves undetectable HBV DNA in over 95% of HBeAg-negative patients, but HBsAg decline is slow [95], and annual HBsAg loss remains low [92], reflecting persistent antigen production from integrated HBV DNA. Tenofovir amibufenamide (TMF) shows antiviral efficacy and safety comparable to TAF [101]. In elderly patients with decompensated hepatitis B cirrhosis, TMF remains non-inferior to TAF with a similarly favorable safety profile [102]. However, its availability and use are currently limited in mainland China.

Peg-IFN-α is the only therapy capable of inducing HBsAg loss through both antiviral and immune-modulatory mechanisms [103]. Unlike NUCs, Peg-IFN-α is administered for a finite duration and consistently achieves higher HBsAg clearance, particularly in patients with genotypes A and B. A network meta-analysis of 47 randomized trials (13,826 patients) identified Peg-IFN-α-based regimens as the most effective approach for HBsAg loss

across both HBeAg-positive and HBeAg-negative treatment-naïve populations [104]. Response to Peg-IFN-α strongly correlates with baseline HBsAg levels, with markedly higher functional cure rates seen in patients who initiate therapy with low pretreatment HBsAg [105].

While NUCs efficiently suppress viral replication and prevent disease progression [15], their effect on HBsAg loss is limited. Exploring strategies combining NUCs and PegIFN to enhance HBsAg loss rates, a meta-analysis of 49 studies assessed different antiviral treatment combinations [106]. The findings revealed that, compared to NUCs monotherapy, the initial combination of NUCs and IFN improved HBsAg seroclearance rates by 15 times (risk ratio 15.59, 95% CI 3.22–75.49), and IFN add-on NUCs also significantly improved HBsAg loss (RR: 4.52, 95% CI 1.95–10.47). These findings highlight the relevant role of interferon in achieving a functional cure for HBV. Combining long-term NUCs therapy with finite Peg-IFN-α-based regimens in selected patients offers the most promising

Table 4 Effectiveness of current CHB treatment strategies

Treatment Outcome	TDF	TAF	ETV	Peg-IFN	Combination (PegIFN add on NUCs)	Combination (NUC switch to PegIFN)
Short-term goals						
HBV DNA suppression(%)	1y: 67(e+)[8]; 93(e-)[7] 2y [9]: 75(e+); 91(e-) 10y [15]: 98(e+); 100(e-)	1y: 64(e+)[8]; 94(e-)[7] 2y[9]: 73(e+); 90(e-) 8y[10]: 95(total)	1y: 67(e+)[1]; 90(e-)[2] 5y: 99(e+)[3]; 98(e-)[5]	1.5y: 14(e+)[12]; 19(e-) [13]	Compare with NUCs: Similar rate of HBV DNA suppression	
ALT normalization(%)	1y: 67(e+)[8]; 75(e-)[7] 2y [9]: 68(e+); 71(e-) 10y [15]: 78(e+); 83(e-)	1y: 72(e+)[9]; 83(e-)[7] 2y [9]: 75(e+); 81(e-) 8y [10]: 87(total)	1y: 68(e+)[9]; 78(e-)[2] 5y [10]: 95(total)	1.5y: 41(e+)[12]; 59(e-) [13]	Similar with NUCs	
Intermediate goals						
Necroinflammation resolution(%)	5y [11]: 87(total) 91(Ishak ≥ 3)		1y: 72(e+)[1]; 70(e-) [2]	1.5y: 49(e+)[12] (Reduced HAI) 55(e-)[13]		
Fibrosis regression(%)	5y [11]: 51(total) 74(Ishak ≥ 5)		1y: 39(e+)[1]; 36(e-) [2] 5y [6]: 80.4(total)	1.5y: 49(e+)[12] (Reduced HAI) 55(e-)[13]		
Long-term goals						
HBsAg loss (End of Follow-up)	annual: <1% [19]	annual: <1%	annual: <1% [20]	3y: 11% (e+); 8–14% (e-)[21]	Compared to NUCs monotherapy, PegIFN add on improved HbsAg loss. RR: 4.52; 95% CI 1.95–10.47 [22, 23]	Compared to NUCs monotherapy, NUCs switch-to IFN strategy improved HBsAg loss. RR: 12.15, 95% CI 3.99–37.01 [22]
HBV-related morbidity	TDF vs. treatment-naïve aHR [17]: HCC: 0.46; Decomp: 0.28	TAF vs. treatment-naïve HR [16]: HCC: 0.27	ETV vs. treatment-naïve HR [14]: HCC: 0.55	Peg-IFN vs. ETV (e+) 5y incidence [18]: Cirrhosis or HCC: 0% vs. 9.1%		
HBV-related mortality	LT or death: 0.06		LR death: 0.26; Death: 0.34			

e-: HBeAg-Negative; e+: HBeAg-positive

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approach to achieving functional cure, balancing efficacy, safety, and feasibility [107].

Patient education, regular monitoring, and adherence support are critical in CHB therapy. A formal, language-concordant HBV educational intervention significantly improved clinic follow-up, laboratory monitoring, and appropriate antiviral treatment [108]. Meta-analyses show that roughly 75% of patients adhere to NUCs, with limited understanding and forgetfulness among the main barriers [109]. Poor adherence is strongly linked to virologic breakthrough and drug resistance [110]. Health-education interventions more than double adherence for chronic communicable diseases [111].

