Indian National Association for the Study of the Liver Position Statements on Prevention, Diagnosis, and Management of Hepatitis B Virus Infection in India

Anil Arora [*], Praveen Sharma [*], Radha K. Dhiman [†], Ajay Duseja [‡], Vivek A. Saraswat [§], V. G. Mohan Prasad [¦], Shiv K. Sarin [¶], Subrat K. Acharya [**], Shivaram P. Singh [††], Padaki N. Rao [‡‡], Ramesh R. Rai [§§], Anil C. Anand [¦¦], Manisha Dwivedi [¶¶], S. P. Misra [¶¶], Ashish Goel [***], Ashish Kumar [*], Satyendra K. Tyagi [†††], C. E. Eapan [***], Sethu Babu [‡‡‡], Jayanthi Venkataraman [§§§], Bhaskar Nandi [¦¦¦], Pankaj Puri [¦¦¦], Anand V. Kulkarni [‡‡], Shalimar [¶¶¶], Sunil Dadhich [****], Bhabadev Goswami [††††], Parveen Malhotra [‡‡‡‡], Varghese Thomas [§§§§], Pradeep K. Agarwal [¦¦¦¦], Pradip Bhaumik [¶¶¶¶], Premashis Kar [*****], Manav Wadhawan [†††††], Manoj Kumar [¶], Yogesh K. Chawla [*****], Ameet Mandot [‡‡‡‡‡], Akash Shukla [§§§§§], Kaushal Madan [¦¦¦¦¦], Sanjiv Saigal [¦¦¦¦¦], Neeraj Saraf [¶¶¶¶¶], Dharmesh Kapoor [******], Chittaranjan C. Chaubal [††††††], Gaurav Pande [†], Ajeet S. Bhadoria [‡‡‡‡‡‡], Venkatakrishnan Leelakrishnan [§§§§§§], Barjesh C. Sharma [¦¦¦¦¦¦], Sunil Taneja [‡], Ashok Chowdhary [¶], Charles Panackel [¶¶¶¶¶¶], Rakhi Maiwall [¶], Sandeep Nijhawan [*******], Karam R. Singh [†††††††], Vinod K. Dixit [‡‡‡‡‡‡‡], K. T. Sheony [§§§§§§§]

[*]*Department of Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India,* [†]*Department of Gastroenterology, SGPGI, Lucknow, Uttar Pradesh, India,* [‡]*Department of Hepatology, PGI, Chandigarh, India,* [§]*Department of Hepatology, Mahatma Gandhi Institute of Medical Sciences and Technology, Jaipur, India,* [¦]*Department of Gastroenterology, Coimbatore, India,* [¶]*Department of Hepatology, ILBS, New Delhi, India,* [**]*Department of Gastroenterology, Fortis Escorts Liver and Digestive Diseases Institute, Delhi, India,* [††]*Department of Translational Gastroenterology, Kalinga Gastroenterology Foundation, Cuttack, India,* [‡‡]*Department of Hepatology, AIG, Hyderabad, India,* [§§]*Department of Gastroenterology, SMS Jaipur, Rajasthan, India,* [¦¦]*Department of Gastroenterology, Kalinga Institute of Medical Sciences, Bhubaneswar, India,* [¶¶]*Department of Gastroenterology, Motilal Nehru Medical College, Allahabad, Uttar Pradesh, India,* [***]*Department of Hepatology, CMC, Vellore, India,* [†††]*Gastroenterologist, Merrut, Uttar Pradesh, India,* [‡‡‡]*Krishna Institute of Medical Sciences, Hyderabad, India,* [§§§]*Department of Gastroenterology, Gleneagles Hospital, Chennai, Tamil Nadu, India,* [¦¦¦]*Department of Gastroenterology, Amrita Hospital, Faridabad, India,* [¶¶¶]*Department of Gastroenterology, AIIMS, Delhi, India,* [****]*Department of Gastroenterology, Dr Sampurnanand Medical College, Jodhpur, Rajasthan, India,* [††††]*Head of the Department at Dispur Hospital, Assam, India,* [‡‡‡‡]*PGI Rohtak, Haryana, India,* [§§§§]*MMC Hospital. Erinjippalam, Kozhikode, India,* [¦¦¦¦]*Astha Hospital, Dehradun, India,* [¶¶¶¶]*Department of Medicine, Agartala Govt Medical College, Tripura, India,* [*****]*Department of Gastroenterology, Max Hospital, Delhi, India,* [†††††]*Department of Gastroenterology, BLK Hospital, New Delhi, India,* [‡‡‡‡‡]*Department of Hepatology, Gleneagles Hospital Mumbaii, India,* [§§§§§]*Sir H. N. Reliance Foundation Hospital and Research Centre, Mumbai, India,* [¦¦¦¦¦]*Department of Liver Transplantation, Max Hospital, Saket, India,* [¶¶¶¶¶]*Division of Clinical and Transplant Hepatology, Medanta Hospital New Delhi, India,* [******]*Department of Liver Transplantation, Yashoda Hospitals, Hyderabad, India,* [††††††]*Medicine PCMS and RC Bhopal, India,* [‡‡‡‡‡‡]*Department of Community and Family Medicine, AIIMS, Rishikesh, India,* [§§§§§§]*Department of Gastroenterology and Hepatology, PSG Institute of Medical Sciences, Coimbatore, India,* [¦¦¦¦¦¦]*Department of Gastroenterology, G.B. Pant Hospital, New Delhi, India,* [¶¶¶¶¶¶]*Aster Medcity Hospital, Kochi, India,* [*******]*Department of Gastroenterology, Mahatma Gandhi Medical College, Jaipur, India,* [†††††††]*RIIMS, Imphal, India,* [‡‡‡‡‡‡‡]*Department of Gastroenterology, B.H.U, India and* [§§§§§§§]*Department of Gastroenterology, Sree Gokulam Medical College and Research Foundation Trivandrum, India*

Hepatitis B virus (HBV) remains a significant global health problem, particularly in India, where its prevalence is gradually decreasing, both in the general population and among healthcare workers. The management of HBV treatment should be individualized based on key factors such as HBV DNA levels, alanine transaminase (ALT) levels, and the presence of comorbid conditions like diabetes mellitus (DM), metabolic dysfunction associated steatotic liver disease (MASLD), pregnancy, cirrhosis, and decompensated cirrhosis. The "treat for all" strategy, although debated, was partially endorsed by the Indian National Association for the Study of the Liver (INASL). Pegylated interferon (Peg IFN) was not widely recommended due to limited practice, and genotype testing was

Keywords: hepatitis B, acute on chronic liver failure, acute liver failure, HBV reactivation, HBV flare
Received: 3.2.2025; *Accepted:* 1.6.2025; *Available online 9 June 2025*
Address for correspondence: P. Sharma, Department of Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India.
E-mail: drpraveen_sharma@yahoo.com

Abbreviations: AFP: Alpha feto protein,; APRI: Aspartate aminotransferase to Platelet Ratio Index; CAP: Controlled Attenuation Parameter; CHB: Chronic hepatitis B; CKD: Chronic kidney disease; CLD: Chronic liver disease; FIB-4: Fibrosis 4 score; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; HCW: Health care worker; INASL: Indian National Association for the Study of the Liver; MASLD: Metabolic dysfunction associated steatotic liver disease; NAT: Nucleic Acid Amplification Test; POC: point-of-care; TAF: Tenofovir alafenamide; TE: Transient elastography; TP-CECT: Triple phase contrast enhanced computed tomography; VCTE: Vibration-controlled Transient Elastography

https://doi.org/10.1016/j.jceh.2025.102608

avoided. Hepatitis D was not considered a prevalent condition; thus, testing for it was not emphasized. Special conditions, including immunosuppression and steroid therapy, were also discussed, and INASL provided comprehensive guidelines to address these unique scenarios in HBV management. High-resistance-barrier drugs like tenofovir alafenamide (TAF) were highlighted for their effectiveness and safety, particularly in pregnant women. Vaccination was strongly recommended for special risk groups, including healthcare workers and high-risk populations, while the debate on universal screening and vaccination continues, weighing its potential benefits against logistical challenges. (J Clin Exp Hepatol 2025;15:102608)

Hepatitis B poses a significant health problem worldwide[1]. The majority of patients are from the eastern part of the world, including China, Taiwan, and Southeast Asian countries such as India. The epidemiology and treatment practices for hepatitis B virus (HBV) infection vary in different parts of India based on socioeconomic and healthcare structures.[1–3] The Indian National Association for the Study of the Liver (INASL) developed, for the first time, 'India-specific' consensus guidelines for the diagnosis and management of HBV infection in 2018.[4] These guidelines helped in creating a framework for affordable management options for HBV in our country.

To update these guidelines based on recent data available in India and across the world, the HBV taskforce identified common issues based on day-to-day clinical practices and on epidemiological, clinical, preventive, and treatment aspects of HBV. For this update, all the taskforce members (from different states representing different geographical region) reviewed the existing literature, particularly from India, and developed consensus statements on each of these issues. Before the physical meeting, all the members were subdivided into groups under the various group leaders to have their own preliminary consensus. Once all groups completed their submeetings and reached a final conclusion on the statements on their individual topics, a two-day round table discussion was held in July 2024 in Coimbatore, Tamil Nadu, India, to discuss and finalize the consensus statements. Statements approved by the taskforce members were accepted according to evidence and recommendation grades. The evidence and recommendations in these statements have been graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system with minor modifications (Table 1). The strength of recommendations (strong: 1, weak: 2) reflects the quality (grade) of the underlying evidence (high, moderate, low, and very low).

EPIDEMIOLOGY OF HBV IN INDIA

There have been no large population-based studies from the Indian subcontinent since the publication of the first consensus statements in 2018.[4] Therefore, most of the available data is based on retrospective data analysis, blood bank donor data, and antenatal screening for viral hepatitis. Earlier studies reported the HBsAg carrier rate in India to be around 4%, placing India in the intermediate range of Hepatitis B prevalence, resulting in a total of 36 million carriers.[2] Among the estimated 400 million HBsAg carriers worldwide, it was believed that India contributed 9% of the total pool of hepatitis B cases to the world.[1,3] Socioeconomic disparities play a significant role in HBV prevalence. States with higher poverty levels and lower literacy rates often have less effective public health interventions, leading to higher rates of HBV infection.

The Indian Council of Medical Research (ICMR) study in 2021 on the seroprevalence of Hepatitis B, based on the National Health Survey (NHFS), suggests that the seroprevalence was minimal (0.0–0.5%) in the states of Jammu and Kashmir, Punjab, Chandigarh, and Delhi. It was 0.5–1% in Odisha, Chhattisgarh, Uttar Pradesh, and Madhya Pradesh; 1.0–1.5% in Bihar, Jharkhand, West Bengal, Daman and Diu, Lakshadweep, and Kerala; while the seroprevalence was higher (1.5–2.0%) in Sikkim, Tripura, and Assam. Notably, the highest HBV seroprevalence was reported in Andhra Pradesh and Telangana (2–2.5%).[5] The seroprevalence of HbsAg in the general population in India is therefore between 0.5% and 0.95%, based on retrospective data and the latest ICMR survey.[2]

Statement: The prevalence of HbsAg positive in general population in India is between 0.5% and 0.95%. Level of evidence: Moderate.

MODES OF TRANSMISSION

In an early study from India (8575 pregnant females—HBsAg+ 322, HBeAg+ 7.8%), Nayak *et al.*[6] estimated that vertical transmission accounted for up to one-third of Hepatitis B cases; rest of the infection being due to horizontal transmission. This estimate of vertical transmission is highly dependent on the proportion of pregnant mothers with replicative (HBeAg +ve) viral status, which has varied greatly across Indian studies from 8% to 57%.[7–9]

A recent sero-survey conducted by ICMR reported that increasing acceptance of the hepatitis B vaccination with the Universal Immunization Program (UIP) has resulted in lowered prevalence of childhood carriers, indicating reduction in vertical transmission[10,11]. Alexander *et al.*,[12] in a study (12,977 pregnancies—HBsAg+ 1.58%, HBeAg+ 16%), where the children received hepatitis B vaccination (birth dose: 88%, 3 doses: 76%), showed that 6% developed vertical transmission. This was much lower than the initial estimate of one third by Nayak *et al.*,[6] suggesting a significant impact of hepatitis B vaccination on vertical transmission. Close contact with a carrier, sharing of bed/bedding or

Table 1 Level of Evidence and Grade of Recommendations (Adapted From Grading of Recommendations, Assessment, Development, and Evaluations [GRADE] System With Minor Modifications[a]).

Level of evidence[b]		Confidence in the evidence
High	Information obtained from meta-analyses or systematic reviews, or from numerous randomized trials that have high quality data.	It is improbable that additional research will significantly alter our level of confidence in the assessment of potential benefits and risks.
Moderate	Information obtained from either a singular randomized controlled trial (RCT) or various nonrandomized studies.	Additional research, if conducted, may potentially alter our estimation of the benefit and risk and have an impact on our level of confidence in the estimate.
Low	Studies of limited sample size, observational studies conducted retrospectively, and registries.	There is a degree of uncertainty associated with any estimate of the effect.
Recommendations – Grade[c]		**Wording associated with the grade of recommendation**
Strong	The strength of the recommendation was influenced by several factors, such as the quality of the evidence, the presumed outcomes that are important for the patient, and the cost implications.	"Must", "should", or "we recommend"
Weak	The recommendation may be made with less certainty and may result in higher costs or resource consumption due to variability in preferences and values, or increased uncertainty.	"Can", "may", or "we suggest"

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]To make the GRADE system more objective, the type of studies from which the evidences are derived have been mentioned in the Level of Evidence section.
[b]Level was graded down if there was a poor quality, strong bias or inconsistence between studies; level was graded up if there was a large effect size.
[c]Recommendations reached by consensus of the members and included the quality of evidence, presumed patient-important outcomes and costs.

personal hygiene items, and eating in common utensils were significantly associated with the horizontal transmission of HBV in Indian studies[7,9]

Statement: Predominant mode of transmission in India is primarily horizontal, vertical transmission is on the decline (evidence: moderate).

HBV GENOTYPE AND ITS RELEVANCE TO IN TREATMENT

Most HBV infections in India are due to genotypes A and D, but the eastern part of the country presents an interesting epidemiologic pattern with three different HBV genotypes i.e. A, C, and D in comparable proportions.[13–16] Despite increasing knowledge on the clinical relevance of HBV genotypes, routine testing is not warranted in day-to-day practice except in HBeAg positive patients who are contemplating interferon therapy. There is a higher rate of HBeAg and HBsAg loss in those with genotype A, particularly subgenotype A2.[15] According to the latest World Health Organization (WHO) guidelines, which has simplified the treatment of HBV, the relevance of genotype testing is becoming increasingly weak as a recommendation.[17]

Statements:

1 Most HBV infections in India are due to genotype A and D (evidence: moderate).
2 HBV genotype testing is not recommended for the diagnosis and treatment of HBV infection in routine clinical practice (evidence: moderate, recommendation: strong)

HBV IN HEALTHCARE WORKERS

Among the 35 million healthcare workers (HCWs) working globally, approximately 3 million each year have occupational exposure to HBV infection, leading to up to 66 thousand HBV infections annually.[18,19] Healthcare workers are at an increased risk of HBV infection as their work exposes them to a highly transmissible infection virus, wherein accidental needle stick-injuries and cuts are common. The risk of HBV infection is primarily related to the degree and duration of contact with blood in the workplace and also to the HBeAg status of the source.[20] The prevalence of HBV infection in HCWs was 10% in 1992.[21] This figure was 2.21% 1998,[22] and a recent study from a tertiary care hospital in Delhi reported a 1% positivity.[23,24] This decline is attributed to the increasing vaccination rates and the adoption of universal precautions at the workplace by HCWs.

Statement: Prevalence of chronic HBV infection is more in HCW than the general population in India (evidence: moderate).

HBV IN SPECIAL POPULATIONS

The prevalence of HBV in special populations across Indian states highlights significant regional variations influenced by healthcare infrastructure, public health initiatives, and cultural practices. About 5–10% of human immunodeficiency virus (HIV)-infected individuals worldwide are coinfected with HBV.[25] HBV infection remains a

significant concern among hemodialysis patients in India, with prevalence rates varying across different regions and healthcare settings. Globally, HBV prevalence in dialysis patients ranges from 1% to 14%.[26] Developing countries have a higher prevalence, at times exceeding 10%, due to limited resources and less stringent infection control.[27,28] Approximately 5–10% of liver transplant recipients have HBV-related liver disease.[29,30] HBV prevalence among kidney transplant recipients ranges from 1% to 7%.[31,32] In India, the HBV-HIV co-infection prevalence ranges from 0.2 to 8% in peripheral HIV/sexually transmitted disease and tuberculosis clinics.[33]

STRATEGIES AND MODALITIES FOR SCREENING HBV IN GENERAL POPULATION

The Centers for Disease Control (CDC) recommends universal screening of all adults over 18 years old based on a cost-effective analysis done by Toy *et al.*.[34] Screening policies differ significantly from country to country. In India, screening of 1417 million people through a door-to-door campaign is difficult due to other health priorities and a shortage of healthcare resources. Screening for HBV in the general population is a huge task; hence, we need strategies targeting areas with passive inflow of population. Secondly, the difficulty in linking diagnosed cases and carriers to care takers, needs to be addressed. A few important strategies discussed by INASL members to eliminate HBV by 2030 for passive screening include screening all students before admission to school and colleges, need for a hepatitis B vaccination card before interstate bus, airline booking, and before vehicle registration or mobile phone connection.

