Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Summary

The updated EASL Clinical Practice Guidelines on the management of hepatitis B virus (HBV) infection provide comprehensive, evidence-based recommendations for its management. Spanning ten thematic sections, the guidelines address diagnostics, treatment goals, treatment indications, therapeutic options, hepatocellular carcinoma surveillance, management of special populations, HBV reactivation prophylaxis, post-transplant care, HBV prevention strategies, and finally address open questions and future research directions. Chronic HBV remains a global health challenge, with over 250 million individuals affected and significant mortality due to cirrhosis and hepatocellular carcinoma. These guidelines emphasise the importance of early diagnosis, risk stratification based on viral and host factors, and tailored antiviral therapy. Attention is given to simplified algorithms, vaccination, and screening to support global HBV elimination targets. The guidelines also discuss emerging biomarkers and evolving definitions of functional and partial cure. Developed through literature review, expert consensus, and a Delphi process, the guidelines aim to equip healthcare providers across disciplines with practical tools to optimise HBV care and outcomes worldwide.

Introduction

Hepatitis B virus (HBV) infection continues to be a significant global health challenge, affecting millions of individuals worldwide. Chronic HBV infection can lead to severe liver diseases, including cirrhosis and hepatocellular carcinoma (HCC), causing substantial morbidity and mortality. As the medical community strives to improve the management of this complex and evolving disease, there is a critical need for comprehensive and up-to-date guidance that addresses the diagnosis, treatment and prevention of HBV infection.

The European Association for the Study of the Liver (EASL) clinical practice guidelines (CPGs) on HBV have been developed to serve as a practical resource for physicians, encompassing both general practitioners and specialists, who play a pivotal role in the care of individuals with HBV infection. With its evidence-based recommendations and expert insights, the aim of this guideline is to empower healthcare professionals with the knowledge and tools necessary to make informed clinical decisions tailored to the unique needs of each patient.

The guideline covers a wide spectrum of topics, ranging from diagnostics, patient evaluation and treatment indications to antiviral therapy options, monitoring strategies, HCC surveillance, considerations for special populations, prophylaxis of HBV reactivation (HBVr), and finally the prevention of HBV infection. It emphasises the importance of screening, regular follow-up, early intervention, and personalised care to enhance patient outcomes. Furthermore, this guideline addresses a pressing issue that pertains to resource-limited regions, such as many parts of Africa and Asia. Recognising the challenges faced in these areas, where healthcare resources may be scarce, the guideline explores strategies for simplifying HBV management while maintaining efficacy. By acknowledging the diverse healthcare landscapes around the world, this guideline aims to contribute to the improved management of HBV infection on a global scale.

Methodology and implementation

The development of this guideline was guided by a rigorous and systematic approach based on EASL standard operating policies.[1] The methodology employed a comprehensive and evidence-based process to ensure the validity, reliability, and applicability of the recommendations provided within this guideline.

Expert panel formation

An expert panel consisting of hepatologists and infectious disease specialists was selected by the EASL Governing Board.

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Clinical Practice Guideline Panel: Chair: Markus Cornberg; Secretary to the Chair: Lisa Sandmann; Panel members: Jerzy Jaroszewicz, Patrick Kennedy, Pietro Lampertico, Maud Lemoine, Sabela Lens, Barbara Testoni, Grace Lai-Hung Wong; EASL Governing Board representative: Francesco Paolo Russo.

https://doi.org/10.1016/j.jhep.2025.03.018

Panel members were selected based on their expertise, clinical experience, and contributions to the field of HBV research and management. The EASL ethics committee reviewed the conflicts of interest of the panel members. The CPG panel held multiple videoconferences and face-to-face meetings. The process began with the identification of the main topics and the elaboration of key questions according to the PICO format (P - Patient, Problem or Population; I - Intervention; C – Comparison, Control or Comparator; O - Outcome).