Recommendations

1. TAF, TDF, TMF*, and ETV are the first-line NUCs treatment for CHB. **(A1)**
2. For those without contraindication[#] for immune therapy, Peg-IFN- α can be considered as a first-line treatment for CHB. **(A1)**
3. In NUCs-treated patients with sustained viral suppression (persistent undetectable HBV DNA) and low serum HBsAg levels (< 1500 IU/mL), the addition of Peg-IFN- α for a finite duration of up to 96 weeks may be considered in pursuit of functional cure, after evaluating patient willingness and clinical suitability. **(B1)**
4. Patients should receive structured education on the need of treatment, the importance of regular monitoring, and adherence to antiviral therapy to ensure optimal clinical outcomes. **(C1)**

* Available in China mainland.

[#] Pegylated interferon alfa-2a is contraindicated in patients with [112]:

- Known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens–Johnson syndrome to alpha interferons, including PEGASYS, or any of its components.
- Autoimmune hepatitis
- Hepatic decompensation (Child–Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child–Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfecting with HIV before treatment
- Pegylated interferon alfa-2a is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications which are sometimes fatal in neonates and infants.

What biomarkers should guide treatment?

Quantitative HBsAg reflects intrahepatic covalently closed circular DNA (cccDNA) activity [113] and integrated HBV DNA [114]. Declining HBsAg indicates reduced viral replication, and HBsAg loss sustained 24 weeks after treatment cessation represents functional cure. In HBeAg-negative CHB, HBV DNA $< 2,000$ IU/mL with HBsAg $< 1,000$ IU/mL suggests inactive infection, while HBsAg $> 1,000$ IU/mL predicts higher risk of reactivation and HCC. HBsAg < 10 IU/mL strongly predicts eventual HBsAg loss [82, 115–117].

Baseline HBV DNA is a key prognostic marker. Long-term cohort studies, including REVEAL-HBV [118], demonstrate a graded increase in cirrhosis and HCC risk with higher viral loads, independent of ALT and HBeAg status. This underscores the importance of integrating HBV DNA with HBsAg levels for treatment initiation.

HBsAg level can guide CHB therapy. Low end-of-treatment baseline levels predict sustained remission after NUCs discontinuation [119, 120], and on-treatment declines during Peg-IFN- α indicate higher response likelihood, whereas persistently high levels ($> 20,000$ IU/mL) suggest limited benefit from Peg-IFN- α treatment [121].

Emerging biomarkers, including HBV RNA, HBcrAg, and quantitative anti-HBc, offer additional insights into cccDNA activity, relapse risk, and HCC, but remain research tools until standardized [48, 122]. Quantitative HBsAg remains the most practical and validated biomarker for clinical decision-making.

Recommendations

1. HBV DNA with lower limit of quantification (< 10 – 20 IU/mL), by real-time quantitative polymerase chain reaction, should be tested before and during treatment. **(B1)**
2. Serum HBsAg levels should be tested at baseline and monitored during Peg-IFN- α and for discontinuation of long-term NUCs in non-cirrhotic patients. **(B1)**

How should treatment decisions be guided by cost-effectiveness, long-term safety, and patient preferences?

CHB management is shifting toward broader antiviral coverage. Economic models from China [123], Korea [124] and the US [125] show that treating lower-risk or “minimally active” patients are cost-effective in reducing HBV-related complications and mortality. A global review reports that early initiation of antiviral treatment is highly cost-effective in saving HBV-related mortality, reinforcing broader antiviral treatment strategies beyond Asia Pacific [126].

Collectively, these data support “treat-all” strategy that aligns with “WHO 2030” viral elimination goals.

High-resistance-barrier NUCs provide potent, persistent viral suppression with minimal resistance. The first-line NUCs are ETV, TDF, TAF, and TMF. However, long-term TDF use is associated with a higher fracture risk than ETV [127]. TAF offers similar efficacy to TDF with superior renal and bone safety, preferred in patients with renal disease, osteoporosis, or older age [128].

Shared decision-making improves adherence and addresses psychosocial burdens, such as stigma, fear of transmission, and treatment fatigue [129]. Achieving viral suppression can improve mental well-being. For instance, one study showed a 4.5-point increase in SF-36 mental component score after one year of ETV therapy [130]. While psychosocial improvement alone is not an indication for treatment initiation, these benefits underscore the broader value of antiviral therapy in enhancing patient-reported outcomes and quality of life.

Recommendations

1. Treatment should be prioritized for patients at highest risk of disease progression regardless of HBV DNA level or ALT. **(A1)**
2. Where resources allow, a “treat-all” approach should be adopted, initiating therapy for CHB patients beyond traditional high-risk criteria. **(B1)**
3. Therapy selection should consider long-term safety and presence of comorbidities. TAF or ETV are preferred over TDF in patients at risk for renal or bone disease. **(A1)**
4. Shared decision-making should be integrated into treatment planning, incorporating patient preferences, psychosocial factors, and willingness to commit to long-term therapy. **(B1)**

Should treatment be initiated in CHB patients at earlier fibrosis stages or specific groups that do not meet traditional treatment initiation criteria?

HBeAg-negative patients younger than 40 years old with low viral loads often appear clinically stable but may have ongoing necroinflammation or fibrosis, predisposing them to silent progression toward cirrhosis or HCC [131]. Evidence shows favorable antiviral responses in this group [132]; in a large Chinese cohort, Peg-IFN- α -based therapy achieved HBsAg loss in up to 35% of patients [133], supporting early intervention.

The conventional concept of the “inactive carrier” phase is increasingly questioned. Since 2015, this term has largely been replaced by “chronic HBV infection” to better reflect the persistent oncogenic potential despite low

viral activity [12]. Patients with HBsAg ≥ 100 IU/mL, even with HBV DNA $< 2,000$ IU/mL, face higher HCC risk, up to 3.6-fold greater when HBsAg $\geq 1,000$ IU/mL compared with < 100 IU/mL [86]. Moreover, patients with low-level viremia or HBsAg seroclearance remain at risk, with an annual HCC incidence of approximately 0.86% [134].