Modalities Used for Screening: Compared to conventional blood tests, which heavily relies on centralized laboratory facilities, point-of-care (POC) testing for hepatitis B broadens testing access in low-resource settings and engages hard-to-reach populations. The WHO recommends that an ideal POC test meets the ASSURED criteria: "affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users." Multiple HBsAg POCs are commercially available. Most are qualitative lateral-flow chromatographic immunoassays, which are one-step, easy to use, can be used with whole blood, serum, and plasma, and provide rapid results (usually within 15–30 min). 'Determine' and 'Bioline' HBsAg rapid tests have met WHO prequalification criteria. A meta-analysis that included 30 studies evaluating the performance of 33 different HBsAg tests found an overall sensitivity of 90.0% (95% CI, 89.1–90.8%) and specificity of 99.5%.[35] Dried blood spot testing can be used for mass screening as it is convenient, easy to store, can be shipped by normal post, and utilized for serological and molecular tests.[36,37]

Statement:

1 There is no data related to universal screening in low to intermediate-prevalence countries; hence, universal screening cannot be recommended in India (evidence: low, recommendation: weak)

Screening for HBV in blood bank: Screening for HBsAg is mandatory in blood banks in India. However, the absence of HBsAg in the blood of apparently healthy individuals is not sufficient to ensure the lack of circulating HBV. Various screening strategies have been explored to prevent occult HBV infection in donor samples in blood banks. Two important screening tests suggested for HBsAg-negative samples suggested are Anti-HBc (total core antibody or IgG Anti-HBc) and Nucleic Acid Amplification Test (NAT) to minimize the transmission of HBV infection through blood and blood components. Anti-HBc as a screening test in samples tested negative for HBsAg is simple, inexpensive, and practical. However, core committee members expressed concerns that the inclusion of anti-HBc testing that will result in a high discard rate of 18–30% of blood units.[34,38] NAT, either minipool NAT or ID-NAT, is expensive and not practical in resource-constrained countries.

SCREENING AND VACCINATION OF HEPATITIS B IN GENERAL POPULATION

The goal of screening for hepatitis B infection is to lower the rates of cirrhosis, liver cancer, and death resulting from chronic HBV (CHB) infection. Although there is currently no direct evidence that screening leads to these improved health outcomes, there is evidence that screening is an accurate way to diagnose hepatitis B infection, which then leads to treatment. Treatment of CHB infection is effective in improving outcomes related to cirrhosis, cancer, and death. Potential harms of screening are small, as false-positive rates are low and available treatments are safe and effective. The hepatitis B vaccine as a part of universal immunization, is both cost-effective and efficacious with minimal side effects.

In planning and recommending an adult vaccination program, there is a need to evaluate the patient population under consideration for screening hepatitis B infection. This recommendation applies to adults and adolescents who are not pregnant and are at increased risk of hepatitis B infection. People at increased risk include: 1) People born in countries or regions with a high prevalence of hepatitis B infection regardless of vaccination history, 2) People who were not vaccinated during infancy 3) Past or current users of injectable drugs, 4) Men who have sex with men, 5) People with HIV and HCV infection, 6) Close contacts with known HBsAg positive individuals, 7) Individuals who

require frequent blood or blood products, dialysis patients, and recipients of solid organ transplant, and 8) Healthcare workers and others who may be exposed to blood and blood products through the nature of their work.[37]

WHO recommends universal hepatitis B vaccination for all infants, with the first dose given as soon as possible after birth.[38] Hepatitis B vaccine was universalized nationwide in India in 2011. The UIP schedule recommends hepatitis B birth dose to all infants within 24 h, followed by three doses at 6, 10, and 14 weeks to complete the schedule. The hepatitis-B birth dose coverage among the total live births was 45% in 2015 and 60% in 2016. The coverage among institutional deliveries for hepatitis B birth dose was reported to be 76.36% as of December 2017. Under India's Universal Immunization Programme (UIP), the target for the hepatitis B vaccine birth dose (HepB-BD) is to achieve 90% coverage by 2030(39). Apart from infants, HBV vaccination is advisable for all children and adults who were not previously vaccinated. It is rational to vaccinate all contacts of HBV-positive individuals, with or without overt disease. Unscreened adult vaccination at the community level is impractical, cost-ineffective, and unfeasible. The estimation of mortality-to-incidence ratios modeled with spatiotemporal Gaussian process regression to estimate the incidence of liver cancer oversimplifies HBV-related HCC. Another estimate used the Cause of Death Ensemble Modeling (CODEm) model, a tool that selects models and covariates based on out-of-sample performance, to estimate mortality due to cirrhosis, liver cancer, and acute hepatitis B.[40] Currently, adults attending healthcare clinics are being offered three doses of the vaccine on a Day 0, 1 month, 6-month schedule. There is no strong recommendation or guideline that the HBV vaccine be incorporated into the adult immunization schedule. To recommend adult HBV vaccine as statutory, we need community data on both HBV antigen and antibody status in the adult population from a large national cohort. However, since the cost of the vaccine is low and the need for three doses makes the vaccine readily available at peripheral health centers, test-and-vaccinate policy may not be necessary.

Statements

1 **Universal hepatitis B vaccination is recommended for all infants, and the first dose should be given as soon as possible after birth (within 24 h) (evidence: high, recommendation: strong).**
2 **HBV vaccination is also recommended in people with risk factors for acquiring HBV infection, such as those who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, as well as healthcare workers and others who may be exposed to blood and blood products through their work (evidence: high, recommendation: strong).**
3 **HBV vaccination is advisable for all children and adults who are not previously vaccinated; however, data are limited to know its effectiveness in terms of reducing morbidity and mortality due to HBV (evidence: moderate, recommendation: strong).**

SHOULD WE ROUTINELY TEST ANTI-HBS AFTER VACCINATION?

Routine testing of Anti-HBs in the general population was discussed in detail, but it was concluded that it would place an additional burden on the government's health budget and therefore should not be done routinely. Testing for anti-HBs after vaccination is recommended for the following groups whose subsequent clinical management depends on knowledge of their immune status:

1. People for whom vaccination is recommended (as described in the recommendation under the section "Screening and Vaccination in General Population").
2. Postvaccination in infants born to HBsAg-positive mothers. Serologic testing should consist of testing for anti-HBs and HBsAg. Testing is not done before the age of 9 months to avoid inadvertent detection of hepatitis B immunoglobulin administered at birth and to maximize the likelihood of detecting HBV infection, if present.
3. Patients who are anti-HBc (total) positive and negative for anti-HBs (or < 10 mIU/mL) and are likely to receive chemotherapy. Anti-HBs titer is checked a month after one dose of vaccination. If the anti-HBs is still negative, one needs to complete the vaccine series and test again 1–2 months after the last dose of vaccine.
4. Postneedle prick in those vaccinated, for adequacy of protection.[41–44]

Prevention and Management of HBV after Needle Stick Injury: Accidental exposure to blood and body fluid presents a serious public health concern, especially among HCWs, and constitutes a risk of transmission of the HBV. The exposed person should immediately report the exposure to the department of occupational health or infection control authority so that essential postexposure prophylaxis (PEP) may be initiated immediately to prevent postexposure transmission. The source patient must be tested for HBsAg as soon as possible after obtaining their consent. If the report is found to be positive (reactive for HBsAg), the exposed person must also be tested for anti-HBsAg. If the exposed person has received 3 doses of vaccination in the past, one needs to test for anti-HBsAg titers; if the titers are ≥10 mIU/mL, no further vaccination dose is required. If the exposed person is unvaccinated or

incompletely vaccinated and the source patient is HBsAg-positive, the PEP must be started as early as possible, preferably within 24 h (but not later than 7 days after exposure). The exposed person should receive 1 dose of hepatitis B immunoglobulin (HBIG) (0.06 mL/kg or 5.0 mL for adults) and 1 dose (1 mL = 20 μg) of hepatitis B vaccine administered after the exposure. Hepatitis B vaccine can be administered simultaneously with HBIG at a separate anatomical injection site (e.g. separate upper limb). The exposed person should complete the hepatitis B vaccine series as per the vaccination schedule (0, 1, and 6 months).[4,43,44]

Statement: Postexposure prophylaxis requires HBIG and HBV vaccination, preferably within 24 h based on the vaccination status.

SOCIAL STIGMA ASSOCIATED WITH HBV

Hepatitis B is often accompanied by significant social stigma, primarily stemming from misconceptions about its transmission and moral incursions, inferences, and judgments associated with liver disease. Those affected may experience discrimination in various contexts, such as in the workplace and healthcare settings, leading to feelings of isolation and shame. This stigma can prevent individuals from seeking essential medical care and support, negatively impacting their health outcomes.[45] As hepatologists, it is vital to cultivate a supportive and nonjudgmental environment, educate patients and communities, and advocate for destigmatization to improve treatment adherence and overall well-being.

PHASES OF HBV INFECTION

The natural history of chronic HBV infection is categorized into several phases: the immune-tolerant phase, the immune-active HBeAg-positive phase, the inactive carrier phase, the HBeAg-negative immune reactivation phase, and the HBsAg-clearance phase. Distinguishing between these phases based solely on a single measurement of HBV-DNA levels, serum alanine transaminase (ALT) and aspartate aminotransferase (AST) values, and the presence or absence of liver inflammation in a biopsy can be challenging. Therefore, ongoing monitoring with these tests is necessary. However, repeated testing can impose a significant financial burden on patients or the healthcare system, potentially discouraging follow-up visits.

The European Association for the Study of the Liver (EASL) has revised the terminology to include: HBeAg-positive chronic infection, HBeAg-positive chronic hepatitis, HBeAg-negative chronic infection, HBeAg-negative chronic hepatitis, and HBsAg-negative phase, based on AST and ALT levels (Table 2)[44]. Members of the INASL support this new nomenclature as it is more straightforward and user-friendly for patients.[44] Nevertheless, it may not resolve all ambiguities, as a single measurement of ALT, AST, and HBV DNA will not lead to proper classification of the category of HBV infection stage in every case.

Evaluation of an HBV Patient

Hepatitis B infection is usually detected when a person tests positive for HBsAg. HBV testing may be done in various settings, as shown in (Table 3).

The goals of further testing in patients who are HBsAg positive include assessing the likelihood of horizontal or vertical transmission of the infection between individuals (such as from mother to child, between sexual partners, or among healthcare workers). For patients incidentally diagnosed as asymptomatic hepatitis B positive (IDAHS) or those suspected of having chronic liver disease (CLD), it is essential to evaluate their eligibility for antiviral treatment. According to INASL guidelines, it is crucial to determine the phase of chronic HBV infection, assess liver health—including the presence of inflammation, fibrosis, cirrhosis, portal hypertension, and related complications

Table 2 Different Phases of Chronic HBV Infection.

HBV phase	HBsAg	HBeAg	HBV DNA in blood	ALT	Liver histology
HBeAg-positive chronic infection (Previously immune-tolerant phase)	Positive	Positive	Very high (>10^7 IU/mL)	Normal	No/minimal inflammation and fibrosis
HBeAg-positive chronic hepatitis (Previously immune-active phase)	Positive	Positive	High (>10^4 IU/mL)	Elevated	Moderate-severe necroinflammation and fibrosis
HBeAg-negative chronic infection (Previously inactive carrier phase)	Positive	Negative	Low (<2000 IU/mL)	Normal	No/minimal inflammation and fibrosis
HBeAg-negative chronic hepatitis (Previously HBeAg-negative active phase)	Positive	Negative	High (>2000 IU/mL, often >20,000 IU/mL)	Elevated	Moderate-severe necroinflammation and fibrosis
HBsAg-negative phase (Previously resolved HBV infection)	Negative	Negative	Undetectable	Normal	No ongoing inflammation

HBV, hepatitis B virus; ALT, alanine transaminase.

Table 3 Settings in Which HBV Infection is Tested.

Asymptomatic persons	Symptomatic persons
Before voluntary blood donation	Jaundice
Before surgery or invasive procedures	Acute hepatitis
During pregnancy	Liver failure (acute, subacute, or acute-on-chronic)
Screening family members of an index patient	Suspected chronic liver disease (CLD)
Executive health check-up	Suspected liver tumor (hepatocellular carcinoma; HCC)
Visa applications of some countries	Before solid organ transplantation
	After accidental needle stick injury
	Prior to immunosuppressive cancer treatment

HBV, hepatitis B virus; CLD, Chronic liver disease; HCC, hepatocellular carcinoma; DNA, Deoxyribonucleic Acid

or hepatocellular carcinoma (HCC)—and consider the patient's overall health status, including any comorbidities (such as alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease [MASLD], and its components like diabetes, obesity, coronary artery disease, hypertension, and dyslipidaemia), autoimmune hepatitis, and other forms of CLD.[4] Additionally, evaluating for coinfections (such as HDV, HCV, and HIV) and the family history of cirrhosis or HCC is important to determine the most appropriate treatment approach for each patient suffering from with HBV infection.[4,17,46]

Tests to establish the phase of HBV infection include HBeAg, anti-HBe, and quantitative HBV DNA (Table 4). Specific tests are utilized in special situations. For example, serum total anti-HBc may be tested prior to the use of strong immunosuppression for cancer (e.g. prior to the use of Inj. Rituximab) in a patient who is HBsAg negative. Serum IgM anti-HBc may be tested when acute hepatitis B or reactivation of hepatitis B is suspected, and serum HBsAg quantitation may be needed to assess true inactive disease or response assessment for antivirals, especially for patients in whom interferon therapy is contemplated.

Tests to establish the stage of liver disease usually include liver biochemistry (serum bilirubin [total and conjugated], liver enzyme levels [i.e. aspartate and alanine aminotransferases [AST, ALT]], serum alkaline phosphatase [SAP] or gamma-glutamyl transaminase [GGT], serum total proteins, serum albumin, prothrombin time/INR). Liver ultrasonography identifies features of liver cirrhosis like surface nodularity, volume redistribution, and portal hypertension (portal vein diameter, collaterals, ascites, splenomegaly, etc.).[4,39,44,46,47] In patients with chronic hepatitis B (CHB), liver stiffness correlated with fibrosis stage based on the METAVIR system. The AUROC for detecting significant fibrosis ($F \geq 2$) was 0.85, with a cut-off value of 6.0 kPa, while for advanced fibrosis ($F \geq 3$) and cirrhosis (F4), the cut-off values were 9.0 kPa and 13.0 kPa, respectively. Liver stiffness was primarily influenced by inflammation, with other factors showing no significant impact.[48] In settings where Vibration-controlled Transient Elastography (VCTE) is not readily available or affordable, noninvasive tests (NITs) such as the Aspartate Aminotransferase to Platelet Ratio Index (APRI; F2 cutoff value of 0.5 and F4 cutoff of 1.0) and FIB-4 (F2 cutoff <1.45 and F4 cutoff >3.25) can be used for the determination of liver fibrosis.[49] It was decided by the INASL HBV taskforce that the upper limit of normal (ULN) ALT level should be 40 U/L, as per previous INASL guidelines.[4]

Upper endoscopy for the presence of varices is indicated in specific situations as per Baveno VII guidelines; liver stiffness measurement (LSM) by VCTE ≤ 15 kPa plus platelet count ≥150 x $10^3/\mu$L rules out clinically significant portal hypertension (CSPH) with sensitivity and negative predictive value > 90%, obviating the need for endoscopy, while VCTE ≥25 kPa rules in CSPH with a specificity and positive predictive value > 90%; endoscopy should be performed in such patients and if already on beta-blockers endoscopy for screening esophageal varices can be deferred.[47] Alpha-fetoprotein (AFP) testing and triple-phase contrast-enhanced computed tomography

Table 4 Initial Testing in a Newly Detected HBV Infected Person.

Phase of CHB	Stage of liver disease	Comorbid condition	Coinfection
HBsAg	Liver biochemistry	CAP by TE	Anti-HCV, HCV RNA
HBeAg/anti-HBe	Liver sonography	HbA1c	HDV testing deferred
Quantitative HBV DNA	VCTE	Lipid profile	Anti-HIV-1 and 2
Total anti-HBc	APRI or FIB-4		
IgM anti-HBc	AFP, TP-CECT		
Quantitative HBsAg*			

CAP, controlled attenuation parameter; TP-CECT, triple phase contrast enhanced computed tomography; TE: transient elastography; CHB, chronic hepatitis B, VCTE, Vibration-controlled Transient Elastography; APRI, aspartate aminotransferase to platelet ratio index; AFP, Alpha feto protein; FIB-4, fibrosis 4 score; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

scanning (TP-CECT) are needed when HCC is suspected on screening ultrasound of the abdomen or when screening for HCC is warranted in special situation where ultrasound visualization score is poor.