Literature review and evidence synthesis

A non-systematic thorough and exhaustive literature search was conducted by the panellists to identify relevant studies, systematic reviews, meta-analyses, and clinical trials related to HBV infection, its diagnosis, and treatment. The literature considered was up to date as of February 2025. At the time of writing, some data from ongoing major studies had not yet been published in detailed form, so the experts agreed to include abstracts presented at international meetings as bibliographic references but to label them as non-peer-reviewed articles accordingly.

Evidence grading

The quality of evidence was scored according to the OCEBM (Oxford Centre for Evidence-based Medicine) (adapted from The Oxford 2011 Levels of Evidence) (Table 1).

Recommendations and statements

Our recommendations were carefully developed through a collaborative process that integrated the results of a comprehensive literature search (to assess the level of evidence), expert opinion, and the Delphi process. Each recommendation was carefully crafted, taking into account several key factors, including level of evidence, clinical experience, potential benefits, associated risks, and patient preferences. The OCEBM-based classification system was used to evaluate the evidence and, from that, categorise the recommendations into two different levels: strong or weak (Table 2). In translating the level of evidence into our recommendations, whether to upgrade or downgrade the strength of recommendation relative to the level of evidence was carefully considered. If there were strong discrepancies between the level of evidence and the strength of recommendation, they are explicitly stated in the explanatory comments. These recommendations were discussed in detail by our expert panel and unanimously approved before being presented to the Delphi panel for consensus.

It is important to note that statements and recommendations are distinguished in our guideline. Statements provide clarifications, factual information, or commentary on specific topics. They are included in our formal consensus process and may be based on either study results or expert opinion.

Delphi process and achieving consensus

To achieve consensus among all members of the expert panel on the guideline recommendations, the Delphi method was used. This method included several rounds of questionnaires and in-depth discussions that allowed the experts to share their insights, express opinions, and evaluate the strength and quality of the recommendations. The composition of the Delphi panel was carefully selected, taking into account the recommendations of the National Societies, the EASL Governing Board, and the CPG panel. Final approval by the EASL Governing Board took into account expertise, conflict of interest, geographic representation, and gender balance. Of particular note, two patient representatives were included on the panel. Initially, PICO questions were shared with the Delphi panel to gather consensus on the topics and elicit suggestions for potential additions. Subsequently, once the CPG panel had finalised the recommendations, they were presented to the Delphi panel to obtain consensus. Our definition of consensus was structured as follows: less than 50% agreement indicated that consensus could not be reached, resulting in a revision of the recommendation and resubmission to the Delphi panel; 50-75% agreement denoted weak consensus or majority agreement and required refinement of the recommendation with the option to resubmit to the Delphi panel; ≥75-95% agreement indicated consensus that did not require a complete rewriting of the recommendation but encouraged consideration of comments

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level*	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

*Level may be graded down on the basis of study quality, imprecision, indirectness (study does not match questions), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

to improve the recommendation; ≥95% agreement demonstrated a strong consensus and implied that no changes were needed, although minor non-substantive corrections could still be considered (Table 3). Although consensus was reached on all recommendations after the second Delphi round, the panel's comments were incorporated and 25 recommendations were submitted to a third Delphi round and two recommendations to a fourth Delphi round. Some of the recommendations that did not reach strong consensus are marked with an asterisk, with an explanation for why they did not reach strong consensus provided in Appendix table at the end of the manuscript.

External review and validation

For section "Prevention of HBV infection," two additional external experts, Dieter Glebe (Gießen, Germany) and Thomas Vanwolleghem (Antwerp, Belgium), were consulted prior to the final Delphi process.

The final draft guideline was subjected to external review by a panel of additional experts, ensuring diverse perspectives and minimising bias. Feedback from external reviewers was incorporated into the final version of the guideline. The final guideline was approved by the EASL Governing Board.

Documentation and dissemination

The guideline will be disseminated through various platforms, including medical journals, online repositories, and professional associations. The primary audience is clinicians from various specialties who manage patients affected by HBV, such as hepatologists, gastroenterologists, and infectious disease specialists. In addition, the sections on screening and prevention are of particular relevance to clinicians who encounter individuals at risk of HBV infection or HBVr. A concise version of the guideline will also be made available.