As vaccination coverage expands and the CHB population ages, more patients fall into this “low-viraemia” category but retain residual oncogenic risk due to HBV integration and clonal hepatocyte expansion. With potent, safe, and affordable NUCs now widely available, expanding antiviral therapy to earlier fibrosis stages and low-viremia populations is both clinically justified and cost-effective [7]. This simplified “treat-all” approach addresses residual oncogenic risk, overcome the limitations of traditional phase-based classifications, and supports the broader goal of eliminating HBV-related morbidity and mortality by 2030 [135].

Recommendations

1. Antiviral therapy should be initiated for chronic HBV infection with detectable HBV DNA and ALT level over ULN (e.g. ≥ 40 IU/L), irrespective of fibrosis stage, or HBeAg status. This includes patients with minimal or no fibrosis (earlier fibrosis stages) and other specific subgroups at increased risk of disease progression, such as those with a family history of cirrhosis or hepatocellular carcinoma and those presenting with MAFLD. **(B1)**
2. Antiviral therapy should be prioritized for high-risk patients, irrespective of HBV DNA level. This includes patients with hepatocellular carcinoma, liver failure, advanced liver disease (cirrhosis or decompensation), HBV-related extrahepatic manifestations; patients underwent liver transplant, undergoing or planned for immunosuppressive or cytotoxic therapy, and co-infected with HIV/HCV/HDV. **(A1)**

Under what conditions can antiviral therapy be safely stopped, and how should relapse be monitored post-cessation?

Sustained HBsAg seroclearance (confirmed on two occasions ≥ 6 months apart), with or without anti-HBs seroconversion, is regarded as a criterion for discontinuing NUCs therapy in both HBeAg-positive and HBeAg-negative patients [136, 137]. The prognosis following both spontaneous [138] and NUCs-induced HBsAg seroclearance [139] are generally favorable.

Long-term evidence showed that structured NUCs discontinuation, even in patients with compensated cirrhosis, was associated with higher rates of HBsAg loss, lower HCC incidence, and improved overall survival compared with those maintained on continuous therapy [140]. But

discontinuation of NUCs carries a risk of virologic relapse, commonly defined as HBV DNA > 2,000 IU/mL, often followed by ALT flares, though rarely triggering severe exacerbations or death. Consolidation therapy reduces relapse risk, with ≥ 1 year after HBeAg loss in HBeAg-positive patients and ≥ 3 years after confirmed undetectable HBV DNA in HBeAg-negative patients [141].

Relapses typically occur within 6–24 weeks post-withdrawal [142], though late flares (> 1 year) can occur [143]. Given the dynamic patterns of virologic relapse and ALT flare, monitoring should include HBV DNA and ALT at least monthly for the first 6 months, quarterly during the first year, and biannual-to-annual thereafter. Patients with cirrhosis should continue lifelong NUCs therapy due to the risk of decompensation.

Emerging biomarkers, including HBV RNA and HBcrAg, show potential for relapse risk stratification prior to discontinuation of NUCs, but clinical application remains limited by availability, heterogeneous assays and lack of standardized cutoffs.

Recommendations

1. For both HBeAg-positive and HBeAg-negative non-cirrhotic patients, NUCs therapy can be discontinued upon achieving sustained HBsAg seroclearance* and undetectable HBV DNA regardless of anti-HBs seroconversion status. (A1)
2. For HBeAg-negative non-cirrhotic patients, upon achieving persistent undetectable HBV DNA for more than three years, NUCs therapy may be discontinued by experienced clinicians. Patients should be closely monitored with HBV DNA and ALT at least monthly for the first 6 months after discontinuation, and the monitoring interval may be extended thereafter based on clinical judgment. (B2)
3. For both HBeAg-positive and HBeAg-negative cirrhotic patients, discontinuation of NUCs therapy is *not* recommended. (A2)
4. HBsAg loss should be confirmed on two occasions ≥ 6 months apart to establish the durability of HBsAg loss. (A1)

* Sustained HBsAg seroclearance is defined as negative HBsAg for at least 6 months after treatment cessation.

In special populations

How to manage HBV in pregnant women?

All pregnant women should be screened for HBsAg early in pregnancy. Women who test positive should be assessed for antiviral therapy based on the same treatment

indications as non-pregnant adults with chronic hepatitis B (HBV DNA level, ALT, HBeAg status, and fibrosis stage).

MTCT can occur in highly viremic mothers despite appropriate newborn active–passive vaccination, with risk increasing up to 30% as maternal HBV DNA exceeds 6–8 log₁₀ IU/mL [144]. Reducing maternal viral load below 200,000 IU/mL with antiviral therapy effectively prevents perinatal transmission [145]. If HBV DNA is < 200,000 IU/mL and timely postpartum vaccination is ensured, antiviral therapy is not required [146].

HBeAg positivity is associated with high maternal HBV DNA levels, which significantly increase the risk of perinatal transmission. In pregnant CHB women, HBeAg status can be used as a surrogate marker of viral replication to guide the need for antiviral therapy.

Women identified as HBsAg-positive during pregnancy represent an important population for postpartum follow-up testing. Antenatal screening provides a critical opportunity to establish structured follow-up after delivery for women newly diagnosed with chronic HBV infection [147, 148]. Postpartum follow-up is essential to ensure long-term maternal health, prevent MTCT in future pregnancies, and guide ongoing clinical management. Postpartum assessment with HBsAg, HBV DNA, and ALT allows confirmation of infection status, evaluation of disease activity, and determination of the need for antiviral therapy [149]. Counseling and appropriate clinical management should be provided to reduce the risk of horizontal transmission to sexual partners and optimize outcomes in subsequent pregnancies.