Comorbid conditions are usually identified based on clinical history and biochemistry. Confirmation of diagnosis, assessment of severity of liver disease, and related complications should be conducted according to suggested guidelines. The tests for common comorbid conditions that should be considered include VCTE for CAP (controlled attenuation parameters) values to determine the grade of steatosis (S0–S3; values < 238, 238–260, 260–290, >290 dB/m),[17] HbA1c for type 2 diabetes mellitus (DM), autoimmune panel for autoimmune hepatitis (AIH), and tests for other etiologies as per standard guidelines. Coinfection with HIV or HCV should be routinely tested for in patients with chronic HBV infection (CHB), as their presence will affect treatment decisions and choice of medications. Hepatitis D virus (HDV) infection has rarely been reported in India. Routine HDV testing, as advocated in the recent WHO 2024 guidelines, should be deferred until more Indian data are generated regarding the prevalence of HDV infection.[17,50]

Point-of-Care HBV Testing

The very low global rates of screening for HBV infection (~13%) and poor linkage to treatment (~2.6%), highlighted by the WHO Guidelines 2024, warrant an intensified effort for testing and finding the ~221 million patients with CHB who have yet to be diagnosed globally, including ~29 million in India.[17] Point-of-care (POC) testing has proven to be a very effective tool in the test-and-treat strategy being followed for chronic hepatitis C (CHC). POC tests for HBsAg, adhering to the ASSURED guidelines (2004) and the REASSURED guidelines (2019) have been developed and preapproved for HBsAg testing by the WHO.[17,51] These include the Determine HBsAg 2™ assay from Alere Medical and the Bioline HBsAg™ assay from Abbott Diagnostics. POC HBV DNA NAT, such as the DETECTOR and the SHERLOCK assays, are being developed but have not yet been approved by regulatory authorities. Efforts to develop these POC tests for hepatitis B indigenously in India are warranted.

Impact of Comorbidities

HBV poses significant complications when coexisting with MASLD, HIV, HCV, and alcohol use disorder. MASLD and Met-ALD frequently overlaps with chronic HBV, exacerbating liver damage and increasing the risk of liver fibrosis and HCC. Patients with HBV and MASLD are at a higher risk of severe liver complications due to the combined effects of metabolic dysfunction and viral infection.[52]

In individuals living with HIV, the prevalence of MASLD is elevated, with contributing factors such as antiretroviral therapy (ART) and HIV-related metabolic changes leading to rapid progression of liver fibrosis. This is further complicated by HBV and HCV coinfections, which intensify liver inflammation and damage.[53] Abstinence from alcohol and smoking should be strongly recommended during the initial evaluation of patients with chronic HBV infection. Additionally, excessive alcohol consumption in HBV-infected individuals significantly amplifies the risk of cirrhosis and HCC due to the compounded liver injury from both alcohol and viral hepatitis.[54] Comprehensive management strategies must address viral suppression, metabolic health, and lifestyle modifications to mitigate disease progression and improve patient outcomes.

Role of HBsAg Quantification, HBcrAg, HBV RNA in Evaluation of HBV

An ideal biomarker for HBV should not only be sensitive and specific for diagnosis but should also correlate with viral load and the phase of HBV replication. Additionally, it should be reproducible, simple, and economical. Conventional biomarkers of HBV include hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg), and HBV DNA levels, which have been used for the assessment of infection and the need for treatment. These markers are found in peripheral blood and can be easily assayed universally.[4,46,47]

HBsAg Quantification

The role of quantifying HBsAg levels has long been recognized to guide the cessation of interferon therapy for HBV. However, its role in the era of nucleos(t)ide analogues (NUCs) is less clear. Nevertheless, HBsAg values remain important in identifying the risk of recurrence, liver-related complications, and HCC, even in the absence of detectable DNA levels.[55] HBsAg can be secreted as noninfectious subviral particles (spherical and filamentous forms of HBsAg) and as the glycosylated envelope protein of infectious mature virions, known as Dane particles. Commercially available kits, such as the Architect HBsAg QT assay (Abbott Diagnostics, Abbott Park, IL, USA) and the Elecsys HBsAg II assay (Roche Diagnostics, Indianapolis, IN, USA), detect both noninfectious and infectious virions. The range of the Architect assay is 0.05–250 IU/mL, while the Elecsys assay has a range of 0.05–52,000 IU/mL. The World Health Organization (WHO) reference standard for 1 IU/mL is equivalent to 1–10 ng/mL of HBsAg or 5×10^7 virions. HBsAg levels correlate directly with HBV DNA, covalently closed circular DNA (cccDNA), and the stage of HBV infection.[56]

The levels of HBsAg correlate with the phase of infection. A study from India reported median HBsAg titers in the immunotolerant phase to be 4.62 log10 IU/mL, 3.88 log10 IU/mL in the immune clearance phase, 2.76

log10 IU/mL in the low replicative phase, and 2.94 log10 IU/mL in the e-negative hepatitis phase.[57]

HBsAg levels are usually higher in HBeAg-positive patients than in HBeAg-negative patients. A value of over 1000 IU/mL in HBeAg-negative patients with DNA levels below 2000 IU/mL is associated with an 8% risk of developing HCC at 20 years, compared to a 2% risk if HBsAg is below 1000 IU/mL. Similarly meta-analysis reported a risk of 2.46 (95% CI, 2.15–2.83) for HCC with HBsAg levels above 1000 IU/mL, compared to those with levels below 1000 IU/mL.[58]

HBsAg levels is a useful guide in the management of patients with HBV who receive pegylated interferon (Peg IFN). A ≥1 log decline at 24 weeks of therapy can suggest the possibility of seroclearance.[59] However, regarding NUCs, HBsAg loss is rare, and the overall rate of HBsAg decline is slow (0.107 log IU/mL/year), even if NUCs are given for an extended duration of up to seven years in chronic hepatitis B (CHB) patients. A systematic review of 11 studies involving 1716 patients treated with NUCs reported the validity of HBsAg levels in predicting the recurrence of viral reactivation post-treatment. For example, patients with end-of-treatment (EOT) HBsAg levels below 100 IU/mL had significantly lower rates of virological and clinical relapse compared to those with levels above 100 IU/mL.[60]

HBcrAg: Additionally, HBcrAg, a composite antigen of denatured HBeAg, HBV core antigen (HBcAg), and a 22 kDa precore protein found in virion-like particles without HBV DNA, correlates with intrahepatic cccDNA and can indicate active viral replication. Approximately 78% of those with undetectable HBV DNA have detectable HBcrAg. Serum HBcrAg levels also strongly correlate with HBV DNA and HBsAg levels. HBcrAg levels can reflect the effectiveness of antiviral therapy and predict long-term clinical outcomes. For instance, in the REVEAL-NBNC cohort study, which included 129 patients with seronegative for hepatitis B surface antigen and anti- HCV (NBNC HCC), 12.4% had HBcrAg positivity compared to 1.4% of 520 matched populations with NBNC non-HCC patients.[61]

HBV RNA: Another novel biomarker is HBV RNA, which is transcribed directly from cccDNA. HBV RNA strongly correlates with HBsAg levels and HBcrAg, especially in HBeAg-positive patients. HBV RNA levels correlate with HBV DNA, albeit 1.5–2 logs lower. A decline in HBV RNA levels by three to six months post-therapy was found to be a predictor of HBeAg seroconversion in patients treated with NUCs.[62,63]

In summary, an ideal biomarker for HBV should be sensitive, specific, and correlate with viral load and the replication phase, in addition to being reproducible, simple, and economical. Current biomarkers, such as HBsAg, HBeAg, HBV DNA, HBcrAg, and HBV RNA, provide critical information for diagnosis, monitoring, and treatment decisions in HBV infection. These biomarkers help assess infection status, guide treatment, predict clinical outcomes, and manage patients effectively.

Role of Fibrosis Assessment Using Noninvasive Tests

Among noninvasive methods for assessing liver fibrosis, transient elastography (TE) stands out as the most extensively studied, demonstrating higher diagnostic accuracy for detecting advanced fibrosis, cirrhosis, and even portal hypertension.[48,49] Other noninvasive tests include the APRI and the fibrosis-4 (FIB-4) index, which are widely used scoring systems for assessing liver fibrosis in patients with chronic liver disease. While noninvasive methods, including LSMs and serum biomarkers, show moderate accuracy in identifying significant fibrosis (stage 2 or greater on the METAVIR scale), they exhibit good diagnostic accuracy in excluding advanced fibrosis, making them useful tools in clinical decision-making. However, it is important to be aware that intermittent exacerbations of hepatitis B can lead to the overestimation of fibrosis stage by these noninvasive tests. Therefore, different cutoffs for significant and advanced fibrosis based on ALT levels have been proposed to improve accuracy.[64,65]

Role of Liver Biopsy in HBV

The major value of a liver biopsy in a patient with CHB infection is to rule out other causes of liver disease, assess the degree of liver damage, and provide information regarding disease progression. The issue is not always as simple as it seems; liver histology can improve significantly in patients who experience spontaneous hepatitis B e antigen (HBeAg) seroconversion or sustained response to antiviral therapy. The ideal candidates for treatment are those individuals with positive predictors of response. These patients can be identified based on serum HBV DNA levels, hepatic biochemical tests, and serologic studies. The liver biopsy is of limited value in predicting response to interferon therapy, and data are limited regarding its value in predicting response to any of the oral antiviral agents (4, 46,47 64).

Family Screening of Index HBV Patient

Screening should involve testing all first-degree relatives, including parents, siblings, and children, as they are at the highest risk of infection due to shared living conditions and practices. The screening typically includes serological tests for Hepatitis B surface antigen (HBsAg), and antibodies to hepatitis B core antigen (anti-HBc) and anti HBsAg to determine current infection and past exposure.[66]

Consensus statement:

1 **Initial evaluation of HBsAg positive persons should focus on evaluation of possible mode of acquisition, liver disease staging, need for antiviral treatment,**

presence of additional risk factors such as co-morbidities, co-infections, alcohol use, and family history of cirrhosis and liver cancer (evidence: high, recommendation: strong).

2 **Laboratory tests should include assessment of liver function (AST, ALT, GGT, alkaline phosphatase, bilirubin, serum albumin, serum globulins, complete blood count and INR), markers of HBV replication (HBeAg, anti-HBe, quantitative HBV DNA), and tests for coinfection with HCV and HIV. An ultrasound examination of the liver is recommended in all patients (evidence: high, recommendation: strong).**

3 **An ALT of 40 U/L should be considered normal for Indian patients (evidence: low, recommendation: weak).**

4 **There is insufficient data to recommend HBV genotype testing in the diagnosis and treatment of HBV infection in routine clinical practice (evidence: moderate, recommendation:strong).**

5 **There is insufficient data to recommend testing for HBV RNA and HBcrAg in the diagnosis and treatment of HBV in routine clinical practice (evidence: moderate, recommendation: strong).**

6 **In select situations, HBsAg quantification should be utilized to define the natural history, establish stopping rules for treatment and predict treatment response (evidence: moderate, recommendation: strong).**

7 **A liver biopsy or noninvasive test should be performed to determine disease stage and need for antiviral treatment in cases where biochemical tests and ultrasonography reveal inconclusive results (evidence: moderate, recommendation: strong).**

8 **Family screening of index HBV patient should be done with HBsAg, and total HBc and antibody to HBsAg (evidence: moderate, recommendation: strong).**

Aim of HBV Treatment and Relevance of Different Types of Cures

The primary goals of HBV treatment are to achieve viral suppression, prevent disease progression to cirrhosis and HCC, and enhance the quality and duration of life of affected individuals. The concept of a "cure" in HBV is complex and can be classified into functional and complete cure (Table 5). A functional cure is characterized by the sustained loss of HBsAg without the need for ongoing antiviral therapy, indicating a restored immune response, which is crucial for reducing long-term complications like cirrhosis and HCC. Treatment with Peg IFN alpha (PegIFN-α) can facilitate HBsAg loss, especially in HBeAg-positive patients; however, the overall rates of achieving a functional cure remain low, typically under 10% after one year of therapy, highlighting the need for continued research for innovative treatment[67] A complete cure entails the eradication of HBV, including the clearance of cccDNA from hepatocytes, an outcome currently unattainable with existing therapies. Novel approaches, such as RNA interference and therapeutic vaccines, are being investigated to target cccDNA and enhance immune responses, but these strategies require further validation in clinical trials[68–70]

Treatment of HBV Patients

There have recently been several attempts to simplify treatment decisions for patients with HBV infection, especially in resource-poor countries.[17,47,71] The aim was to capture a nearly 50% larger proportion of all HBsAg-positive individuals and to include treatment options for those without access to an HBV DNA assay. While INASL agrees with the spirit of these publications, it decided to chart its own path as suggested by the available evidence. After much deliberation and discussion, six consensus statements for indications were agreed upon.

The phases of HBV natural history where treatment is clearly indicated are during the immuno-clearance phase (HBeAg-positive chronic hepatitis B) and during the reactivation phase (HBeAg-negative chronic hepatitis B). Both these phases are recognized by the presence of two factors: (a) evidence of viral multiplication, as indicated by HBeAg or high HBV DNA levels; and (b) evidence of liver inflammation/fibrosis, as indicated by raised ALT levels or evidence of fibrosis either on liver biopsy or by noninvasive tests. It has also been realized that HBV DNA levels and ALT levels are imperfect measures of viral replication and liver inflammation, respectively, as these parameters fluctuate over time. A single test may miss evidence of phase transition. There is a higher chance of detecting raised ALT when this test is monitored frequently. Therefore, a persistently normal ALT can only be diagnosed if ALT remains normal over three values tested over a six-month period.

Table 5 Different Types of HBV Cures.

Cure Type	HBsAg	HBV DNA	HBV RNA	HBcrAg	cccDNA (hepatic reservoir)
Partial cure	± detectable	Undetectable in serum	Detectable	Detectable	Persistent in hepatocytes
Functional cure	Undetectable	Undetectable in serum	Undetectable	Low or undetectable	Persistent but inactive
Complete cure	Undetectable	Undetectable	Undetectable	Undetectable	Minimal residual cccDNA
Sterilizing cure	Undetectable	Undetectable	Undetectable	Undetectable	Absent (erased from liver cells)

HBV, hepatitis B virus; RNA Ribonucleic Acid.

Some of the current recommendations are almost similar to earlier published INASL guidelines, with a small difference.[4] The normal level of ALT has been controversial, as different guidelines use different cut-offs for normal.[4,44,46,47,72–77] While the AASLD has used 35 and 25, respectively, for males and females as the ULN, arbitrarily,[46] other guidelines use a fixed level of 40 as ULN(4). What has gone unheeded is the finding of American Pathologists that ALT levels are also dependent on the method used for analysis; using different systems of assessment, ULN may vary from 32 to 72 (median 63) in males and from 31 to 55 (median 52) in females.[77]

Taking cue from these findings, we have aligned with the Asian consensus to accept the ULN given by local lab data as the ULN for a given patient, and anything above that is considered raised ALT levels.[78] All HBsAg-positive patients, irrespective of HBV DNA or ALT levels, should be treated if they have compensated or decompensated cirrhosis. The diagnosis of advanced fibrosis or cirrhosis may be based on clinical and imaging features, liver biopsy (F4 fibrosis), or based on non-invasive measures, such as an APRI score of >1 or a FIB-4 score of >2.67, and a transient elastography value of >12.5 kPa. In cases of decompensated cirrhosis, the diagnosis could be based on clinical or imaging evidence of portal hypertension (such as ascites, variceal bleeding, or hepatic encephalopathy) and liver dysfunction with coagulopathy.