Regular updates

The guideline will undergo periodic updates to remain aligned with the latest advances in HBV research and clinical practice. New developments will be carefully evaluated and incorporated through amendments as needed to ensure the guideline reflects the most current scientific evidence and best practices.

Target audience of the guideline

The guideline is primarily intended for specialists in gastroenterology, hepatology, and infectious diseases, as well as for physicians in internal medicine and transplant medicine who manage and treat individuals with HBV infection. Additionally, it is relevant for primary care practitioners, who play a key role in screening individuals with risk factors for HBV infection and administering hepatitis B vaccinations when necessary. Furthermore, the recommendations for prophylaxis of HBVr are essential for all physicians prescribing immunosuppressive therapies (*e.g.* haematologists, oncologists, rheumatologists, dermatologists, and neurologists).

Table 3. Consensus building.

Definition of consensus	Consent in %
Strong consensus	≥95%
Consensus	≥75-95%
Majority agreement	≥50-75
No consensus	<50

Relevance of the topic

Epidemiology

HBV infections represent a significant burden on both individuals and healthcare systems worldwide. In 2022, an estimated 1.2 million new HBV infections occurred globally, while 254 million people were living with chronic HBV infection. Hepatitis B-related complications, including cirrhosis and HCC, contributed to 1.08 million deaths.[2] The prevalence of chronic HBV infection shows considerable geographical variation, with the highest rates reported in sub-Saharan Africa, East Asia and the Pacific Islands. In Europe, countries in Eastern and South-Eastern Europe are the most affected, with an intermediate prevalence. Nevertheless, the incidence and prevalence of HBV infection in Europe continues to evolve due to factors such as globalisation, migration and the movement of refugees.[3] In regions with high endemicity, vertical transmission from mother to child during childbirth or through close personal contact contributes significantly to the prevalence of HBV infection. However, HBV can be transmitted through various routes, including perinatal transmission, sexual contact, sharing of contaminated needles or other injection equipment, and exposure to infected blood.

The introduction of universal HBV vaccination programmes has significantly impacted the epidemiology of the disease, particularly in countries that have implemented widespread vaccination. Vaccination at birth and in childhood has proven effective in reducing the prevalence of chronic HBV infection and its associated complications.

The economic and societal burden of HBV infection is substantial, encompassing costs associated with healthcare utilisation, treatment, and loss of productivity. Importantly, the Polaris Observatory Collaborators model study 2022 estimated that only 36 million of the total hepatitis B surface antigen (HBsAg)-positive population have been diagnosed, and only 6.8 million of the estimated 83.3 million individuals eligible for treatment are on treatment.[4] These data highlight a critical gap in the cascade of care, emphasising the urgent need to strengthen prevention efforts, improve early diagnosis, and expand access to effective treatment.

Natural history

Acute HBV infection is often asymptomatic but can lead to severe hepatitis and, in some adult cases, to fulminant hepatitis and liver failure. It may also progress to chronic infection, particularly if transmitted from mother to child or acquired during childhood or adolescence. In contrast, progression to chronic HBV infection is rare when infection occurs in immunocompetent adults. Chronic HBV infection is a significant risk factor for the development of cirrhosis, end-stage liver disease, and HCC, and it may also be associated with extrahepatic manifestations. Both chronic and resolved HBV infections carry a risk of reactivation, leading to severe, potentially fatal outcomes in individuals undergoing immunosuppression.[5] Consequently, the morbidity and mortality associated with

HBV infection is considerable. HBV-related deaths are projected to rise globally from 858,000 in 2015 to 1,149,000 in 2030, alongside increasing HCC incidence (from 644,000 to 857,000) and cases of decompensated cirrhosis (from 296,000 to 403,000), assuming that current levels of diagnosis and treatment remain unchanged.[4]

Understanding the natural history of HBV infection is crucial for identifying individuals at risk of disease progression. The transition from acute to chronic infection and the potential for reactivation necessitate comprehensive surveillance and timely intervention. Chronic HBV infection is a dynamic and complex condition that progresses through distinct phases (Table 4), each characterised by unique virological, immunological and clinical features. A comprehensive understanding of these phases is essential for accurate diagnosis, tailored management, and informed decision-making in patient care.