Tenofovir (TDF or TAF) is preferred, with comparable efficacy in reducing the risk of HBV MTCT [150–152]. Initiation between 28–32 weeks of gestation is optimal. Recent trial showed that in pregnant women with high levels of viremia, TDF beginning at gestational week 16 combined with infant HBV vaccine is also effective to prevent MTCT where HBIG is not available [153]. Therapy may continue even after pregnancy if maternal indications exist; otherwise, it can be safely discontinued shortly after delivery or within 1–3 months postpartum with close monitoring. However, hepatitis flares have been reported in a substantial proportion of women following treatment cessation, most commonly within 24 weeks postpartum [154, 155], underscoring the need for enhanced postpartum monitoring. Currently, there are no safety concerns regarding tenofovir as HIV therapy or pre-exposure prophylaxis in breastfeeding women. Therefore, breastfeeding should not be discouraged if tenofovir (TDF, TAF) therapy is continued [156].

Recommendations

1. Screen all pregnant women for HBsAg early in pregnancy. (A1)

2. Pregnant women who test positive HBsAg should be assessed for antiviral therapy according to standard CHB indications. (A1)
3. In pregnant women with HBeAg-positive and/or HBV DNA $\geq 200,000$ IU/mL, antiviral therapy with tenofovir (TDF or TAF) should be given during the third trimester of pregnancy for preventing mother-to-child transmission. (A1)
4. In women identified as HBsAg-positive during pregnancy, postpartum follow-up testing with HBsAg, HBV DNA, and ALT is recommended to confirm infection status, assess disease activity, and determine the need for antiviral therapy. Counseling and appropriate management should be provided to reduce the risk of transmission to sexual partners and in future pregnancies. (B1)
5. Breastfeeding is safe while the mother is on antiviral therapy with tenofovir (TDF or TAF). (A1)

How to manage HBV in patients with metabolic comorbidities?

The rising prevalence of fatty liver and metabolic comorbidities has added complexity to CHB management. The redefinition of MAFLD emphasizes both hepatic and systemic metabolic factors [157], with heterogeneous prognostic implications. Early studies linked MAFLD to accelerated fibrosis and increased HCC risk in CHB [158]. In contrast, while recent studies suggested simple hepatic steatosis may be protective, associated with lower liver-related mortality and higher HBsAg seroclearance [159–162], coexisting metabolic dysfunctions, including diabetes, obesity, and hypertension, drive dose-dependent increases in cirrhosis, HCC, and mortality, even during long-term NUCs therapy [163]. Diabetes is the strongest risk factor, particularly with poor glycemic control.

In children, MAFLD is increasingly common and primarily linked to metabolic risk factors rather than HBV [164–166]. HBV may increase necroinflammation but does not appear to accelerate fibrosis; higher HBsAg loss has been observed during antiviral therapy in children with MAFLD [167, 168]. Diagnostic criteria for metabolic syndrome, hepatic fibrosis (LSM), steatosis (CAP), and at-risk MAFLD (FAST) remain heterogeneous in pediatric populations [169].

Lifestyle intervention, encompassing dietary modification, physical activity, and behavioral change, remains the cornerstone of management in both adults and children with MAFLD. Low-carbohydrate or low-fat diets and combined diet–exercise programs improve liver and metabolic outcomes. Pharmacologic agents, such as metformin, incretin-based therapies (e.g., GLP-1 receptor agonists), and other emerging agents, may be adjunctive in children with pre-diabetes or type 2 diabetes though evidence for sustained

ALT reduction is limited [170]. Early identification and management of metabolic comorbidities alongside antiviral therapy are essential to optimize long-term outcomes in CHB with MAFLD [171].

Recommendations

1. Optimal glycemic control should be offered in CHB patients with concurrent diabetes in collaboration with endocrinologists or primary care teams. (A1)
2. Lifestyle interventions are recommended for CHB patients with modifiable metabolic comorbidities. (A1)

How to manage HBV in patients with coinfections (HDV/HCV/HIV)?

In HIV coinfecting patients In 2023, an estimated 39 million people were living with HIV [172], of whom 8.4% had HBV coinfection, rising to 9.8% in the Asia Pacific region [173]. Coinfecting patients face increased risks of cirrhosis and HCC, supporting prompt initiation of antiretroviral therapy (ART) regardless of ALT, HBV DNA, or CD4 count, unless contraindicated.

ART regimens should include two anti-HBV agents, typically TAF or TDF plus lamivudine or emtricitabine. TAF is preferred in patients with renal or bone disease [174], while switching from TDF to TAF maintains viral suppression with reduced toxicity [175]. Lamivudine- or emtricitabine-only regimens should be avoided to prevent HBV resistance. When TDF/TAF are contraindicated, entecavir may be added to fully suppressive ART with close monitoring [176]. Peg-IFN- α is generally not recommended due to limited efficacy and tolerability.

Patients with low CD4 counts should be monitored for hepatic flares due to immune reconstitution inflammatory syndrome (IRIS), which may coincide with HBsAg loss [177]. Sustained HBV suppression through optimized ART adherence is crucial to prevent liver complications, including HCC.

Recommendations ART should be initiated promptly regardless of ALT levels, HBV DNA levels, or CD4 cell count, with ART regimens requiring two antiviral agents active against HBV. The NUCs backbone should include TDF or TAF plus lamivudine or emtricitabine. (A1)

In HDV co-infected patients HDV infects 12–60 million people globally, with 4.5–13% prevalence among HBsAg-positive individuals. Active infection is confirmed via HDV RNA; NITs including elastography, APRI, FIB-4 may assist, but liver biopsy is recommended if results are inconclusive or guide treatment [178].