All patients who are positive for HBsAg (including pregnant women and nonpregnant women of reproductive age) and who have any of the following should be treated regardless of HBV DNA or ALT levels:

a) Presence of coinfections (such as HIV, hepatitis D or hepatitis C);
b) Family history of liver cancer or cirrhosis; need of immune suppression (such as long-term steroids, solid organ or stem cell transplant);
c) Extrahepatic manifestations (such as glomerulonephritis or vasculitis);
d) Patients presenting as acute liver failure and acute on chronic liver failure regardless of HBV DNA or ALT levels.[17,78–80]
e) Regardless of NIT results (APRI score, FIB-4 score, or transient elastography), and irrespective of the HBeAg status, HBsAg-positive patients with DNA levels >2000 IU/mL and an ALT level above the ULN on at least two occasions in a 6-month period should be started on treatment.
f) The working party had decided to treat patients with chronic hepatitis B who have comorbidities such as DM and MASLD only in the presence of significant fibrosis and detectable HBV DNA. Inactive HBsAg status (Normal ALT and negative HBV DNA) with mere presence of DM or MASLD (without significant fibrosis) will not qualify for treatment.
g) Patients in the immunotolerant phase (HBeAg-positive HBV infection) are generally considered ineligible for treatment. However, recent opinions have been expressed to include them in the treatable category for several reasons[80]: (a) persistently normal ALT (PNALT) may be associated with significant (~22.3%) fibrosis/necrotic inflammation. One possible reason for this finding may be, as has been pointed out earlier, that the patient may have an intermittent rise in ALT indicating phase transition, which has been missed due to inadequate monitoring; (b) HBV DNA levels in this phase are very high, and high DNA levels have been shown to correlate with a high risk of developing cirrhosis as well as HCC;[81,82] (c) *In vitro* studies show immune system is active to get rid of the virus in these cases;[83] and finally, (d) HBV DNA integration, a major event in HCC carcinogenesis, has been demonstrated in 11 immunotolerant patients.[84] However, these arguments have limitations. If we closely scrutinize the patients included in these studies, it appears that the participants were not in the true immunotolerant phase. In the Reveal study quoted earlier, 85% were not in the immunotolerant phase. Even in other studies, persistently normal ALT was not established, and where DNA integration was checked, several of the patients included had significant fibrosis.[85] Several studies have shown that patients in the true immunotolerant phase have benign prognoses. Paired biopsy studies show <5% risk of fibrosis progression.[86,87] Many such patients show gradual progression to the immuno-clearance phase after a variable period (10–30 years).[88,89]

There is limited efficacy of interferon and/or nucleos(t)ide analogues (NAs) monotherapy, and results show 0–5% HBeAg seroconversion, incomplete HBV DNA suppression (0–23%), and rapid rebound increase in DNA upon stopping therapy. On long-term follow-up, the majority have spontaneous eAg seroconversion, and the risk of HCC is extremely low.[90–92]

Considering all the foregoing facts, the INASL recommends that patients in the Chronic HBeAg-positive infection (immunotolerant phase) should be started on antiviral treatment if they are over 30 years of age, have raised ALT levels above the ULN on follow-up, or have evidence of significant fibrosis.[93]

Detecting the phase transition from inactive carrier (HBeAg-negative HBV infection) to the reactivation phase may also be challenging. The APASL (2016) recommends that if such patients are over 35 years of age, have a family history of HCC/cirrhosis, or have elevated ALT or noninvasive tests (NITs) suggesting significant fibrosis, these patients should undergo a liver biopsy. Patients with F2 fibrosis and above should be treated, as they have a high risk of HCC and liver-related events.[94] There are conflicting

reports about the outcomes of such patients, as the definition of this phase has not been strict.[95] However, a recent study has shown that reactivation without any therapy occurs in 10.2% of cases by 5 years, 17.4% of cases by 10 years, and in 20.2% of cases by 25 years.[96]

Spontaneous HBsAg loss and/or seroconversion occurs in 1–3% per year, while increased flares are seen mainly in those with pre-core mutations, male sex, and age over 30 years at presentation.[97] A recent report has introduced the concept of gray zone carrier.[98] The authors divided their inactive carrier group of patients into four groups: (a) patients with HBV-DNA either undetectable or <2000 IU/mL and ALT <40; (b) patients with HBV-DNA <2000 IU/mL and abnormal ALT 40–80 U/L; (c) patients with HBV-DNA between 2000 and 20,000 IU/mL and ALT <40 U/L; and (d) patients with HBV-DNA between 2000 and 20,000 IU/mL and abnormal ALT 40–80 U/L. They checked an additional parameter, i.e. quantitative HBsAg levels, and found that most patients considered true inactive carriers had qHBsAg levels below 1000 IU/mL. After nearly 8 years of follow-up, 15% HBsAg seroconversion was observed in this group. It has also been noted that the high risk for HCC among HBV-infected patients is denoted by male sex, older age, hepatitis B antigen status, HBV genotype (B or C), levels of ALT, and HBV DNA, but not qHBsAg. On the other hand, among inactive carrier phase patients with low viral loads (<2000 IU/mL), the HCC risk is determined by levels of qHBsAg, alanine aminotransferase, and age.[99]

Keeping this information in mind, the INASL has recommended that patients in the inactive carrier phase (chronic HBeAg-negative infection) with any of the following should also be started on treatment if they meet any of these criteria (a) so-called gray zone carriers, i.e. patients with HBV DNA >2000 IU/mL but persistently normal ALT, or any detectable level of HBV DNA with ALT levels above ULN, will be subjected to qHBsAg tests, and treatment will be offered if the qHBsAg level is > 1000 IU/mL; or (b) patients with any detectable level of HBV DNA who are over 30 years of age, have a family history of cirrhosis/HCC, or have associated significant liver inflammation/fibrosis (>F1).

Treat-all strategy: The latest 2024 guidelines from the WHO and the Chinese National Guidelines for hepatitis B recommend a "treat-all" strategy for patients with chronic hepatitis B, emphasizing the need for expanded antiviral treatment.[17,71] The WHO has highlighted the importance of initiating treatment for all HBsAg-positive individuals, even in resource-limited settings where HBV DNA testing may not be readily available. This approach is particularly relevant for patients over the age of 30 with detectable HBV DNA, given their higher risk of progression to liver disease. In addition, individuals with comorbid conditions such as diabetes, metabolic-associated steatotic liver disease (MASLD), and extrahepatic manifestations should also be considered for treatment. The Chinese guidelines similarly stress treating all HBsAg-positive patients, including those with elevated ALT levels or those at high risk for liver complications, regardless of the availability of advanced diagnostic tools. By broadening the treatment criteria, both sets of guidelines aim to reduce the global burden of hepatitis B, prevent liver complications, and lower transmission rates. These recommendations are pivotal for tackling the disease in areas where healthcare resources are limited, ensuring that more individuals have access to life-saving antiviral therapy. INASL members have debated the WHO and Chinese guidelines advocating the "treat-all" strategy for hepatitis B. While they acknowledge the importance of broadening treatment eligibility, they recommend a more tailored approach, considering treatment on a case-by-case basis, especially when HBV DNA testing is not available. In such situations, treatment may be initiated based on clinical factors such as persistent elevated ALT levels or comorbid conditions, rather than solely relying on viral load measurements.

Elimination of Hepatitis by 2030

The WHO has set a goal to eliminate viral hepatitis as a public health threat by 2030, targeting a 90% reduction in new HBV infections and a 65% reduction in HBV-related mortality.[17] To achieve this, the WHO recommends key interventions, including universal HBV 3-dose vaccination with a birth dose coverage of at least 90%, early diagnosis and linkage to care for at least 90% of HBV-infected individuals and expansion of antiviral treatment to at least 80% of eligible patients[17]. The WHO Hepatitis report 2024 mentions a total 30 million hepatitis B infections (all ages) in India, accounting for 11.6% of global cases in 2022, 50 thousand new cases and 98 thousand deaths.[100] The 2015–16, National Family Health Survey (NFHS) data documented low seroprevalence to 0.95% (0.89–1.01) of HBsAg in India[39]. This can be attributed to improved HBV vaccination in India. The universal infant HBV vaccination program, introduced in 2002 and expanded nationwide in 2011, has significantly reduced perinatal transmission. Current HBV 3-dose coverage is >90%, and HBV birth dose coverage is 80–90% in India. A fully domestically funded National Viral Hepatitis Control Program (NVHCP), was launched in 2018, providing free screening, testing and treatment to all Indian citizens. It has improved HBV screening and treatment access, particularly for pregnant women and high-risk populations in the last 6 years. Despite these achievements, gaps remain in achieving HBV elimination by 2030 which includes:

Limited Adult Vaccination: Unlike childhood immunization, adult vaccination coverage is poor, particularly among healthcare workers and high-risk groups.

Screening Challenges: Universal screening is logistically difficult in India, leading to underdiagnoses.

Treatment Gaps: Only a small proportion of diagnosed patients receive antiviral therapy, mainly due to financial and infrastructure constraints.

INASL members are dedicated to eliminating hepatitis from India. To accelerate this effort, INASL will update its position statement with SMART (specific, measurable, achievable, relevant, and time-bound) goals aligned with the 2030 elimination target. A comprehensive roadmap will be developed, outlining strategic actions to achieve this goal. INASL will enhance collaborations with government agencies, healthcare providers, and community organizations, advocate for increased funding and resources for hepatitis programs, and establish robust monitoring and evaluation mechanisms to assess intervention effectiveness. By addressing key challenges and implementing focused strategies, INASL aims to play a pivotal role in eliminating viral hepatitis in India by 2030.

Statements

Indications to Start Treatment

1 **Regardless of NIT results (APRI score, FIB4 score, or transient elastography) and irrespective of HBeAg status, HBsAg-positive patients with DNA levels >2000 IU/mL and an ALT level above the ULN on at least two occasions in a 6-month period should be started on treatment (E: high, R: strong).**

2 **All chronic HBsAg-positive patients irrespective of HBV DNA or ALT levels, should be treated if they have compensated or decompensated cirrhosis (E: high, R: strong).**

3 **All patients who are positive for HBsAg (including pregnant women, girls, and nonpregnant women of reproductive age) and who have any of the following should be treated regardless of HBV DNA or ALT level (E: high, R: strong).**

   a. **Presence of coinfections (such as HIV, hepatitis D or hepatitis C);**
   b. **Family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, solid organ or stem cell transplant);**
   c. **Extrahepatic manifestations (such as glomerulonephritis or vasculitis),**
   d. **Patients presenting as Acute Liver failure (ALF) and acute-on-chronic liver failure (ACLF).**

3 **Patients with any detectable levels of HBV DNA along with any of the following risk factors should also be treated**

   a. **Detected to have significant fibrosis levels (E: moderate, R: strong)**
   b. **Comorbidities such as DM and metabolic dysfunction-associated steatotic liver disease (MASLD), if significant fibrosis is present (E: moderate, R: moderate)**

4 **Patients with HBeAg-positive chronic infection (immunotolerant phase) with the following conditions should be started on antiviral treatment (E: moderate, R: strong).**

   a. **Age above 30**
   b. **Raised ALT above ULN on follow-up**
   c. **Evidence of significant fibrosis**

5 **Patients with chronic HBeAg-negative infection (inactive carrier phase) with any of the following should started on treatment (E: moderate, R: strong).**

   a. **HBV DNA >2000 IU/mL with normal ALT or any detectable level of detectable DNA with ALT levels above ULN with will be subjected to qHBsAg tests, and treatment will be offered if the qHBsAg level is >1000 IU/mL (gray zone carriers).**
   b. **Detectable HBV DNA at any level along with age >30 years and family h/o cirrhosis/HCC, or associated liver inflammation/fibrosis (>F1).**

Recommended Drugs for HBV

The available antivirals for HBV can be divided into two broad groups: NAs and interferons (IFNs). The NAs analogues approved for HBV treatment are tenofovir disoproxil (TDF), tenofovir alafenamide (TAF), entecavir (ETV), telbivudine (TBV), adefovir (ADV), and lamivudine (LMV). Of these, LAM, ADV, and TBV are no longer used in the treatment of HBV except in special circumstances. These three drugs have a low barrier to resistance and low potency against HBV. Currently, only ETV, TDF, and TAF are used in HBV treatment due to their high genetic barrier to resistance. In addition to having a high barrier to resistance and high potency, these drugs are very safe and well-tolerated. The generic version available in India can also be used, given the low cost of these medicines. Current evidence suggests that monotherapy with ETV, TDF, or TAF is equally effective in controlling HBV infection.[101–109] Data on combination therapy is limited and is not currently recommended, except in special circumstances like HIV coinfection or inadequate response to monotherapy.[108,109] However, therapy must be individualized for each patient, and no specific guidelines have been considered.

There are two changes from the previously published INASL guidelines.[4] There is sufficient evidence that in cases of established osteoporosis and renal dysfunction, TAF (or ETV in modified dosages) should be preferred over TDF. Secondly, TAF is now proven to be safe in pregnancy and can be considered a first-line therapy, in addition to TDF.[110,111]

Role of PEG-IFN in HBV

The primary advantages of Peg IFN-α compared to NAs include the absence of resistance development and the attainment of higher rates of HBeAg and HBsAg loss. However, PegIFN-α has several significant drawbacks, including lower efficacy, with fewer than 50% of treated individuals achieving a response, as well as high cost, the necessity for injection administration, and frequent adverse effects. Additionally, various contraindications limit its use, particularly in resource-limited settings, where these factors hinder its widespread application.[4,46,47,112–114]

PegIFN-α may be considered for patients with either HBeAg-positive or HBeAg-negative chronic hepatitis after thorough discussion and careful assessment of the patient's safety profile.

Consensus statements:

1 **The following drugs should be used for treatment: TDF, TAF, ETV (evidence: high, recommendation: strong).**
2 **All the drugs should be used as monotherapy. Combination therapy or sequential therapy of NA and PegIFN-a is not recommended at present (evidence: moderate, recommendation: strong).**
3 **The following drugs should not be used for treatment: Lamivudine, ADV, and telbivudine (evidence: high, recommendation: strong).**
4 **In patients with cirrhosis: Oral antiviral therapy with tenofovir or ETV is preferred (evidence: high, recommendation: strong).**
5 **With the advent of highly potent NAs, the use of PegIFN-α has declined due to its high variability in overall response and an unfavorable safety profile, rendering many patients ineligible or reluctant to pursue this treatment (evidence: high; recommendation, strong).**
6 **PegIFN-a should not be administered in patients with immune-related extrahepatic manifestations (evidence: moderate, recommendation: strong).**

Monitoring of Patients on Antiviral Therapy

1 During antiviral therapy, close monitoring for side effects of each drug is mandatory (evidence: high, recommendation: strong).
2 Monitoring of drug compliance of patient is of paramount importance, as poor adherence to antiviral treatment may lead to increased risk of drug resistance and treatment failure (evidence: moderate; recommendation: strong).
3 All patients treated with NAs should undergo: Periodical assessment of ALT (3–6 months) and serum HBV DNA (every 6 month) (evidence: high, recommendation: strong).
4 following patients should undergo periodical renal monitoring that includes estimated glomerular filtration rate (eGFR) and serum phosphate levels: Patients at risk of renal disease treated with any NA (evidence: high, recommendation: strong)
   - All patients, regardless of renal risk, who are treated with TDF (evidence: high, recommendation: strong)
   - Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF (Evidence: Moderate, recommendation: strong).
5 Patients with decompensated cirrhosis should be closely monitored for drug tolerability and the development of rare side effects like lactic acidosis or kidney dysfunction (evidence: weak, recommendation: strong).

Extrahepatic manifestations and need for antivirals: Extrahepatic manifestations of HBV include polyarteritis nodosa, vasculitis, purpura, peripheral neuropathy, arthralgias, and glomerulonephritis. Patients may have mixed cryoglobulinemias and elevated inflammatory markers. HBsAg-positive patients with active HBV replication often respond to antiviral therapy, but PegIFN-a can worsen immune-mediated symptoms and should be avoided. Instead, NAs are recommended, with additional treatments such as plasmapheresis and corticosteroids potentially beneficial in special cases.[4,44,46,47]

Monitoring of HBV Patients on and off Antiviral Treatment

Patients who are not eligible for antiviral therapy require regular monitoring of their disease. This should include checking serum ALT and HBV DNA levels. If necessary, a noninvasive assessment of liver fibrosis should also be conducted to screen for any development of significant fibrosis. In light of the expanded criteria for the treatment of HBV, any possible indication mentioned above in the treatment section should prompt an offer of treatment to the individual. For patients with HBV DNA levels over 2000 IU/mL, ALT tests should be performed at least every 3–6 months, while HBV DNA tests should take place every 6–12 months, and liver fibrosis assessments should be done annually. For those with HBV DNA levels below 2000 IU/mL, ALT tests should be conducted every 6–12 months, along with periodic assessments of HBV DNA and liver fibrosis, possibly every 2–3 years.[4,47]

When and how to stop antiviral therapy in hepatitis B: The decision to discontinue antiviral therapy in hepatitis B patients should be highly individualized, taking into account various clinical factors. Current guidelines suggest that treatment cessation may be appropriate for noncirrhotic patients who have achieved sustained HBeAg seroconversion and undetectable HBV DNA for at least 24 months. For HBeAg-negative patients, virological suppression should be maintained for at least three years on therapy before considering discontinuation (Table 6). It is also

Table 6 Stopping Therapy in Patients with CHB Patients.