A significant proportion of individuals with chronic HBV infection cannot be easily classified into the four phases outlined in the 2017 EASL CPGs,[5] which are also adopted in this new guideline. For example, numerous publications have classified patients as being in a "grey zone" or “intermediate phase”,[6–8] highlighting the large heterogeneity within chronic HBV infection. For clarity, it is recommended to avoid these terms and to define the treatment indication based on the current phases (section “Treatment indications” of this guideline), while a simplified treatment algorithm independent of hepatitis B e antigen (HBeAg) status is proposed (Fig. 1). That said, a differentiated nomenclature is suggested for research purposes, which is described in detail in Appendix Table 2. While categorising patients into “disease phases” is pertinent for research purposes, patient stratification for clinical trials, and indications for antiviral therapy, this complexity can pose challenges in clinical practice. Therefore, the recommendations in this guideline aim to simplify these categorisations, providing healthcare professionals with clear guidance for the effective management of chronic HBV infection to ensure optimal care and improved patient outcomes.

Screening and diagnosis

The level of evidence for diagnostic tests and general screening is not specified, as recommendations are primarily based on clinical experience, observational studies, epidemiological data, and expert consensus.

How and who should be screened for HBV infection?

Recommendations

- For initial screening of HBV infection, HBsAg and anti-HBc should be determined **(strong recommendation, consensus).***
- HBV screening should be performed in individuals **(strong recommendation, strong consensus)**:
  - with elevated liver enzymes and/or clinical signs of liver disease
  - with cirrhosis/fibrosis of the liver
  - with liver cancer (HCC or biliary tract cancer)
  - with extrahepatic manifestations possibly related to HBV
  - with end-stage kidney disease undergoing haemodialysis
  - with HIV infection
  - with HCV infection
  - being considered for or undergoing immunosuppressive/immunomodulatory therapy or chemotherapy
  - with congenital immunodeficiency
  - considered for stem cell/bone marrow or organ transplants and recipients of such transplants
  - with an increased risk of exposure to HBV
    - individuals from regions with intermediate to high HBsAg prevalence
    - family or household members of HBV-infected individuals
    - sexual partners of HBV-infected individuals
    - individuals in care/correctional facilities
    - individuals with multiple sexual partners
    - individuals who seek examination or treatment for sexually transmitted diseases
    - individuals with nonmedical exposure to body fluids
    - active and former people who inject drugs
- HBV screening (HBsAg [anti-HBc not required) should be performed to prevent transmission in **(strong recommendation, strong consensus)**:
  - Blood, tissue, semen, and organ donors
  - Healthcare workers
  - Pregnant women

Statement

- Because of the importance of early diagnosis of HBV infection (prevention of transmission, availability of safe and effective treatment measures), EASL advocates population-based screening beyond risk groups to identify unknown cases, especially in countries with intermediate to high endemicity **(strong consensus).**

The initial screening for HBV should include HBsAg (hepatitis B surface antigen) and anti-HBc (hepatitis B core antibody) assessments.

HBsAg positivity is the most important screening parameter. When the HBV infects hepatocytes, large amounts of HBsAg are secreted. This excess antigen is released into the bloodstream, making it relatively easy to detect even in the early stages of infection.[9] HBsAg testing is well-established and standardised worldwide, making it reliable and easy to interpret in different clinical and epidemiological settings. HBsAg is typically measured using highly sensitive enzyme immunoassays with a limit of detection (LOD) of <0.05 IU/ml. However, during the early stages of acute HBV infection, HBsAg levels may fall below the detection threshold, potentially leading to false-negative results. This pre-HBsAg window where HBV DNA is positive but HBsAg is not detectable may last weeks.[10] Low HBsAg levels can also occur in