For patients with HBV/HDV co-infection, Peg-IFN- α remains an established therapy, typically administered at Peg-IFN- α 180 μ g weekly for up to 96 weeks, achieving 29% virological response at the end of 24-week post-treatment [179]. Week-96 phase III data show Bulevirtide (2–10 mg daily) provides consistent antiviral activity, with > 50% HDV RNA response, ALT normalization, and improving liver stiffness [180]. Responses increased with continued therapy, supporting long-term therapy due to frequent relapse after stopping. Despite its clinical efficacy, bulevirtide is currently associated with substantial cost and limited global availability, posing significant challenges for policy adoption and market access, particularly in low- and middle-income countries [181]. These considerations currently limit its widespread use outside selected settings. Combination BLV and Peg-IFN- α may enhance HDV RNA suppression and HBsAg decline, but evidence is still emerging and no finite stopping strategy exists.

There is no approved treatment for decompensated cirrhosis: Peg-IFN- α is contraindicated, and data for BLV in this population remain limited [182]. NUCs should be continued in all patients with active HBV replication or cirrhosis. Given the high relapse risk in HDV, close monitoring of HDV RNA, HBV DNA, ALT, synthetic function, and imaging is essential regardless of therapeutic strategy.

Recommendations

1. All patients with chronic HBV/HDV coinfection and compensated liver disease should be considered for anti-HDV treatment with Peg-IFN- α or bulevirtide. (A1)
2. Patients with decompensated cirrhosis should be evaluated for liver transplantation. (A1)

In HCV co-infected patients Patients with HBV/HCV coinfection have higher risks of liver-related death and HCC than monoinfected individuals [183]. Currently, direct-acting antiviral (DAA) therapy is recommended for all HBV/HCV-co-infected patients, with sustained virological response comparable to HCV mono-infection. However, HBV reactivation occurs in 5.9–24% during DAA therapy, and hepatitis flares in 1.9–9% [184, 185]. Prophylactic NUCs therapy reduces reactivation risk, especially in patients with cirrhosis [186, 187]. HBsAg-negative, anti-HBc-positive individuals are at low risk (< 2% [188]) but require ALT monitoring and NUCs initiation if clinically indicated.

Recommendations

1. Patients with HBV/HCV coinfection should receive anti-HCV treatment with DAAs. (A1)

2. For HBsAg-positive patients, prophylactic NUCs treatment is recommended before initiation of DAA treatment. (A1)
3. For HBsAg-negative but anti-HBc-positive patients, close monitoring of ALT, HBV DNA and HBsAg is required during DAA treatment. (A1)

How to manage HBV in patients with alcohol-associated liver diseases (ALD)?

CHB combined with excessive alcohol accelerates cirrhosis and HCC by increasing oxidative stress, liver injury, and reducing antiviral efficacy and adherence [189]. Complete abstinence is essential [190, 191], supported by psychosocial [192] and pharmacologic [193] interventions to maintain sobriety. Potent NUCs provide sustain viral suppression, whereas interferon is contraindicated. Long-term, often infinite NUCs therapy is recommended.

Regular monitoring of HBV DNA, liver and renal function, alcohol intake, and HCC surveillance is critical. Multidisciplinary care, including hepatology, addiction, nutrition, and psychosocial support, optimizes adherence, reinforces abstinence, and improves outcomes.

Recommendations

1. All patients with HBV and ALD should be strongly advised to abstain completely from alcohol. Pharmacological aids and structured psychosocial or addiction support should be offered to promote abstinence. (A1)
2. A multidisciplinary approach including hepatology, addiction medicine, nutrition, and mental health should be implemented, with structured patient education to reinforce abstinence, adherence to antiviral therapy, and recognition of decompensation. (A1)

How to manage HBV in those with end-stage liver disease?

Management of HBV-related end-stage liver disease (ESLD) focuses on antiviral therapy, complication control, and timely liver transplant evaluation.

Antiviral therapy with ETV, TAF, or TDF is safe and effective in decompensated cirrhosis, improving MELD and Child–Pugh scores [194], reducing HCC risk, and enabling hepatic recompensation (transplant-free survival > 80% [195]). TAF is preferred for renal and bone safety [196]. Lamivudine, adefovir, and pegylated interferon are not recommended [197, 198]. Therapy should continue indefinitely with renal dose adjustment.

Standard management of ascites, variceal bleeding, encephalopathy, and hepatorenal syndrome is essential, with HCC surveillance every six months. Patients with advanced disease, recurrent decompensation, or HBV-related HCC

should be evaluated for transplantation. Pre-transplant goals include HBV DNA suppression, nutrition optimization, and complication control. Post-transplant, antivirals should continue. HBIG plus NUCs should be used in high-risk patients, while monotherapy (TAF or ETV) may suffice in low-risk cases. HBcAb-positive donor livers can be used with prophylaxis in HBV-naïve recipients.

Immunosuppressed and coinfecting (HBV/HIV, HBV/HDV, HBV/HCV) patients require prophylactic or tailored antiviral therapy, with tenofovir-based regimens preferred in HBV/HIV.

Recommendations

1. Antiviral therapy should be initiated in all decompensated cirrhosis regardless of ALT or HBeAg status. **(A1)**
2. TAF, TDF, or ETV are first-line treatment, with preference for TAF over TDF due to better renal/bone safety. **(A1)**
3. Treatment must be continued infinitely in those with decompensation or prior HCC; discontinuation is *not* recommended. **(A1)**

Prevention of hepatitis B reactivation related to the use of immunosuppressive therapy

Recommendation

Please refer to APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy [44].

III. HCC surveillance

Risk prediction

How do risk prediction models best guide HCC surveillance?