Patient Group	Ideal treatment endpoint	Proposed stopping rule
HBeAg-positive CHB patients	Achieve HbeAg seroconversion or HBsAg loss - Undetectable HBV DNA - Complete at least 12 months of consolidation therapy	After achieving HbsAg seroconversion and undetectable HBV DNA - Complete at least 12 months of consolidation therapy before considering cessation
HBe Ag negative CHB patients	Achieve HBsAg loss (functional cure)	After at least 3 years of treatment - Undetectable HBV DNA documented on three occasions each 6 months apart - Close monitoring is essential postcessation

HBV, hepatitis B virus; CHB, chronic hepatitis.

crucial that liver function tests remain stable and that there is no evidence of cirrhosis. After stopping therapy, close monitoring is essential to manage the risk of virological relapse. This includes regular assessments of liver function, HBV DNA levels, and HBsAg status every 1–3 months during the first year off therapy. For patients with cirrhosis or significant liver disease, continuous antiviral therapy is typically recommended to prevent reactivation and related complications. However, there has been no study directly comparing the various frequencies of monitoring.[4,46,47,115,116]

On antiviral treatment: The ideal timing and frequency for monitoring serological and biochemical markers (such as HBeAg, anti-HBe, serum ALT, and HBV DNA) to evaluate treatment response and changes in disease phases during therapy are not clearly defined. It is generally recommended that ALT and HBV DNA levels be checked every 3–6 months, while HBeAg and anti-HBe should be monitored every 6 months. HBsAg levels can be assessed every 6–12 months for patients receiving NA therapy. Additionally, renal function, including eGFR and serum phosphate levels, should be evaluated every 3–6 months for those using TDF or for patients at risk of renal issues while on any NA. These include patients with decompensated cirrhosis, creatinine clearance (eGFR) < 60 mL/min, poorly controlled hypertension and diabetes with or without proteinuria, active glomerulonephritis, concomitant nephrotoxic drugs, or solid organ transplantation. For patients on TDF who are at risk of developing renal or bone problems, consideration should be given to switching to ETV or TAF.

WhileNAs generally have a good safety profile, studies indicate that patients with advanced cirrhosis may experience adverse drug reactions. Reported issues include lactic acidosis, myalgia, neuropathy, azotemia, hypophosphatemia, muscular weakness, pancreatitis, and allergic reactions. Therefore, patients with decompensated cirrhosis (MELD>20) on NAs should be carefully monitored for drug tolerability and potential rare side effects, such as lactic acidosis or kidney dysfunction.[117,118]

HCC surveillance in HBV: HCC surveillance has been well studied and advised for patients at high and moderate risk based on various scores like the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) score, Chinese University – Hepatocellular Carcinoma score (CU-HCC) score, Guide with Age, Gender, HBV DNA, Core Promoter Mutations, and Cirrhosis – Hepatocellular Carcinoma score (GAG-HCC) score, and Platelets, Age, Gender – Hepatitis B score (PAGE-B) score.[44,46,47] However, we lack studies validating the aforementioned HCC scores in Indian HBV patients. Only one study has validated these scores in 154 Indian HBV patients, with the incidence of HCC reported in only 3 cases.[119] This study documented the age-male-ALBI-platelets (aMAP) score as the best-performing score, with an area under the receiver operating curve (AUROC) of more than 90 percent. The aMAP score is on a scale from 0 to 100 and is calculated using only five parameters: age, male gender, the albumin-bilirubin (ALBI) grade, and platelet count.

The PAGE-B score was the second-best performing score, with an accuracy rate of about 80% among Indian HBV patients.[119] The PAGE-B score ranges from 0 to 25 and is calculated using only three parameters: age, gender, and platelet count. This would augment the efforts of the NVHCP, which targets screening, treatment eligibility assessment, fibrosis assessment, and initiation of treatment at peripheral centers in India.

However, based on our understanding of the natural history of HCC in hepatitis B and the well-documented risk of HCC even in patients with undetectable DNA while on treatment, all patients receiving treatment with oral antivirals (even in the mild-risk category) should undergo surveillance for HCC. The evidence for this recommendation is, however, limited.[120–122]

Non-cirrhotic patients with HBV and HCC surveillance: Patients with chronic HBV infection, even in the noncirrhotic stage, are at risk of HCC development, although the exact risk is not very well defined. Certain factors have been found to influence the risk of HCC development. These include geographical region (higher in Asia and Africa), high HBV replication, age, and gender. Studies considering cost-effectiveness have shown that semi-

annual ultrasound-based surveillance improves quality-adjusted life expectancy at a reasonable cost, but studies in noncirrhotic patients are still lacking.[123–126]

Consensus statement

Patients who do not fulfill any of the above treatment indications should be followed as follows:

1 **Patients with HBV DNA >2000 IU/mL: ALT levels should be checked at least every 3–6 months, HBV DNA quantitative assay every 6–12 months and assessment of liver every 12 months (evidence: moderate, recommendation: strong).**
2 **Patient with HBV DNA <2000IU/mL: ALT levels should be checked at 6–12 month intervals, and HBV-DNA and noninvasive fibrosis tests should be conducted every 2–3 years (evidence: moderate, recommendation: strong).**
3 **During the first year after the cessation of antiviral treatment, liver function should be monitored, and serum HBV DNA should be measured every 3 months, and HBeAg and anti-HBe should be checked at 6-month intervals (evidence: moderate, recommendation: strong).**
4 **Beyond 1 year after cessation of antiviral treatment, liver function and serum HBV DNA should be tested every 6 months to detect viral relapse (evidence: weak, recommendation: weak).**

HCC surveillance is mandatory for all patients with chronic HBV, with or without treatment (evidence: high, recommendation: strong).

6 **Patient with cirrhosis are at risk of HCC and should be screened for HCC using abdominal ultrasound and AFP levels (evidence: high, recommendation: strong).**

How to Differentiate Between Acute HBV and Reactivation of HBV?

Differentiating acute hepatitis B from HBV reactivation involves assessing clinical history, serological markers, and virological data. Acute hepatitis B typically presents in individuals without a history of chronic HBV infection, characterized by the presence of HBsAg, anti-HBc IgM, and elevated ALT levels. In contrast, HBV reactivation occurs in patients with a prior HBV infection or chronic HBV carrier state. It is marked by a sudden increase in HBV DNA levels, reappearance or rise in HBsAg, and a switch from anti-HBc IgG to IgM. Reactivation is often triggered by immunosuppression or chemotherapy. Close evaluation of patient history, previous HBV status, and serological profiles is essential to accurately distinguish between these two conditions. Though it is difficult to differentiate between the two but titers of IgM HBc >1:1000 in acute viral hepatitis and DNA $>10^5$ IU/mL in reactivation help to distinguish between the two[47,127,128]

Management of Decompensated Liver Disease due to HBV

HBV-related decompensated liver disease often results from heightened viral replication or additional hepatic insults. Management strategies focus on aggressive antiviral therapy to reduce HBV DNA levels and mitigate further liver damage, along with comprehensive supportive care to manage complications. In patients with advanced disease, liver transplantation may be the definitive treatment option, necessitating timely evaluation and referral. Treatment should be initiated lifelong, irrespective of HBV DNA level and ALT/AST levels. It should be continued even after transplantation. Patient should be monitored for any side effects of the drugs on regular basis.[4,17,44,47,78]

Role of Antiviral in ACLF

Antiviral therapy plays a crucial role in the management of ACLF due to HBV infection. These agents, particularly NAs such as tenofovir and entecavir, can effectively suppress viral replication, reduce liver inflammation, and improve overall liver function. Recent studies highlight that early initiation of antiviral treatment can significantly enhance survival rates and reduce the risk of decompensation in patients with HBV-related ACLF (already decompensated). Ongoing research emphasizes the need for timely antiviral intervention in this population to mitigate the severe complications associated with ACLF.[44,47,116,128,129]

Statements

1 **Patient with HBV related ACLF should be treated early with NAs of high barrier to resistance, without waiting for HBV DNA levels (evidence: high, recommendation: strong).**

Antivirals in HBV Related HCC

CHB is the leading cause of HCC and the second-largest cause of cancer-related deaths globally. By 2040, fatalities due to HBV-related HCC are expected to double. Long-term treatment with NAs significantly reduces the risk of HCC[130]

The treatment for HBV-related HCC aligns with protocols for HCC caused by other etiologies. Key factors in determining the treatment include the patient's performance status, liver function, and tumor stage. Treatments such as systemic therapy, locoregional therapy, resection, and transplantation can supress host immunity, leading to HBV reactivation. Therefore, suppressing the HBV virus is crucial to halt disease progression.[131,132] HCC can recur after curative therapy, particularly in patients with high viral loads and hepatic necroinflammatory activity. Systematic reviews and meta-analyses highlight that a high viral load and the lack of antiviral medication increase the risk of HCC recurrence post-treatment. Studies

indicate that patients receiving antiviral treatment post-resection or locoregional therapy (LRT) show lower rates of HBV reactivation, liver dysfunction, and HCC recurrence compared to untreated individuals. Antiviral therapy also improves liver function reserves, enabling more patients to undergo curative treatments upon recurrence.[133–135]

Efficacy of Antiviral Treatments: A Taiwanese study compared 4051 untreated CHB patients with 518 CHB patients who received NA treatment and underwent HCC resection. The study revealed a significantly lower HCC recurrence rate in NA-treated patients (20.5% compared to 43.6% in untreated patients).[136] A meta-analysis by Yuan *et al.* involving 8060 patients, found that antiviral medication increased overall survival rates by 40% at five years and improved disease-free survival rates by 17%.[137]

Role of immune checkpoint inhibitors (ICIs) have emerged as first-line systemic therapy for advanced HCC. However, the optimal HBV DNA cut-off for starting ICIs in HBV-related HCC patients is unclear. Most clinical trials use conservative HBV DNA cut-offs (100–500 IU/mL) as inclusion criteria. Retrospective studies and cohort studies indicate that prophylactic antiviral therapy, rather than baseline HBV DNA levels, is the key predictor for HBV reactivation during ICI treatment. Therefore, baseline HBV viral load might be less critical than prophylactic antiviral therapy in managing HBV reactivation during ICI treatment. For patients scheduled for systemic therapy, NAs are typically started one week before initiating ICIs.[138–141]

Monitoring and Prophylactic Treatment: In general, HBsAg-negative, anti-HBc-positive patients have a lower risk of HBV reactivation compared to HBsAg-positive patients and a carefully monitoring is required in these patients. The future use of novel immunotherapeutic agents necessitates further exploration of safety data for immunotherapy in HBsAg-negative and anti-HBc-positive patients.

Recommendations and Long-term Management: Antiviral medication should be administered to all patients undergoing HCC treatment, regardless of liver damage severity or HBV DNA levels, to prevent HBV reactivation, which can severely impair liver function and survival. Antiviral therapy reduces the likelihood of HCC recurrence by decreasing viral load and necroinflammatory activity. Patients already on NA therapy at the time of HCC diagnosis typically continue the treatment. For those not yet on treatment, the decision to initiate NAs depends on the potential for successful HCC treatment and the patient's overall prognosis. The primary goal is to preserve liver function and prevent new or recurring HCCs.[142,143]

Efficacy of Nucleos(t)ide Analogues: Initiating NAs before curative treatment for HBV-related HCC is recommended. Patients awaiting liver transplants for HBV-related HCC should begin NAs upon HCC diagnosis. Retrospective analyses and prospective trials have shown that tenofovir is more effective than ETV in preventing HCC recurrence. Meta-analyses indicate that tenofovir is superior in preventing late recurrence, though not early recurrence. Lifelong NAs treatment is essential in managing HBV-related HCC, effectively preventing hepatitis flare-ups and significantly reducing liver cancer development[130,131,142,143]

In summary, the management of HBV-related HCC requires a comprehensive approach that includes antiviral therapy to prevent HBV reactivation and recurrence, alongside the careful use of ICIs and ongoing monitoring. Lifelong NAs treatment plays a crucial role in maintaining liver function and improving patient survival rates.

Statements

1 **Treatment with antivirals is recommended in HBV-related HCC patients undergoing curative therapy (resection/ablation) (evidence: high, recommendation: strong).**
2 **Patients with chronic HBV and HCC patients undergoing liver transplantation should be treated with antiviral agents and continue therapy after transplant (evidence: high, recommendation: strong).**
3 **HBV-related HCC patients undergoing TACE/TARE/SBRT should receive treatment with antiviral agents (evidence: low, recommendation: strong).**
4 **HBV-related advanced HCC patients undergoing systemic therapy with Tyrosine kinase inhibitor (TKI) or ICI should be treated with antiviral agents (evidence: low, recommendation: strong).**
5 **Chronic HBV patients with untreatable HCC should remain on antiviral therapy treatment, as there may still be a possibility of severe flare with cessation of therapy. (evidence: low, recommendation: strong).**

Special Consideration of HBV and HIV Coinfection

Cirrhosis and HCC are more prevalent in patients coinfected with HBV and HIV compared to those with only HBV[144] As a result, European and American guidelines recommend starting ART in patients with both HIV and HBV, regardless of their CD4 cell count.[145] The recommended ART should include either TDF or TAF, as both are effective against HIV and HBV. Using ETV or tenofovir alone in HBV/HIV coinfected patients is discouraged due to the risk of developing HIV resistance[146]

When modifying ART regimens, it is crucial to include agents effective against HBV to prevent reactivation. Discontinuing TDF or TAF in these patients can lead to severe hepatitis flares and liver decompensation due to HBV reactivation. Therefore, drug toxicity, particularly concerning renal, bone, and liver health, should be closely monitored

during ART. Since TDF has been linked to higher risks of nephrotoxicity and bone mineral density (BMD) loss, TAF-based regimens are being explored as alternatives.

Recent research has shown that switching from TDF to TAF in patients with stable HIV and HBV suppression maintains viral suppression while improving kidney function and bone density. It is also recommended to screen all HBsAg-positive patients for HIV before initiating TDF, TAF, or possibly ETV to prevent the development of HIV resistance mutations.

Statement.

1 Consensus Statements

All HIV-positive patients with HBV coinfection should start ART irrespective of CD4 cell count (evidence: moderate, recommendation: strong).

2 HIV-HBV coinfected patients should be treated with a TDF- or TAF-based ART regimen (evidence: high, recommendation: strong).

Antiviral Therapy of HBV in CKD Patients

An increased association between hepatitis B and chronic kidney disease (CKD) has been reported. Hepatitis B can cause CKD, while the infection can also occur as a consequence of CKD. The mechanisms by which the HBV contributes to CKD include the direct cytopathic effect of the virus, the deposition of antigens and host antibodies in the glomeruli, virus-mediated T-cell activation, indirect mechanisms mediated by the cytokine storm, and the deposition of HBsAg and HBcore antigen in renal tubule epithelial cells, leading to apoptotic damage of the renal tubules.[147] The morphological phenotypes of nephropathies directly associated with HBV include membranous nephropathy as the most common form. Others include membranoproliferative glomerulonephritis, mesangoproliferative glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis, and polyarteritis nodosa.[147]

Cai *et al.*[148] in a meta-analysis of 189,709 patients from 6 studies, examined the association between HBV and CKD. They found no significant association, with an adjusted relative risk (RR) of 1.16 (95% CI, 0.78, 1.71; $P = 0.46$) between HBsAg and CKD. However, a lot of heterogeneity in the included studies were noted.[156] CKD was defined as the presence of proteinuria or a low GFR. Fabrizi *et al.*[149] conducted another recent meta-analysis that included 33 studies with 7,849,849 patients investigating the association between HBV and CKD. Interestingly, they observed a significant association in the cohort studies, with a risk ratio of 1.40 (1.16–1.69). However, no increased risk was noted in the cross-sectional studies. In a large cohort of 299,913 patients, Hong *et al.*.[150] found a significant association between HBsAg infection and CKD risk, with an odds ratio of 1.11 (1.03–1.21; $P = 0.01$).

Another cohort study of 32,578 patients by Lin and colleagues[151] examined HBV and nonalcoholic fatty liver disease (NAFLD) in relation to CKD. After adjusting for age, sex, body mass index, DM, and hypertension, the highest risk was observed when NAFLD and HBV were present concurrently. Almost all drugs with a high genetic barrier to resistance require dose modifications when used in patients with CKD.[152] However, ETV and TAFare the safest options for patients with renal dysfunction. A head-to-head comparison of ETV and TDF in patients with low GFR suggested a safety advantage for ETV.[153–158] In a retrospective cohort study with propensity-score matching, patients with eGFR ≥60 showed that the 5-year cumulative incidences of renal impairment were 42.64% for ETV and 48.03% for TDF ($P = 0.0023$). On multivariable Cox regression analysis, TDF compared to ETV (HR 1.26, 1.11–1.43) was associated with a higher risk of worsening renal function.[154]

Another multicentric retrospective cohort study involving nearly 54 centers in Europe followed patients who experienced moderate-to-severe renal dysfunction (creatinine clearance 20–60 mL/min) either "before" TDF/ETV initiation (including 107 TDF- and 91 ETV-treated patients) or "after" TDF/ETV initiation (including 212 TDF- and 77 ETV-treated patients) for a median of 3.1 years (both treatments). Only TDF-treated patients experienced renal tubular dysfunction (6.5% "before", 1.9% "after") as well as renal adverse events leading to treatment discontinuation (8.4% "before", 7.1% "after").[155] The safety of ETV was also demonstrated in a multicentric retrospective study of patients with severe renal dysfunction requiring hemodialysis.[155] Additionally, multicentric retrospective cohort studies have shown improvement in GFR when patients were switched from TDF to TAF, suggesting that switching to TAF is a good option for achieving viral suppression and ensuring renal safety in patients on TAF.[156]

Statements and recommendations

- ETV or TAF is recommended over TDF because of the better renal safety profile in CKD patients in treatment naõve patients (evidence: low, recommendation: strong).
- Switching to TAF because of its ability to improve GFR can be considered for the management of HBV patients with CKD; however, limited evidence is currently available in CKD (evidence: low, recommendation: weak).
- Dose modifications of all antivirals agents should be performed based on the estimated GFR in CKD patients (evidence: moderate, recommendation: strong).
- Antivirals should also be considered in all patients planned for immunosuppressive therapy or renal transplantation (evidence: moderate, recommendation: strong).