Table 4. Phase of chronic HBV infection, modified based on.[5]

	Phase 1	Phase 2	Phase 3	Phase 4
	HBeAg-positive chronic infection	HBeAg-positive chronic hepatitis	HBeAg-negative chronic infection	HBeAg-negative chronic hepatitis
HBsAg	High	Intermediate to high	Low, usually <1,000 IU/ml	Intermediate, usually >1,000 IU/ml
HBV DNA	High, usually ≥10^7 IU/ml	Moderate to high, usually 10^4-10^7 IU/ml	Usually <2,000 IU/ml	Usually, >2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease progression (if untreated)	None/minimal	Moderate to severe	None	Mild to severe

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
*Either persistently or intermittently.

persistent or reactivated HBV infection under immunosuppression.[11] More sensitive HBsAg assays (LOD <0.005 IU/ml) can be useful when nucleic acid testing (NAT) is not available.[11–14]

False-negative and -positive HBsAg results can complicate the diagnosis. False-negative HBsAg results may occur due to variations in HBsAg epitopes not recognised by all assays.[15,16] Additionally, different HBsAg tests use various antibodies and have different capabilities to dissociate HBsAg from immune complexes, potentially leading to conflicting results. Anti-HBc and HBV DNA testing are reliable methods to resolve these discrepancies.[17]

False-positive HBsAg results, which can occur in patients on haemodialysis, post-mortem organ donors, individuals with heterophilic antibodies, or those receiving G-CSF, can generally be ruled out by performing neutralisation with anti-HBs, the manufacturer-recommended confirmatory test.[18–21] Sequential HBsAg measurements, combined with other virological markers, can further enhance diagnostic accuracy and provide a more comprehensive understanding of the infection status.

Anti-HBc antibodies may arise after any encounter with HBV and indicate a past or current infection.[22,23] Although historically there were many versions of anti-HBc tests, nowadays most countries and laboratories are using state-of-the-art FDA-approved or CE-marked assays, which are more than 99.8% specific and are considered the most sensitive for donor screening and assessment of past HBV exposure. These are total anti-HBc assays, since they detect both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to HBcAg; no test for IgG anti-HBc alone is commercially available.[24] Importantly, detection of anti-HBc IgG alone does not indicate whether the infection is ongoing or resolved. These individuals may be HBsAg-negative but anti-HBc-positive, necessitating monitoring and/or preventive measures (see section "Prophylaxis of HBV reactivation"). Thus, anti-HBc screening enhances the understanding of an individual's HBV history and informs appropriate clinical actions to manage reactivation risks.

Anti-HBs can provide valuable insights into vaccination status, particularly when both HBsAg and anti-HBc are negative, and can aid in risk stratification for HBVr in patients undergoing immunosuppressive treatment.[25] However, routine anti-HBs testing is not essential for determining HBV infection status. While including anti-HBs testing in initial screening may offer additional information, it is likely not cost-effective.

Screening for HBV in diverse populations is crucial for early detection, transmission prevention, and effective infection management, ultimately alleviating the disease burden on individuals and society. Given the global prevalence of chronic HBV infection (HBsAg-positive) at approximately 3.2%,[4] a proactive approach to HBV diagnosis is warranted.

HBV infections are widespread, with highly endemic regions, such as parts of Asia, the South Pacific, sub-Saharan Africa, South America, and the Middle East, showing anti-HBc positivity rates exceeding 50%. Intermediate-prevalence regions, including the Mediterranean and Eastern Europe, have anti-HBc positivity rates of 10-50%. Individuals born in these regions, or whose mothers are from these areas, are at an elevated risk of being HBsAg-positive.[26] Screening migrants from these regions enables early diagnosis, helps to slow the progression of liver disease, and has been proven to be cost-effective.[27,28]