Over the past two decades, multiple HCC risk models have been developed (Table 5). Age and cirrhosis (or surrogate markers) are the most consistent predictors, followed by sex. Early models, such as REACH-B, GAG-HCC, and CU-HCC, were derived from untreated cohorts and remain useful for identifying treatment-naïve patients who may benefit from antiviral therapy [199]. Among treated populations, PAGE-B and modified PAGE-B (mPAGE-B) are the most validated tools [200, 201]. These simple models, based on age, sex, and platelet count ($\pm$ albumin), are practical for routine risk assessment. The mPAGE-B was adapted for Asian populations to improve accuracy [202].

HCC risk scores are particularly valuable for non-cirrhotic patients, refining surveillance beyond standard age

thresholds (> 40 years in men, > 50 years in women). In a Hong Kong cohort of $> 32,000$ treated patients, PAGE-B and mPAGE-B effectively identified low-risk individuals who might safely forgo routine HCC surveillance [202]. The predictive accuracy of these scores may decline after 5 years of antiviral therapy as HCC risk decreases with sustained viral suppression [203–205]. Diabetes independently increases HCC risk [163], prompting newer models, such as CAMD and REAL-B, to incorporate metabolic factors for improved risk discrimination.

Recommendations

1. HCC risk scores which integrate age, fibrosis severity, and sex can identify at-risk patients on NUCs eligible for HCC surveillance. **(A1)**
2. Patients on NUCs with intermediate-to-high HCC risk (PAGE-B ≥ 10 and/or mPAGE-B ≥ 9) should receive HCC surveillance. **(B1)**
3. Interpretation of HCC risk scores should be approached with caution in patients with prolonged treatment duration (over 5 years) or those with diabetes. **(B2)**

Surveillance strategies

What surveillance strategies are needed for those with mPAGE-B ≥ 9 ?

Regular surveillance reduces HCC mortality by 37% [206], improving early detection (Relative Risk [RR] 1.86), curative treatment (RR 1.83), and survival (Hazard Ratio: 0.67) [207]. The mPAGE-B score effectively stratifies risk in Asian population, with ≥ 9 indicating high risk [202, 208].

Current guidelines recommend biannual ultrasound and AFP [209, 210], which are cost-effective [211] but have less than 50% sensitivity for early HCC [212], further reduced in cirrhosis or fatty liver [213].

Protein induced by vitamin K deficiency or antagonist II (PIVKA-II), a marker linked to tumor aggressiveness [214], enhances diagnostic accuracy when combined with AFP [215, 216], achieving $> 90\%$ sensitivity and detecting up to 43% more early HCC cases [217]. Thus, AFP + PIVKA-II + ultrasound is recommended for surveillance, especially in the Asia Pacific region.

Recommendations

1. AFP and ultrasound examinations are recommended every 6 months. **(A1)**
2. Combined testing with AFP, ultrasound, and PIVKA-II is recommended to improve early detection accuracy. **(B1)**

Table 5 Available HCC risk scores applicable to treatment-experienced patients with chronic hepatitis B based on large external validation studies and systematic review, and meta-analysis

Score (year of publication)	Parameters	Population for score development	Interpretation of HCC risk*
PAGED-B (2024)	Age, sex, platelets, HBV DNA (year 0), diabetes	Asian (South Korea) (0% cirrhosis, 100% HBeAg-positive)	Low: 0–6 High: 7–12
aMAP (2020)	Age, sex, platelets, albumin, bilirubin	Asian (China) (19% cirrhosis, 40% HBeAg-positive)	Low: 0–49.9 Intermediate: 50–59.9 High: 60–100
CAGE-B (2020)	Age (at year 5), cirrhosis (year 0), LSM (year 5)	Caucasian (Greece, Spain, Netherlands, Turkey) (27% cirrhosis; 18% HBeAg-positive)	Low: 0–5 Intermediate: 6–10 High: 11–16
SAGE-B (2020)	Age (at year 5), LSM (year 5)	Caucasian (Greece, Spain, Netherlands, Turkey) (27% cirrhosis; 18% HBeAg-positive)	Low: 0–5 Intermediate: 6–10 High: 11–15
REAL-B (2020)	Age, sex, cirrhosis, diabetes, platelets, AFP, alcohol use	Asia-Pacific (China, South Korea, Hong Kong, Taiwan, Japan, New Zealand) (20% cirrhosis, 37% HBeAg-positive)	Low: 0–3 Intermediate: 4–7 High: 8–13
AASL-HCC (2019)	Age, sex, cirrhosis, albumin	Asian (South Korea) (39% cirrhosis, 56% HBeAg-positive)	Low: 0–5 Intermediate: 6–19 High: 20–29
modified PAGE-B (2018)	Age, sex, platelets, albumin	Asian (South Korea) (20% cirrhosis, 34% HBeAg-positive)	Low: 0–8 Intermediate: 9–12 High: 13–21
CAMD (2018)	Age, sex, cirrhosis, diabetes	Asian (Taiwan) (26% cirrhosis)	Low: 0–7 Intermediate: 8–13 High: 14–23
HCC-RESCUE (2017)	Age, sex, cirrhosis	Asian (South Korea) (39% cirrhosis, 56% HBeAg-positive)	Low: 18–64 Intermediate: 65–84 High: ≥ 85
PAGE-B (2016)	Age, sex, platelets	Caucasian (Greece, Spain, Netherlands, Turkey) (21% cirrhosis; 16% HBeAg-positive)	Low: 0–9 Intermediate: 10–17 High: 18–25
modified REACH-B (2014)	Age, sex, HBeAg, ALT, LSM	Asian (South Korea) (18% cirrhosis, 52% HBeAg-positive)	Low: 0–9 High: 10–16

Scores were listed in reverse chronological order (newest to oldest) by publication date

*Risk stratification based on 3-year HCC risk for CAMD; and 5-year HCC risk for other scores

What surveillance strategies are needed for those post-HBsAg clearance?