Evaluation and Management of Pregnant HBV and Postpartum Patient

Mother-to-child transmission (MTCT), along with horizontal transmission, significantly contributes to the high burden of HBV infection. MTCT is associated with a high rate of chronic infection. The risk of chronic hepatitis B (CHB) is highest (90%) when the infection occurs in neonates. This risk decreases to 30% among children infected between the ages of one and four and is lowest (5%) when the infection occurs in adults. Therefore, to control HBV transmission, it is important to screen all pregnant women.

The risk factors for MTCT include maternal HBV viral load > 10^5 IU/mL and HBeAg positivity.[159] A recent study reported that treatment with TDF from the third trimester until 4 weeks postpartum significantly reduced the MTCT rate from 18% to 5% compared to those not treated. Starting antiviral treatment before the third trimester is more effective than starting in the third trimester, with no differences in maternal and fetal safety.[160] Thus, initiating prophylaxis early in the second trimester is more beneficial than starting in the third trimester.

When using tenofovir for MTCT prophylaxis, the optimal time for stopping after delivery is unclear. Expert guidance recommends continuing TDF for 4–12 weeks after delivery.[4,44,46] A recent systematic review reported the safety of antiviral HBV drugs during pregnancy, finding no increased risk of adverse neonatal outcomes (death, preterm birth, and congenital abnormalities) or maternal outcomes (miscarriage/stillbirth, postpartum hemorrhage, and hepatitis flare).[161] Among the antivirals for MTCT, TDF has the most well-documented safety data, with no increased risk of congenital anomalies in patients treated with TDF.[162] Until more data are available, TDF is the recommended drug of choice during pregnancy. Patients on ETV should be switched to TDF.

A recent study from China compared the outcomes of pregnant women treated with TAF (n = 103) and TDF (n = 104). The authors reported TAF to be safe, with nausea as the most common side effect.[163] There were no birth defects, and none of the infants born to mothers treated with TAF were HBsAg positive at 7 months of follow-up.

The exact mechanism of MTCT of HBV is unclear. Postulated routes include exposure of the fetus to maternal blood and vaginal secretions at the time of delivery and swallowing of amniotic fluid. Some evidence suggests that MTCT may be lower with cesarean section than with vaginal delivery.[164] With the use of TDF for prophylaxis, the added benefit of cesarean section needs to be explored in future studies. Until more robust data are available, normal vaginal delivery is an acceptable mode of delivery for women with HBV infection. Newborns of mothers with HBV infection should receive the HBV vaccine and hepatitis B immunoglobulin (HBIG) within 12 h of birth and complete the vaccination series as recommended.

Although HBV transmission can occur through breastfeeding, it is not contraindicated in HBV-positive women—whether untreated or those on TDF treatment. The benefits of breastfeeding outweigh the risks of HBV transmission. With the use of TDF for prophylaxis, the additional risk associated with breastfeeding is minimal. There is no significant risk of complications in the baby after exposure to TDF through breastfeeding. A study from Taiwan compared annual BMD by dual-energy X-ray absorptiometry and estimated GFR in children born to HBV-positive mothers treated with TDF (n = 71) and controls who did not receive TDF (n = 57). Up to the age of 6 years, there was no difference in the long-term growth, renal function, and bone development in children who were exposed to TDF during the antenatal period compared to those who were not.[165] The recent WHO recommendations for MTCT suggests that in cases where HBV DNA or HBeAg testing is not available, all HBsAg-positive pregnant women should be offered antivirals.[17]

Statements:

	Statements	Quality of evidence	Strength of recommendation
1	All women should be screened for HBsAg in the first trimester of pregnancy.	Moderate	Strong
2	Pregnant women with high HBV DNA levels (≥200,000 IU/mL) or positive HBeAg should start prophylaxis with TDF (at least in the 2nd trimester and continue till 12 weeks after delivery).	Moderate	Strong
3	In pregnant women already on NA therapy, TDF should be continued; ETV or other NAs should be switched to TDF.	Moderate	Strong
4	Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery (within 12 h) and complete the recommended vaccination series.	High	Strong
5	Breastfeeding is not contraindicated in HBsAg-positive women- whether untreated or on TDF-based treatment or prophylaxis.	Low	Strong

Safety and Efficacy of Antivirals for HBV in Patients on Biologicals and Steroids

Infliximab and adalimumab are the two most commonly used anti-TNF drugs used for IBD. Assessment of HBsAg and anti-HBc are recommended as initial screening tests

before starting the biologicals[166] In HBsAg-positive patients, the HBV profile, i.e. chronic HBV infection, chronic HBV hepatitis, or cirrhosis, will guide the physician toward HBV treatment, prophylaxis, or simple monitoring. Patients requiring HBV treatment on the basis of their HBV status for their liver disease should be started on antivirals. Treatment duration in these patients is independent of the immunosuppressive therapy for IBD.

Risk of HBV reactivation also depends on the type of biologic agent administered. Patients on anti-TNF drugs and integrin inhibitors are at moderate risk, so prophylaxis is mandatory[167] Prophylaxis is to be continued for the entire duration of immunosuppressive treatment and for a year after the discontinuation of biologics, in order to prevent the risk of HBV reactivation when immune reconstitution occurs. ETV or TDF/TAF are the recommended drugs for prophylaxis of HBV reactivation[116,128]

HBV vaccination is recommended in all IBD patients with negative HBV serology receiving treatment with immunosuppressants, using the standard schedule for HBV vaccination. An accelerated schedule with a double dose of recombinant HBsAg (40 mcg at 0, 1 and 2 months) is suggested to be the best vaccination strategy for IBD patients. Revaccination is recommended if failed to achieve adequate response after the first vaccine course. Regular monitoring of anti-HBs titles should be performed once every 2 years[168]

Corticosteroids are frequently used in IBD patients. Long-term glucocorticoid therapy, especially moderate doses of glucocorticoids for more than 3 months, is associated with an increased risk of HBV reactivation in HBsAg-positive patients. Steroid enhances HBV replication through the glucocorticoid-responsive element, apart from their immunosuppressive effect. Doses greater than 20 mg/day of prednisolone in adults are usually considered immunosuppressive. The HBV reactivation rate is significantly higher in those treated for a continuous period of at least 3 months or those receiving >20 mg prednisolone per day.[116,128]

In IBD, there have been multiple reports of reactivation in patients undergoing corticosteroids treatment, with or without azathioprine or anti-TNF therapy, even resulting in severe acute hepatitis. Most of the findings indicate that the risk of hepatitis reactivation is mostly related to high prednisone doses; however, some cases of reactivation have occurred with low-dose prednisone therapies as well, so caution is advisable[169,170] Many case reports have documented HBV reactivations with high-dose steroids given as monotherapy too. Therefore, pretherapy screening for HBV markers is recommended (HBsAg and anti-HBc), and prophylactic antivirals is to be given if any marker is positive, starting 1–3 weeks before corticosteroids to 1 year after withdrawal of corticosteroids. Pretherapy screening for HBV markers is not recommended if a lower dose and shorter duration of corticosteroid is planned (for example, <20 mg of prednisolone or equivalent for less than two weeks).

Topically acting steroids have low systemic bioavailability due to a high first-pass liver metabolism. So, the typical adverse effects of steroids are partially avoided. Therefore, for local, inhalational or intra-articular corticosteroids, pretherapy screening for HBV markers is not recommended.

Statements

1 **HBsAg should be tested in all patients with inflammatory bowel disease before receiving biologics (evidence: moderate, recommendation: strong).**
2 **Total anti-HBc should also be tested, in addition to HBsAg, among patients who are to receive rituximab, IBD, and for other rheumatological conditions (evidence: moderate, recommendation: strong).**
3 **If HBsAg is found to be positive and patient is eligible to receive antivirals, then treatment should be given as per standard guidelines, simultaneously with biologic therapy (evidence: moderate, recommendation: strong).**
4 **If HBsAg is found to be positive, but the patient is not eligible for antivirals for their liver status, he/she should be started on pre-emptive antivirals before starting biologicals, and continued till 12 months after cessation of biologic therapy (evidence: moderate recommendation strong).**
5 **Patients who are negative for all markers of HBV should be vaccinated for HBV by an accelerated schedule with double-dose recombinant vaccine (evidence: moderate, recommendation: strong).**
6 **For patients to be given > 4 weeks of high-dose oral corticosteroids (>20 mg prednisolone or equivalent), screening should be done for HBsAg and anti-HBc (evidence: low, recommendation: strong).**
7 **Prophylactic antivirals should be started if any marker is positive, starting 1–3 weeks before steroids (evidence: low recommendation: strong).**
8 **For treatment with local, inhalational, or intra-articular steroids, screening with HBV markers is not recommended (evidence: low, recommendation: week).**

Relevance of HBV in Patient Planned for IVF

Effect of HBV on *in vitro fertilization (*IVF)/Intracytoplasmic Sperm Injection (ICSI) Outcomes: Couples with HBV seropositive husbands have similar semen parameters, rates of fertilization, implantation, and clinical pregnancy compared with normal subjects.[171] Females with seropositive status also show no significant differences in clinical pregnancy, ectopic pregnancy, miscarriage (early and late), and preterm delivery; however, few studies report decreased gestational age for delivery. Medically assisted reproduction (MAR)/ART (artificial reproduction technique) are not contraindicated in these patients.[172]

Vertical transmission risk remains same as that of natural pregnancy; IVF/ICSI (MAR techniques) does not eliminate the risk of vertical transmission to neonates.[173] There are no proven benefits of special seminal processing and elective caesarean delivery solely for the purpose of reducting of vertical transmission in HBV-positive couples. Breastfeeding is not contraindicated in HBV-positive mother.[174]

Vaccination for HBV - Partners of HBV-positive individual should be vaccinated, and barrier method of contraception should be followed until the completion of vaccination. Newborns of HBV-infected parent must undergo complete vaccination, along with immunoglobulins.

Consensus statements

1 **Although HBV particles are detected in seminal plasma, sperm, oocyte, placenta, as well as in breastmilk, medically assisted reproduction (MAR) procedures are not contraindicated in these patients (evidence: low, recommendation: strong).**
2 **Partners of hepatitis B virus-positive individuals should be vaccinated (evidence: high, recommendation: strong).**
3 **Barrier contraception should be used until the completion of the HBV vaccination protocol (evidence: moderate, recommendation: strong).**
4 **All patients with an active or chronic HBV-infection must be reviewed by a hepatologist before initiating any assisted reproductive technique (MAR/ART) (evidence: low, recommendation: strong).**
5 **The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR/ART in couples where one or both partners test positive for HBV (evidence: low, recommendation: strong).**

Management of HBV During Peri- and Post-transplant Phase

Antiviral treatment is necessary for all patients diagnosed with hepatitis B-related cirrhosis, including those with decompensation.[44,46] An undetectable viral load at the time of transplantation is associated with a lower rate of HBV recurrence; thus, viral suppression to undetectable or low levels is a crucial part of efforts to prevent HBV recurrence. Studies have shown a direct correlation between HBV DNA levels at the time of LT and the rate of recurrence. In patients with HBV DNA levels higher than 18,000 IU/mL, between 36 and 18,000 IU/mL, and undetectable DNA, hepatitis B recurred in 50%, 7.5%, and 0% of patients, respectively, after transplantation.[30,175]

Risk factors for HBV reinfection include host and viral factors, which encompass high HBV DNA (>10^5), drug-resistant HBV pretransplant, indications for LT (cirrhosis/HCC > fulminant hepatic failure), high immunosuppression (e.g. steroids), and drug-resistant mutants, such as the Tyrosine-Methionine-Aspartate-Aspartate motif (YMDD) variant. Historically, high-dose HBIG was given long-term. Subsequently, data emerged indicating that finite low doses of HBIG effectively prevent recurrence.[176] Currently, evidence suggests that HBIG is not needed except in patients with a high viral load (>10^5 IU/mL).

Recently, data have emerged showing that HBIG-free regimens are effective in preventing recurrence after Liver Transplant Alone (LTA) large study of 362 patients using a completely HBIG-free regimen also demonstrated excellent long-term survival rates of 83% at 8 years. There was no difference in the rates of HBsAg seroclearance and HBV DNA suppression between those on LMV, combination NAs, or ETV. The key difference was the significantly lower rate of virological rebound observed at 3 years after liver transplantation with ETV compared to those treated with combination NA therapy and LMV (0%, 7%, and 17%, respectively, $P < 0.001$).[177]

Statements.

1 **All patients wait-listed for liver transplantation with CHB infection should receive antiviral therapy with NA irrespective of HBVDNA level (evidence: high, recommendation: strong).**
2 **In patients with low risk of HBV recurrence, undetectable HBVDNA or HBV DNA < 10^5, HBIG is not required to prevent HBV recurrence (evidence: high,-recommendation: strong).**
3 **In HBsAg-positive individuals deemed to be at high risk of recurrence, combination therapy with low-dose HBIg and a potent NA can be considered based on the clinical context, from the time of transplantation to prevent HBV reinfection postliver transplant (evidence: high, recommendation: strong).**
4 **HBV DNA and HBsAg should be monitored every three months in the first year and thereafter every six months in HBsAg-positive liver transplant recipients, regardless of treatment or prophylaxis regimen (evidence: high, recommendation: strong).**
5 **After transplantation, lifelong prophylaxis to prevent recurrent hepatitis flares is required (evidence: high, recommendation: strong).**

Liver Transplantation with Occult/Core AB Positive

Occult hepatitis B (OBI) is defined as the presence of replication-competent HBV DNA in the liver and/or detectable HBV DNA in the blood of individuals who test negative for hepatitis B surface antigen (HBsAg).[178]

Prophylactic Strategy in Anti-HBc +ve Recipients or Recipients of Anti-HBc +ve Donor Grafts: The aim of prophylaxis in this cohort of patients is to prevent reinfection of the allograft and to prevent *de novo* hepatitis (DNH). DNH is characterized by the presence of HBsAg and/or HBV DNA in a subject who was previously negative for

these markers. Until the early 2000s, liver grafts from anti-HBc-positive donors were considered extended criteria donor (ECD) grafts due to the risk of reinfection. However, most patients in this cohort have low to absent HBV DNA, making perioperative immune prophylaxis with HBIG unnecessary. With the advent of potent NUCs, allograft infection and DNH have become rare. Despite this, DNH can still occur subclinically, so regular monitoring for HBsAg and HBV DNA every three months in the first year and every six months thereafter is recommended. Standard prophylaxis includes LMV, ETV, TDF, or TAF. LMV is particularly effective in this cohort due to its potency and the low risk of resistance development at baseline HBV DNA levels. A large study from Hong Kong showed a low incidence of DNH (2.8%) in recipients treated with LMV, with no cases in those receiving ETV prophylaxis.[179]

Relationship of DNH with Anti-HBs Status of Donor/Recipient: The occurrence of DNH has been reported in recipients of anti-HBc +ve grafts, even when the recipient is anti-HBs +ve. DNH has been observed when the anti-HBs titers in such recipients are truly seroprotective (>100 mIU/mL) (188). Therefore, antiviral prophylaxis should be offered to all recipients of anti-HBc +ve allografts. Interestingly, the incidence of DNH post-LT is lower in recipients with past HBV exposure (anti-HBc +ve, anti-HBs +ve) than in those with vaccine-induced immunity (anti-HBc -ve, anti-HBs +ve). Some transplant units recommend no prophylaxis for this cohort of patients; however, the INASL does not endorse this view. These patients should be prophylaxed with NUCs (preferably ETV or TAF) for a fair length of the post-transplant period (12–18 months postliver transplant), after which careful withdrawal of NUC therapy may be attempted, provided the anti-HBs titers at this stage are protective (anti-HBs >100 mIU/mL). Anti-HBc +ve donors who are also anti-HBs +ve offer limited protection to recipients who are anti-HBc -ve; therefore, such recipients must be protected with antiviral drugs.[180]

Post-Transplant Vaccination of Anti-HBc + ve Recipients or Anti-HBc -ve Recipients of Anti-HBc + ve Donor Grafts: Anti-HBc +ve recipients who are anti-HBs -ve (or have low to undetectable anti-HBs titers) should be vaccinated against HBV when they are on stable maintenance immunosuppression. This is generally achievable 12–18 months following LT. The vaccination schedule commonly followed is: 40 mcg of recombinant HBV vaccine in 5 doses (0, 1, 2, 6, and 12 months). It has been shown that up to two-thirds of anti-HBc +ve, anti-HBs -ve recipients could achieve seroprotective titers.[181] Those recipients who are able to mount a protective anti-HBs response (anti-HBs titer >100 mIU/mL) may then be candidates for NUC withdrawal. However, this should be done with careful monitoring of HBV markers, as outlined above. On follow-up, those recipients who have persistent anti-HBs titers >100 m IU/mL have a negligible chance of graft reinfection.[182]

Statements and Recommendations:

1 **In HBsAg –ve, anti-HBC +ve liver transplant recipients, or anti-HBc –ve recipients of anti-HBc +ve liver grafts, there is no need for prophylaxis using HBIG in the perioperative period, or thereafter (*strength of recommendation: strong, evidence: high*).**
2 **Allograft dysfunction in a liver transplant recipient who is anti-HBc +ve or an anti-HBc –ve recipient of an anti-HBc +ve liver graft should always include evaluation for *de novo* hepatitis (DNH) due to HBV (*strength of recommendation: strong, evidence: high*).**
3 **Anti-HBc +ve liver recipients or anti-HBc –ve recipients of anti-HBc +ve liver grafts should receive prophylaxis with ETV/TDF/TAF to prevent DNH. LMV is an equally effective alternative in this situation and may be preferred in a resource-constrained scenario (*strength of recommendation: strong, evidence: high*).**
4 **Active immunization with HBV vaccine may be considered in anti-HBC +ve recipients or anti-HBc –ve recipients of anti-HBc +ve liver grafts when they are on stable maintenance immunosuppression (*strength of recommendation: strong, evidence: high*).**
5 **Liver transplant recipients, as described in Statement 4, may be considered for NUC prophylaxis withdrawal, if they have mounted a robust antibody response to HBV vaccination [anti-HBs > 100 miu/mL] (*strength of recommendation: strong, evidence: high*).**

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING

None.