HBV can be transmitted through perinatal, percutaneous (blood-to-blood), and sexual routes. Even minimal exposure to body fluids with high HBV DNA levels can result in infection. Mother-to-child transmission (MTCT) is especially common in high-endemic regions, yet many pregnant women in low-endemic countries are also HBsAg carriers.[29] Therefore, universal HBsAg screening during pregnancy is strongly recommended and has been implemented in numerous countries. Screening should occur as early as possible in the first trimester to allow for timely antiviral treatment if indicated (*e.g.* if HBV DNA levels are ≥200,000 IU/ml), ideally before the 28th week of pregnancy. Additionally, newborns should receive a timely birth dose of the hepatitis B vaccine within 24 hours, ideally within the first 12 hours after birth.,[30] ideally accompanied by hepatitis B immune globulin (HBIG), to prevent MTCT.

Additional risk factors for HBV transmission include activities that may involve blood contact, such as intravenous drug use, body piercing, blood transfusions, haemodialysis, and certain barbering practices. It has also been noted that transmission can occur during surgical, medical, or dental procedures.[31] Individuals living with human immunodeficiency virus (HIV) or those with chronic hepatitis C virus (HCV) infection should be screened due to similar transmission routes.[32] Given that many HBV infections are asymptomatic and can significantly affect the progression and prognosis of non-HBV-related liver diseases, HBV screening should be standard practice for patients with chronic liver disease. Specific conditions, such as HBV-associated extrahepatic manifestations (*e.g.* panarteritis nodosa) and immunosuppressive states, should prompt further screening, as immunosuppression can lead to chronic infections and potential reactivation of previously controlled or resolved HBV infections.

To protect public health and prevent transmission, household members, sexual partners, and close contacts of

individuals with HBV infection should be screened for HBV. Those who test negative for both HBsAg and anti-HBc should be offered vaccination (see section "Prevention of HBV infection").

What serological and virological tests are recommended in HBsAg-positive individuals for initial assessment?

Recommendation

- In HBsAg-positive individuals, the serological and virological diagnostics shown in Table 5 should be considered **(strong recommendation, strong consensus).**

HBV DNA serves as a key marker for HBV viraemia, commonly assessed using sensitive NAT in clinical settings. Numerous commercial NAT assays, predominantly using real-time PCR, are available to quantify HBV DNA in clinical samples. The prognostic significance of HBV viraemia is substantial,[33–35] establishing quantitative HBV DNA detection (standardised in IU/ml) as the gold standard. The LOD of most currently available commercial HBV DNA assays is 10-20 IU/ml.[36]

In resource-limited areas, HBV DNA testing presents challenges, as conventional real-time PCR methods demand specialised infrastructure, trained personnel, and a significantly prolonged turnaround time. An alternative lies in less complex, user-friendly, and cheaper assays with the potential for point-of-care molecular testing, particularly when conventional assays are unavailable. For instance, the Xpert HBV-VL assay, designed for near-point-of-care molecular testing, exhibits excellent performance and robust correlation with assays from Abbott and Roche, making it a reliable method for HBV DNA quantification in remote areas.[37,38]

HBeAg, a marker for the replication of the wild-type virus, is essential for classifying the phase of HBV infection (Table 4). ELISA (enzyme-linked immunosorbent assay) and enzyme-linked fluorescence assays are commonly used to detect HBeAg.

In resource-limited areas where HBV DNA is not available, HBeAg (in combination with alanine aminotransferase [ALT]) can be used to establish the indication for therapy[39] and predict the risk of vertical transmission.[40] Due to their low cost and ease of use, rapid diagnostic tests (RDTs) are widely used in resource-limited countries. However, the diagnostic performance of the currently commercialised HBeAg RDTs is insufficient to recommend their use as an alternative to standard ELISA.[41,42]

Anti-HBe serostatus is used to define the disease phase and to assess the evolution of the disease, as well as a patient's response to therapy, since spontaneous or treatment-induced HBeAg/anti-HBe seroconversion is associated with a decline in viral replication, lower rates of disease progression and improved survival rates.[43]