Although functional cure significantly lowers HCC risk, residual risk persists due to cumulative liver injury, fibrosis, and metabolic or epigenetic factors [134, 218]. Patients with cirrhosis face an annual HCC incidence of 2–4%, justifying continued surveillance.

Recommendation Lifelong HCC surveillance with ultrasound and AFP is recommended for patients with advanced fibrosis and liver cirrhosis post-HBsAg clearance every 6 months. (C1)

IV. Prevention of transmission

Prevention of mother-to-child transmission

In infants born to HBV-infected mothers, when should HBV testing be performed?

Please refer to **recommendations for post-vaccination serologic testing**.

Prevention of transmission in other populations

Should NUCs be used prophylactically to prevent HBV transmission in general populations and in HBV-infected healthcare professionals (HCP) performing exposure-prone procedures?

While NUCs therapy also reduces the risk of HBV transmission, vaccination remains the primary and most effective strategy for preventing horizontal spread. In the general population, routine prophylactic NUCs therapy for transmission prevention is unnecessary as it offers minimal additional benefit over vaccination.

For HBV-infected HCPs performing exposure-prone procedures (EPPs), the risk of transmitting HBV to patients is low [219]. Evidence indicates that HCPs who are HBeAg-negative or have low HBV DNA levels present a reduced risk of transmission. Most expert and national guidelines, including those from the US CDC [220], recommend maintaining HBV DNA below 1,000 IU/mL for HCPs performing EPPs. Suppression of HBV DNA with NUCs therapy, ideally to undetectable levels, further minimizes this risk [221].

Recommendations

1. Routine prophylactic use of NUCs solely for preventing horizontal transmission is *not* recommended when hepatitis B vaccination is available. (C2)
2. Healthcare professionals (HCPs) with chronic HBV infection who perform exposure-prone procedures (EPPs) should receive NUCs therapy to maintain undetectable HBV DNA, thereby minimizing the already low risk of patient-to-patient transmission. (A2)

In households or sexual contacts of individuals with chronic HBV infection, should family-based screening be implemented to identify undiagnosed infection and guide vaccination of susceptible persons?

Household and sexual contacts of individuals with HBV are at increased risk of infection through close contact, sexual exposure, or perinatal transmission [222]. Family-based screening facilitates early detection of undiagnosed cases for monitoring or treatment and enables immediate vaccination of susceptible contacts, preventing further spread [43]. Observational and programmatic evidence consistently shows that contact-based screening increases case detection and vaccination uptake, thereby reducing household transmission, with moderate certainty of evidence supporting this approach.

Recommendations

1. Screening should be conducted for all household and sexual contacts of individuals with chronic HBV infection. (B1)
2. Screening should include HBsAg, anti-HBs, and anti-HBc to identify current infection, immunity, or susceptibility. (B1)

V. Open questions

Service delivery models

How can stigma in occupational settings be addressed?

Stigma against people living with HBV in occupational settings undermines workers' rights, contributes to discrimination, job loss, and psychological distress, and perpetuates public health inequities [223]. It is driven by misinformation about transmission [224], moral judgments linking HBV to "immoral" behaviors [225], fear of disease progression [226], and systemic or cultural legacies of discrimination. Workplace interventions are most effective when integrating clear policies, education, and legal safeguards. Confidentiality and employee support systems reduce fear and encourage disclosure in safe contexts. Education programs correct misconceptions, normalize discussion, and foster inclusive attitudes. Legal protections provide enforceable safeguards against discrimination and ensure fair treatment. Together, these measures create safe, inclusive work environments where employees are judged by performance rather than health status, promoting both individual well-being and organizational equity.

Management statements

1. Anti-discrimination policies explicitly covering HBV should be established and enforced, medical confidentiality ensured, and workplace practices aligned with national laws. Job restrictions should be evidence-based rather than stigma-driven.
2. Regular, evidence-based education should be provided to correct misconceptions about HBV and promote supportive workplace environments through awareness, peer support, and clear reporting mechanisms.
3. People living with hepatitis B should be given same status and rights as any other citizen of the world.

What are optimal models of care to enhance access to screening and linkage to treatment?

Achieving WHO 2030 HBV elimination targets requires accessible, safe, and efficient care models. Decentralized, primary care- and community-based approaches increase

testing uptake [227], reduce missed cases, and are cost-effective and scalable [228–230]. Point-of-care testing, reflex testing, mobile diagnostics, and simplified algorithms minimize delays, enable timely treatment initiation, and reduce loss to follow-up [231, 232]. Structured referral pathways ensure specialist oversight for complex cases [233]. Affordable antivirals and adherence strategies, including peer support and reminders, support long-term viral suppression. Integrating vaccination, MTCT prevention, blood safety, workforce planning, and community engagement promotes equity, reduces stigma, and sustains care, accelerating elimination without compromising outcomes.

Management statements

1. HBV testing, treatment, and monitoring can be decentralized to primary and community care providers, using point-of-care diagnostics and simplified algorithms, with clear referral pathways for complex cases.
2. Affordable access to tenofovir or entecavir should be ensured, adherence strengthened through patient-centered support, and HBV services embedded within national health frameworks to ensure equity and sustainability.

Functional cure

What is the role of functional cure as a therapeutic endpoint in the management of chronic hepatitis B?