REFERENCES

1. Polaris Observatory Collaborators. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study. *Lancet Gastroenterol Hepatol*. 2023;8:879–907.
2. Tandon BN, Acharya SK, Tandon A. Epidemiology of hepatitis B virus infection in India. *Gut*. 1996;38:S56–S59 (Suppl 2).
3. Batham A, Narula D, Toteja T, Sreenivas V, Puliyel JM. Systematic review and meta-analysis of prevalence of hepatitis B in India. *Indian Pediatr*. 2007;44:663–674.
4. Arora A, Singh SP, Kumar A, et al. INASL hepatitis B taskforce. INASL position statements on prevention, diagnosis and management of hepatitis B virus infection in India: the andaman statements. *J Clin Exp Hepatol*. 2018;8:58–80.
5. *Seroprevalence of hepatitis B and hepatitis C (based on national family health survey-4) fact sheet*. 2021.
6. Nayak NC, Panda SK, Zuckerman AJ, Bhan MK, Guha DK. Dynamics and impact of perinatal transmission of hepatitis B virus in North India. *J Med Virol*. 1987;21:137–145.

7. Athalye S, Khargekar N, Shinde S, et al. Exploring risk factors and transmission dynamics of Hepatitis B infection among Indian families: implications and perspective. *J Infect Public Health*. 2023;16:1109–1114.
8. Pande C, Sarin SK, Patra S, et al. Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: a randomized controlled trial. *J Viral Hepat*. 2013;20:801–810.
9. Rakesh PS, Sherin D, Hari S, Subhagan S, Shaji M, Salila K. Horizontal transmission of hepatitis B virus among adults in a rural village in Kollam district, southern India. *Trop Gastroenterol*. 2014;35:232–237.
10. Murhekar MV, Santhosh Kumar M, Kamaraj P, et al. Icmr – serosurvey group. Hepatitis-B virus infection in India: findings from a nationally representative serosurvey, 2017-18. *Int J Infect Dis*. 2020;100:455–460.
11. Lahariya C, Subramanya BP, Sosler S. An assessment of hepatitis B vaccine introduction in India: lessons for roll out and scale up of new vaccines in immunization programs. *Indian J Publ Health*. 2013;57:8–14.
12. Alexander AM, Prasad JH, Abraham P, et al. Evaluation of a programme for prevention of vertical transmission of hepatitis B in a rural block in southern India. *Indian J Med Res*. 2013;137:356–362.
13. Kumar A, Kumar SI, Pandey R, Naik S, Aggarwal R. Hepatitis B virus genotype A is more often associated with severe liver disease in northern India than is genotype D. *Indian J Gastroenterol*. 2005;24:19–22.
14. Datta S. An overview of moleculer epidemiology of hepatitis B virus (HBV) in India. *Virol J*. 2008;5:156.
15. Gandhe SS, Chadha MS, Arankalle VA. Hepatitis B virus genotypes and serotypes in western India: lack of clinical significance. *J Med Virol*. 2003;69:324–330.
16. Cooksley WG. Do we need to determine viral genotype in treating chronic hepatitis B? *J Viral Hepat*. 2010;17:601–610.
17. WHO. *Guidelines for the Diagnosis, Care and Treatment of Persons with Chronic Hepatitis B Infection*. Geneva: World Health Organization; 2024 https://www.who.int/publications/i/item/9789240090903.
18. Pruss-Ustun A, Rapiti E, Hutin Y. Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. *Am J Ind Med*. 2005;48:482–490.
19. Schillie S, Murphy TV, Sawyer M, et al. Centres for Disease Control and Prevention (CDC), CDC guidance for evaluating healthcare personnel for hepatitis B virus protection and for administering postexposure management. *Morb Mortal Wkly Rep, Recomm Rep*. 2013;62:1–19.
20. Werner BG, Grady GF. Accidental hepatitis-B surface antigen positive inoculations: use of antigen to estimate infectivity. *Ann Intern Med*. 1982;97:367–369.
21. Lauer JL, van Drunen NA, Washburn JW, Balfour Jr HH. Transmission of hepatitis B virus in clinical laboratory areas. *J Infect Dis*. 1979;140:513–516.
22. Kumar AK, Baghal PK, Shukla CB, Jain MK. Prevalence of hepatitis B surface antigen (HBsAg) among health care workers. *Indian J Comm With*. 2000;25:93–96.
23. Sukriti NT, Sethi A, Agrawal K, et al. Low levels of awareness, vaccine coverage, and the need for boosters among healthcare workers in tertiary care hospitals in India. *J Gastroenterol Hepatol*. 2008;23:1710–1715.
24. Singhal V, Bora D, Singh S. Hepatitis B in healthcare workers: Indian scenario J. *Lab. Phy*. 2009:41–48.
25. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006;44:S6–S9.
26. Johnson DW, Dent H, Yao Q, et al. Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. *Nephrol Dial Transplant*. 2009;24:1598–1603.
27. Raina D, Rawat N, Pandita AK. Prevalence of hepatitis B and hepatitis C in patients undergoing hemodialysis at a teaching hospital in uttarakhand. *J Fam Med Prim Care*. 2022;11:1348–1353.
28. Rani P, Bilolikar AK, Reddy S. Seroprevalence of hepatitis B virus and hepatitis C virus; its incidence and risk factors in incident chronic kidney disease (CKD) stage – V patients on haemodialysis in a tertiary care centre. *J Med Sci Res*. 2018;6:37–43.
29. Kamat SP, Mehta PR, Paranjpe SM, Ingole NA. Hepatitis B virus (HBV) infection in liver disease patients in Mumbai, India with special reference to hepatitis B surface antigen (HBsAg) mutant detection. *J Clin Diagn Res*. 2014;8:19–21.
30. Maiwall R, Kumar M. Prevention and treatment of recurrent hepatitis B after liver transplantation. *J Clin Transl Hepatol*. 2016;4:54–65.
31. Kim WR, Smith JM, Skeans MA, et al. OPTN/SRTR 2011 annual data report: liver. *Am J Transplant*. 2013;13:73–102.
32. Fabrizi F, Martin P, Messa P. Hepatitis B and hepatitis C virus and chronic kidney disease. *Acta Gastroenterol Belg*. 2014;77:41–46.
33. Kumar R, Singla V, Sk Kacharya. Impact and management of hepatitis B and hepatitis C virus co-infection in HIV patients. *Trop Gastroenterol*. 2008;29:136–147.
34. Toy M, Hutton D, Harris AM, et al. Cost-effectiveness of one-time universal screening for chronic hepatitis B infection in adults in the United States. *Clin Infect Dis*. 2022;74:210–217.
35. Amini A, Varsaneux O, Kelly H, et al. Diagnostic accuracy of tests to detect hepatitis B surface antigen: a systematic review of the literature and meta-analysis. *BMC Infect Dis*. 2017;17:698.
36. Tuaillon E, Kania D, Pisoni A, et al. Dried blood spot tests for the diagnosis and therapeutic monitoring of HIV and viral hepatitis B and C. *Front Microbiol*. 2020;11:373.
37. Mohamed R, Desmond P, Suh DJ, et al. Practical difficulties in the management of hepatitis B in the Asia-Pacific region. *J Gastroenterol Hepatol*. 2004;19:958–969.
38. Guidelines for the Prevention. *Care and Treatment of Persons with Chronic Hepatitis B Infection*. Geneva: World Health Organization; 2015.
39. Ministry of Health & Family Welfare, Government of India. *National Program for Surveillance of Viral Hepatitis: Seroprevalence of Hepatitis B and Hepatitis C (Based on National Family Health Survey-4)*. National Centre for Disease Control, Directorate General of Health Services; 2021. Available from: https://nvhcp.mohfw.gov.in/common_libs/Approved%20factsheet_4_10_2021.pdf.
40. Dusheiko G, Agarwal K, Maini MK. New approaches to chronic hepatitis B. *N Engl J Med*. 2023;5:55–69, 388.
41. Cocchio S, Baldo V, Volpin A, et al. Persistence of anti-Hbs after up to 30 Years in health care workers vaccinated against hepatitis B virus. *Vaccines (Basel)*. 2021;9:323.
42. S MJ, Rezai MS. Long-term antibody response and immunologic memory in children immunized with hepatitis B vaccine at birth. *Indian Pediatr*. 2004;4:1232–1237.
43. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices. *Morb Mortal Wkly Rep, Recomm Rep*. 2018;67:1–31.
44. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
45. van der Scheun FC, Nagelkerke MCM, Kilaru A, et al. Stigma among healthcare workers towards hepatitis B infection in Bangalore, India: a qualitative study. *BMC Health Serv Res*. 2019;19:736.

46. Terrault NA, Lok ASJ, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *HEPATOLOGY*. 2018;67:1560–1599.
47. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10:1–98.
48. Verveer C, Zondervan PE, ten Kate FJ, Hansen BE, Janssen HL, de Knegt RJ. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. *Liver Int*. 2012;32:622–628.
49. de Franchis Roberto, Bosch Jaime, Garcia-Tsao Guadalupe, Reiberger Thomas, Ripoll Cristina. On behalf of the Baveno VII Faculty. Baveno VII – renewing consensus in portal hypertension. *J Hepatol*. 2022;76:959–974.
50. Jat SL, Gupta N, Kumar T, et al. Prevalence of hepatitis D virus infection among hepatitis B virus-infected individuals in India. *Indian J Gastroenterol*. 2015;34:164–168.
51. Pauly MD, Ganova-Raeva L. Point-of-Care testing for hepatitis viruses: a growing need. *Life*. 2023;13:2271.
52. Wong GL, Chan HL, Yu Z, et al. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B–a prospective cohort study with paired transient elastography examinations. *Aliment Pharmacol Ther*. 2014;39:883–893.
53. Khalili M, King WC, Kleiner DE, et al. Fatty liver disease in a prospective North American cohort of adults with human immunodeficiency virus and hepatitis B virus coinfection. *Clin Infect Dis*. 2021;73:e3275–e3285.
54. Iida-Ueno A, Enomoto M, Tamori A, Kawada N. Hepatitis B virus infection and alcohol consumption. *World J Gastroenterol*. 2017;23:2651–2659.
55. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology*. 2012;142:1140–1149. e1143; quiz e1113-1144.
56. Mak L-Y, Seto W-K, Fung J, Yuen M-F. Use of HBsAg quantification in the natural history and treatment of chronic hepatitis B. *Hepatol Int*. 2020;14:35–46.
57. Karra VK, Chowdhury SJ, Ruttala R, Polipalli SK, Kar P. Clinical significance of quantitative HBsAg titres and its correlation with HBV DNA levels in the natural history of hepatitis B virus infection. *J Clin Exp Hepatol*. 2016;6:209–215.
58. Thi Vo T, Poovorawan K, Charoen P, et al. Association between hepatitis B surface antigen levels and the risk of hepatocellular carcinoma in patients with chronic hepatitis B infection: systematic review and meta-analysis. *Asian Pac J Cancer Prev APJCP*. 2019;20:2239–2246.
59. Zhang W, Zhang D, Dou X, et al. Consensus on pegylated interferon alpha in treatment of chronic hepatitis B. *J Clin Transl Hepatol*. 2018;6:1–10.
60. Liu J, Li T, Zhang L, Xu A. The role of hepatitis B surface antigen in nucleos(t)ide analogues cessation among Asian patients with chronic hepatitis B: a systematic review. *Hepatology*. 2019;70:1045–1055.
61. Hsieh Y-C, Pan M-H, Jeng W-J, et al. Serum HBcrAg and hepatocellular carcinoma in a Taiwanese population seronegative for HBsAg and anti-HCV. *Clin Gastroenterol Hepatol*. 2023;21:1303–1313.e1311.
62. Ghany MG, King WC, Lisker-Melman M, et al. Comparison of HBV RNA and hepatitis B core related antigen with conventional HBV markers among untreated adults with chronic hepatitis B in North America. *Hepatology*. 2021;74:2395–2409.
63. van Bömmel F, Bartens A, Mysickova A, et al. Serum hepatitis B virus RNA levels as an early predictor of hepatitis B envelope antigen seroconversion during treatment with polymerase inhibitors. *Hepatology*. 2015;61:66–76.
64. Shiha G, Ibrahim A, Helmy A, et al. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. *Hepatol Int*. 2017;11:1–30.
65. European Association for Study of Liver. Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol*. 2015;63:237–264.
66. Chakravarty R, Chowdhury A, Chaudhuri S, et al. Hepatitis B infection in Eastern Indian families: need for screening of adult siblings and mothers of adult index cases. *Public Health*. 2005;119:647–654.
67. Buster EH, Flink HJ, Cakaloglu Y, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. *Gastroenterology*. 2008;135:459–467.
68. Cornberg M, Lok ASF, Terrault NA, et al. The 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty et al. Guidance for Design and Endpoints of Clinical Trials in Chronic Hepatitis B—Report From the 2019 EASL-AASLD HBV Treatment Endpoints Conference. *Hepatology*. 2020;71:1070–1092.
69. Lee HW, Lee JS, Ahn SH. Hepatitis B virus cure: targets and future therapies. *Int J Mol Sci*. 2020;22:213.
70. Asselah T, Loureiro D, Boyer N, Mansouri A. Targets and future direct-acting antiviral approaches to achieve hepatitis B virus cure. *Lancet Gastroenterol Hepatol*. 2019;4:883–892.
71. You H, Wang F, Li T, et al, Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. *J Clin Transl Hepatol*. 2023;11:1425–1442. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022).
72. Martin P, Lau DT, Nguyen MH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2015 update. *Clin Gastroenterol Hepatol*. 2015;13:2071, 87.e16.
73. Lee HW, Chan HL. Unresolved issues of immune tolerance in chronic hepatitis B. *J Gastroenterol*. 2020;55:383–389.
74. Liaw YF. Perspectives on current controversial issues in the management of chronic HBV infection. *J Gastroenterol*. 2022;57:828–837.
75. Beste LA, Icardi M, Hunt CM, et al. Alanine aminotransferase results differ by analyzer manufacturer in a national integrated health setting, 2012-2017. *Arch Pathol Lab Med*. 2020;144:748–754.
76. Dutta A, Saha C, Johnson CS, Chalasani N. Variability in the upper limit of normal for serum alanine aminotransferase levels: a statewide study. *Hepatology*. 2009;50:1957–1962.
77. Neuschwander-Tetri BA, Unalp A, Creer MH, Nonalcoholic Steatohepatitis Clinical Research Network. Influence of local reference populations on upper limits of normal for serum alanine aminotransferase levels. *Arch Intern Med*. 2008;168:663–666.
78. Gane EJ, Charlton MR, Mohamed R, et al. Asian consensus recommendations on optimizing the diagnosis and initiation of treatment of hepatitis B virus infection in resource-limited settings. *J Viral Hepat*. 2020;27:466–475.
79. Zhou J, Wang FD, Wang ML, et al. Antiviral therapy for chronic HBV infection with persistently normal alanine aminotransferase: controversy and consensus. *Front Med*. 2021;8717125.
80. Zhou J, Wang FD, Wang ML, et al. Antiviral therapy for chronic HBV infection with persistently normal alanine aminotransferase: controversy and consensus. *Front Med*. 2021;8717125.

81. Iloeje UH, Yang HI, Su J, et al. Risk evaluation of viral load elevation and associated liver disease/cancer-in HBV (the REVEAL-HBV) study group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*. 2006;130:678–686.
82. Chen CJ, Yang HI, Su J, et al, REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295:65–73.
83. Kennedy PTF, Sandalova E, Jo J, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. *Gastroenterology*. 2012;143:637–645.
84. Mason WS, Gill US, Litwin S, et al. HBV DNA integration and clonal hepatocyte expansion in chronic hepatitis B patients considered immune tolerant. *Gastroenterology*. 2016;151:986–8. e4.
85. Jeng WJ, Wong GL. The truth of the matter: will immune-tolerant chronic hepatitis B patients benefit from antiviral treatment? *Hepatol Commun*. 2023;7e0060.
86. Hui CK, Leung N, Yuen ST, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. *Hepatology*. 2007;46:395–401.
87. Wong GL, Chan HL, Yu Z, Chan HY, Tse CH, Wong V. Liver fibrosis progression in chronic hepatitis B patients positive for hepatitis B e antigen: a prospective cohort study with paired transient elastography examination. *J Gastroenterol Hepatol*. 2013;28:1762–1769.
88. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research work-shop. *Hepatology*. 2007;45:1056–1075.
89. Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology*. 1987;92:1839–1843.
90. Wu JF, Su YR, Chen CH, et al. Predictive effect of serial serum alanine aminotransferase levels on spontaneous HBeAg seroconversion in chronic genotype B and C HBV-infected children. *J Pediatr Gastroenterol Nutr*. 2012;54:97–100.
91. Lee HA, Lee HW, Kim IH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. *Aliment Pharmacol Ther*. 2020;52:196–204.
92. Lee HW, Chon YE, Kim BK, et al. Negligible HCC risk during stringently defined untreated immune-tolerant phase of chronic hepatitis B. *Eur J Intern Med*. 2021;84:68–73.
93. Choi WM, Kim GA, Choi J, Han S, Lim YS. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. *J Clin Investig*. 2022;132e154833.
94. Lee HA, Kim SU, Seo YS, Ahn SH, Rim CH. Comparable outcomes between immune-tolerant and active phases in noncirrhotic chronic hepatitis B: a meta-analysis. *Hepatol Commun*. 2023;7e0011.
95. Koffas A, Kumar M, Gill US, Jindal A, Kennedy PTF, Sarin SK. Chronic hepatitis B: the demise of the 'inactive carrier' phase. *Hepatol Int*. 2021;15:290–300.
96. Chu CM, Liaw YF. Spontaneous relapse of hepatitis in inactive HBsAg carriers. *Hepatol Int*. 2007;1:311–315.
97. Fattovich G, Olivari N, Pasino M, D'Onofrio M, Martone E, Donato F. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut*. 2008;57:84–90.
98. Bonacci M, Lens S, Mariño Z, et al. Anti-viral therapy can be delayed or avoided in a significant proportion of HBeAg-negative Caucasian patients in the Grey Zone. *Aliment Pharmacol Ther*. 2018;47:1397–1408.
99. Lee MH, Yang HI, Liu J, et al, R.E.V.E.A.L.-HBV Study Group. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. *Hepatology*. 2013;58:546–554.
100. World Health Organization (WHO). *Global Hepatitis Report 2024: Actions for Access beyond Viral Hepatitis [Internet]*. Geneva: WHO; 2024. Available from: https://www.who.int/publications/i/item/9789240091672.
101. Asselah T, Marcellin P. Long-term results of treatment with nucleoside and nucleotide analogues (entecavir and tenofovir) for chronic hepatitis B. *Clin Liver Dis*. 2013;17:445–450.
102. Scott LJ, Chan HLY. Tenofovir alafenamide: a review in chronic hepatitis B. *Drugs (Basel)*. 2017;77:1017–1028. 60.
103. Yuen M-F, Ahn SH, Chen D-S, et al. Chronic hepatitis B virus infection: disease revisit and management recommendations. *J Clin Gastroenterol*. 2016;50:286–294.
104. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad*. 2018;4:72–79.
105. Chen MB, Wang H, Zheng QH, et al. Comparative efficacy of tenofovir and entecavir in nucleos(t)ide analogue-naive chronic hepatitis B: a systematic review and meta-analysis. *PLoS One*. 2019;14e0224773.
106. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:185–195.
107. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. *Lancet Gastroenterol Hepatol*. 2020;5:441–453.
108. Berg T, Marcellin P, Zoulim F, et al. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. *Gastroenterology*. 2010;139:1207–1217.
109. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397:1276–1292.
110. Chen R, Zou J, Long L, et al. Safety and efficacy of tenofovir alafenamide fumarate in early-middle pregnancy for mothers with chronic hepatitis B. *Front Med*. 2022;8796901.
111. Zeng QL, Zhang HX, Zhang JY, et al. Tenofovir alafenamide for pregnant Chinese women with active chronic hepatitis B: a multicenter prospective study. *Clin Gastroenterol Hepatol*. 2022;20:2826–2837.
112. Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naöve patients with chronic hepatitis B. *Gastroenterology*. 2012;143:619–628.
113. Chan HLY, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. *Gastroenterology*. 2014;146:1240–1248.
114. Wong GL, Wong VW. Chan HL Combination therapy of interferon and nucleotide/nucleoside analogues for chronic hepatitis B. *J Viral Hepat*. 2014;21:825–834.
115. Hirode G, Hansen BE, Chen CH, et al. Incidence of hepatic decompensation after nucleos(t)ide analog withdrawal: results from a large, international, multiethnic cohort of patients with chronic

hepatitis B (RETRACT-B study). *Am J Gastroenterol*. 2023;118:1601–1608.
116. Lau G, Yu ML, Wong G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatol Int*. 2021;15:1031–1048.
117. Kim JT, Jeong HW, Choi KH, et al. Delayed hypersensitivity reaction resulting in maculopapular-type eruption due to entecavir in the treatment of chronic hepatitis B. *World J Gastroenterol*. 2014;20:15931–15936.
118. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology*. 2009;50:2001–2006.
119. Ray G. Applicability of risk scores to an Indian cohort of hepatitis B-related hepatocellular carcinoma patients. *J Clin Exp Hepatol*. 2024;14101370.
120. Wong VW, Chan SL, Mo F, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J Clin Oncol*. 2010;28:1660–1665.
121. Yuen M-F, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol*. 2009;50:80–88.
122. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. *J Hepatol*. 2016;64:800–806.
123. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol*. 2008;48:335–352. Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009;49:S72–S84.
124. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*. 2011;12:568–574.
125. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–1022.
126. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130:417–422.
127. Kumar M, Jain S, Sharma BC, et al. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. *Dig Dis Sci*. 2006;51:594–599.
128. Arora A, Anand AC, Kumar A, et al. INASL guidelines on management of hepatitis B virus infection in patients receiving chemotherapy, biologicals, immunosupressants, or corticosteroids. *J Clin Exp Hepatol*. 2018;8:403–431.
129. Shi Y, He J, Wei W, et al. The efficacy and safety of nucleos(t)ide analogues in the treatment of HBV-related acute-on-chronicliver failure: a meta-analysis. *Ann Hepatol*. 2013;12:364–372.
130. Xie D, Shi J, Zhou J, Fan J, Gao Q. Clinical practice guidelines and real-life practice in hepatocellular carcinoma: a Chinese perspective. *Clin Mol Hepatol*. 2023;29:206–216.
131. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681–693.
132. Hang TP, Wedd JP. The optimal timing and management of hepatitis B and C in patients with hepatocellular carcinoma. *Chin Clin Oncol*. 2021;10:4.
133. Wong JS, Wong GL, Tsoi KK, et al. Meta-analysis: the efficacy of antiviral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2011;33:1104–1112.
134. Yuan P, Chen P, Qian Y. Evaluation of antiviral therapy performed after curative therapy in patients with HBV-related hepatocellular carcinoma: an updated meta-analysis. *Chin J Gastroenterol Hepatol*. 2016;20165234969.
135. Zhang H, Zhou Y, Yuan G, et al. Antiviral therapy improves the survival rate and decreases recurrences and fatalities in liver cancer patients following curative resection: a meta-analysis. *Mol Clin Oncol*. 2015;3:1239–1247.
136. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308:1906–1914.
137. Yuan P, Chen P, Qian Y. Evaluation of antiviral therapy performed after curative therapy in patients with HBV-related hepatocellular carcinoma: an updated meta-analysis. *Chin J Gastroenterol Hepatol*. 20165234969.
138. Finn RS, Qin S, Ikeda M, et al. Atezolizumabplus bevacizumab in UnresectableHepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–1905.
139. Zhang X, Zhou Y, Chen C, et al. Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. *J Immunother Cancer*. 2019;7:322.
140. Yoo S, Lee D, Shim JH, et al. Risk of hepatitis B virus reactivation in patients treated with immunotherapy for anti-cancer treatment. *Clin Gastroenterol Hepatol*. 2022;20:898–907.
141. Zhang MY, Zhu GQ, Shi KQ, et al. Systematic review with network meta-analysis: comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. *Oncotarget*. 2016;7:30642–30658.
142. Giri S, Agrawal D, Afzalpurkar S, et al. Tenofovir versus entecavir for tertiary prevention of hepatocellular carcinoma in chronic hepatitis B infection after curative therapy: a systematic review and meta-analysis. *J Viral Hepat*. 2023;30:108–115.
143. Linye H, Zijing X, Xiaoyun Z, et al. Tenofovir versus entecavir on the prognosis of hepatitis B-related hepatocellular carcinoma after surgical resection: a randomized controlled trial. *Int J Surg*. 2023;109:3032–3041.
144. Thio CL, Seaberg EC, Skolasky R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360:1921–1926.
145. Ryom L, Boesecke C, Gisler V, et al. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. *HIV Med*. 2016;17:83–88.
146. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr*. 2016;73:294–298.
147. Chacko EC, Surrun SK, Mubarack Sani TP, Pappachan JM. Chronic viral hepatitis and chronic kidney disease. *Postgrad Med J*. 2010;86:486–492.
148. Cai QC, Zhao SQ, Shi TD, Ren H. Relationship between hepatitis B virus infection and chronic kidney disease in Asian populations: a meta-analysis. *Ren Fail*. 2016;38:1581–1588.
149. Fabrizi F, Cerutti R, Donato FM, Messa P. HBV infection is a risk factor for chronic kidney disease: systematic review and meta-analysis. *Rev Clin Esp*. 2021;221:600–611.
150. Hong YS, Ryu S, Chang Y, et al. Hepatitis B virus infection and development of chronic kidney disease: a cohort study. *BMC Nephrol*. 2018;11:353.
151. Lin S, Wang M, Liu Y, et al. Concurrence of HBV infection and nonalcoholic fatty liver disease is associated with higher prevalence of chronic kidney disease. *Clin Res Hepatol Gastroenterol*. 2021;45101483.
152. Pipili C, Cholongitas E, Papatheodoridis G. Review article: nucleus(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease. *Aliment Pharmacol Ther*. 2014;39:35–46.

153. Trinh S, Le AK, Chang ET, et al. Changes in renal function in patients with chronic HBV infection treated with tenofovir disoproxil fumarate vs entecavir. *Clin Gastroenterol Hepatol*. 2019;17:948–956.e1.
154. Mak LY, Hoang J, Jun DW, et al. Longitudinal renal changes in chronic hepatitis B patients treated with entecavir versus TDF: a REAL-B study. *Hepatol Int*. 2022;16:48–58.
155. Lampertico P, Berg T, Buti M, et al. Treatment with tenofovir disoproxil fumarate or entecavir in chronic hepatitis B virus-infected patients with renal impairment: results from a 7-year, multicentre retrospective cohort study. *Aliment Pharmacol Ther*. 2020;52:500–512.
156. Suzuki K, Suda G, Yamamoto Y, et al, NORTE Study Group. Entecavir treatment of hepatitis B virus-infected patients with severe renal impairment and those on hemodialysis. *Hepatol Res*. 2019;49:1294–1304.
157. Ogawa E, Nakamuta M, Koyanagi T, et al, Kyushu University Liver Disease Study (KULDS) Group. Switching to tenofovir alafenamide for nucleos(t)ide analogue-experienced patients with chronic hepatitis B: week 144 results from a real-world, multicentre cohort study. *Aliment Pharmacol Ther*. 2022;56:713–722.
158. Ogawa E, Nakamuta M, Koyanagi T, et al, Kyushu University Liver Disease Study (KULDS) Group. Sequential HBV treatment with tenofovir alafenamide for patients with chronic hepatitis B: week 96 results from a real-world, multicenter cohort study. *Hepatol Int*. 2022;16:282–293.
159. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med*. 2016;374:2324–2334.
160. He T, Bai Y, Cai H, et al. Safety and efficacy of lamivudine or telbivudine started in early pregnancy for mothers with active chronic hepatitis B. *Hepatol Int*. 2018;12:118–125.
161. Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. *Lancet Infect Dis*. 2021;21:70–84.
162. Wang L, Kourtis AP, Ellington S, Legardy-Williams J, Bulterys M. Safety of tenofovir during pregnancy for the mother and fetus: a systematic review. *Clin Infect Dis*. 2013;57:1773–1781.
163. Zeng QL, Zhang HX, Zhang JY, et al. Tenofovir alafenamide for pregnant Chinese women with active chronic hepatitis B: a multicenter prospective study. *Clin Gastroenterol Hepatol*. 2022;20:2826–2837.
164. Pan YC, Jia ZF, Wang YQ, et al. The role of caesarean section and nonbreastfeeding in preventing mother-to-child transmission of hepatitis B virus in HBsAg-and HBeAg-positive mothers: results from a prospective cohort study and a meta-analysis. *J Viral Hepat*. 2020;27:1032–1043.
165. Wen WH, Chen HL, Shih TTF, et al. Long-term growth and bone development in children of HBV-infected mothers with and without fetal exposure to tenofovir disoproxil fumarate. *J Hepatol*. 2020;72:1082–1087.
166. Degasperi E, Caprioli F, El Sherif O, et al. Challenges in treating patients with inflammatory bowel disease and concurrent viral hepatitis infection. *Expet Rev Gastroenterol Hepatol*. 2016;10:1373–1383.
167. Loras C, Gisbert JP, Saro MC, et al. Impact of surveillance of hepatitis B and hepatitis C in patients with inflammatory bowel disease under anti-TNF therapies: multicenter pro- spective observational study (REPENTINA 3). *J Crohns Coli- tis*. 2014;8:1529–1538.
168. Altunöz ME, Senate E, Yeil A, Calhan T, Ovünç AOK. Patients with inflammatory bowel disease have a lower response rate to HBV vaccination compared to controls. *Dig Dis Sci*. 2012;57:1039–1044.
169. Aberra FN, Lewis JD, Hass D, et al. Corticosteroids and immunomodulators: postopera-tive infectious complication risk in inflammatory bowel disease patients. *Gastroenterology*. 2003;125:320–327.
170. Marzano A, Angelucci E, Andreone P, et al. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. 2007;39:397–408.
171. Bu Z, Kong H, Li J, et al. Effect of male hepatitis B virus infection on outcomes of in vitro fertilization and embryo transfer treatment: insights from couples undergoing oocyte donation. *Int J Clin Exp Med*. 2014;7:1860–1866.
172. Ruan L, Chen M, Adu-Gyamfi EA, et al. Maternal hepatitis B virus infection and pregnancy outcomes of freeze-Thaw embryo transfer. *JAMA Netw Open*. 2023;6e2323495.
173. Nie R, Jin L, Zhang H, Xu B, Chen W, Zhu G. Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during in vitro fertilization. *Fertil Steril*. 2011;95:1667–1671.
174. Gianaroli L, Plachot M, van Kooij R, et al. Embryology CO. ESHRE guidelines for good practice in IVF laboratories. *Hum Reprod*. 2000;15:2241–2246.
175. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transplant*. 2005;11:402–409.
176. Choudhary NS, Saraf N, Saigal S, et al. Low-dose short-term hepatitis B immunoglobulin with high genetic barrier antivirals: the ideal post-transplant hepatitis B virus prophylaxis? *Transpl Infect Dis*. 2015;17:329–333.
177. Fung J, Chan SC, Cheung C, et al. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. *Am J Gastroenterol*. 2013;108:942–948.
178. Raimondo G, Allain JP, Brunetto MR, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol*. 2008;49:652–657.
179. Wong T-L, Fung J-Y, Cui T-S, et al. Liver transplantation using hepatitis B core positive grafts with antiviral monotherapy prophylaxis. *J Hepatol*. 2019;70:1114–1122.
180. Hupirkar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus positive donors: consensus guidelines for recipient management. *Am J Transplant*. 2015;15:1162–1172.
181. Yoshizawa A, Yamashiki N, Ueda Y, et al. Long-term efficacy of hepatitis B vaccination as post-transplant prophylaxis in hepatitis B surface antigen (HBsAg) positive recipients and HBsAg negative recipients of anti-hepatitis B core positive grafts. *Hepatol Res*. 2016;46:541–551.
182. Wang S-H, Loh P-Y, Lin T-L, et al. Active immunization for prevention of de novo hepatitis B virus infection after adult living donor liver transplantation with a hepatitis B core antigen-positive graft. *Liver Transplant*. 2017;23:1266–1272.