Functional cure is now recognized as the primary therapeutic endpoint in CHB with sustained HBsAg loss as the hallmark, reflecting a durable restoration of host immune control over HBV replication [234, 235]. HBsAg loss is associated with regression of liver fibrosis [236] and a reduced risk of cirrhosis [237, 238], liver decompensation [139, 237], and liver transplantation [139]. Achieving HBsAg loss also contributes to reduce new infections [239] and improving patients' quality of life [240].

In the past few years, new investigational agents aiming to achieve functional cure have shown limited and often not sustained responses. Hence, the clinical significance of the reduction or loss of HBsAg related to these new investigational therapies might be different to those related to spontaneous or registered anti-HBV therapy, which is highly durable. In addition, there are also uncertainties in optimal dosing strategies, and potential confounding factors which need to be understood [84]. An understanding of the impact of these new therapies on the restoration of host immunity on viral replication is hence urgently required. Given these limitations, current evidence does not yet support broad clinical use of these novel agents outside well-controlled

trials, emphasizing the need for cautious and evidence-based guideline recommendations.

For clinical trials, phase II trials should select endpoints based on the mechanism of the investigational drugs [241], whereas phase III trials should prioritize sustained HBsAg loss with undetectable HBV DNA at 24 weeks post-treatment [122] as the primary endpoint, supplemented by secondary virological, serological, and biochemical markers. Comprehensive safety monitoring, including immune-mediated flares and hepatic events, is essential, with follow-up tailored to the drug's mechanism to ensure an accurate assessment of benefit-risk profiles.

Finally, achieving functional cure in the Asia Pacific region remains challenging due to persistent gaps in prevention and diagnostics, variable access to treatments, financial constraints, limited public awareness, stigma, and fragmented health-system coordination. Multisectoral efforts are required to overcome these barriers and maximize the impact of functional cure strategies.

Management statements

1. Functional cure should be defined as sustained HBsAg loss (with or without anti-HBs seroconversion) accompanied by sustained undetectable HBV DNA at 24 weeks post-treatment cessation.
2. Functional cure should be considered a validated surrogate endpoint for improved clinical outcomes, and clinical trials should focus on immune-active HBeAg-positive and HBeAg-negative patients, with comprehensive safety monitoring tailored to each investigational agent.
3. Partial cure can be considered an intermediate therapeutic endpoint, defined as HBsAg < 100 IU/mL with undetectable HBV DNA.
4. Post-HBsAg clearance, close monitoring for virologic relapse should include HBV DNA and ALT every 3 months for the first year, then biannually and annually thereafter.
5. In the Asia Pacific region, achieving functional cure requires a multifaceted approach, including policies for prevention, early diagnosis, and affordable treatment, adequately trained healthcare providers, collaborative research funding, and patient and community education to reduce stigma and enhance engagement.

Discussion

Both AASLD [242] and EASL [243] updated CHB guidelines in 2025, reflecting converging principles but distinct operational approaches to whom, when, and how to treat, and when therapy may be stopped. Both recommend treatment

for all patients with cirrhosis and those with immune-active disease, but AASLD/IDSA applies stricter quantitative ALT and HBV DNA thresholds and explicitly incorporates shared decision-making for patients near treatment cut-offs or with uncertain disease activity. EASL adopts a broader, risk-based framework that integrates non-invasive fibrosis assessment and HCC risk factors, allowing treatment initiation even in selected patients with normal ALT. Treatment strategies are largely aligned, with both endorsing high-barrier NUCs as first-line therapy. But the guidelines differ sharply on when to stop. AASLD/IDSA generally advises continuing NUCs therapy until HBsAg loss, reserving deviations for shared decision-making, whereas EASL provides structured criteria for finite therapy in carefully selected non-cirrhotic, HBeAg-negative patients with the capacity for intensive post-cessation monitoring.

The current 2026 APASL guideline extends these discussions by offering context-specific recommendations tailored to Asia Pacific epidemiology and resource variability. APASL recommends treating non-cirrhotic patients with detectable HBV DNA, includes peg-IFN- α as first-line therapy in eligible patients, and supports peg-IFN- α add-on for NUC-treated, non-cirrhotic, HBeAg-negative individuals with undetectable HBV DNA and low HBsAg levels to increase the likelihood of functional cure. These criteria, supported by accumulating regional evidence, practical considerations and clinical experience, align with the growing international call [5] and national guidelines [244], for expanding treatment eligibility and leveraging immunomodulatory therapies to reduce long-term disease burden.

Looking ahead, CHB management is expected to shift toward increasingly personalized strategies driven by accessible viral and host biomarkers. Quantitative HBsAg, HBcrAg, and HBV RNA offer surrogates of intrahepatic cccDNA activity and may refine treatment initiation, on-treatment monitoring, and cessation decisions, provided they become affordable and widely available. Emerging immune-profiling and multi-omics approaches may further identify patients capable of achieving sustained off-treatment responses or benefiting from novel curative regimens.

Besides, effective management of CHB requires equitable access to screening, treatment and care. Decentralized care models that promote better coordination and integration of services across different levels of the healthcare systems is an essential pillar for substantially reducing the burden of HBV.

Finally, artificial intelligence and machine learning tools are poised to enhance CHB care by integrating clinical, imaging, and molecular data to improve fibrosis and HCC risk prediction [245, 246], guide treatment selection, and support safe treatment withdrawal [245–248]. Scalable AI-driven decision-support systems, particularly those using federated learning and explainable AI, may

strengthen frontline care and support national hepatitis-elimination strategies [249, 250]. AI-driven models may also improve screening efficiency and case detection by identifying individuals at high likelihood of CHB using routinely collected clinical, laboratory, demographic, and health-system data. Together, these advances promise more precise, equitable, and data-driven CHB management, accelerating progress toward the “WHO 2030 plus” elimination targets.

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Declarations

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