Quantitative HBsAg cannot replace HBV DNA measurement but can provide additional value, such as helping to differentiate the phases of chronic HBV infection (see Table 4) and guiding treatment. Quantitative HBsAg testing is valuable in distinguishing between low viraemic phases of HBeAg-negative chronic HBV infection and HBeAg-negative chronic hepatitis. Individuals with HBeAg-negative infection (formerly "inactive carriers") can be identified by HBV DNA levels <2,000 IU/ml and HBsAg <1,000 IU/ml, achieving a diagnostic accuracy of 85-94% in Asian and European cohorts.[44,45] In a multicentre cohort across Asia, Europe, and Australia, HBsAg <100 IU/ml combined with HBV DNA <2,000 IU/ml offered greater specificity and the highest positive predictive value for identifying HBeAg-negative infection across all HBV genotypes.[46] A higher risk of reactivation, *i.e.* progression from HBeAg-negative infection to HBeAg-negative hepatitis, exists with HBV DNA <2,000 IU/ml and HBsAg >1,000 IU/ml.[9,47] In addition, Asian cohort studies showed that, in HBeAg-negative individuals with HBV DNA <2,000 IU/ml, the risk of HCC is significantly higher in those with HBsAg levels ≥1,000 IU/ml than in those with HBsAg <1,000 IU/ml.[48] In HBeAg-positive individuals, HBsAg levels help to classify the phase of infection, with patients showing exceptionally high HBsAg (>25,000 IU/ml) being less likely to have significant fibrosis, representing a population at lower risk for HCC during HBeAg-positive infection.[49–51] Monitoring HBsAg dynamics in untreated HBeAg-positive individuals can provide valuable insights into disease progression, HCC risk, a possible phase transition, the durability of spontaneous seroconversion, and

Table 5. Recommended serological and virological diagnostics for HBsAg-positive/anti-HBc-positive individuals.

Diagnostic test	Recommendation	Grade
HBV DNA quantitative	HBV DNA should be tested, as it serves as the most important prognostic marker and is critical for treatment indication and treatment monitoring	Strong
HBsAg quantitative	HBsAg quantification should be tested to characterize disease phase, define prognosis and guide treatment	Strong
Anti-HBs	Anti-HBs is not necessary for diagnosis of HBV infection; anti-HBs is useful to determine immunisation status if HBsAg is negative and to evaluate seroconversion after HBsAg loss	Weak
HBeAg	HBeAg should be tested to define the disease phase	Strong
Anti-HBe	Anti-HBe can be tested to define the disease phase (especially if HBeAg is negative)	Weak
Anti-HBc IgM	If acute hepatitis B is suspected, anti-HBc IgM can be tested (ideally quantitative)	Weak
HBV genotype	Genotype can be tested to optimise stratification for interferon-based treatment and estimate risk of HCC	Weak
HDV screening	Anti-HDV should be tested	Strong
HCV screening	Anti-HCV should be tested	Strong
HIV screening	Anti-HIV1/2 should be tested	Strong

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus.

the potential for subsequent HBsAg seroclearance.[51–54] HBsAg quantification is important for managing pegylated interferon-alfa (PEG-IFNα) treatment and stratification of patients eligible for stopping therapy with nucleos(t)ide analogues (NAs).

Quantitative HBsAg testing is increasingly important for defining treatment endpoints. While the ultimate goal of treatment and the primary endpoint for phase II/III trials of finite treatments for chronic HBV infection is a "functional" cure, defined as sustained HBsAg loss (at least 24 weeks off therapy) with HBV DNA below the limit of quantification (LOQ), a sustained HBsAg level <100 IU/ml with HBV DNA <LOQ at 24 weeks off therapy is now being proposed as an alternative intermediate endpoint, or "partial cure".[55]

Anti-HBc IgM is typically present in high concentrations during acute hepatitis B and usually declines to undetectable levels within 6 months. However, lower concentrations can also be detected in chronic HBV infection and during exacerbations of chronic hepatitis B. Consequently, anti-HBc IgM alone has limited diagnostic value, as it may be present in both acute and chronic stages of infection. However, quantifying anti-HBc IgM can help differentiate acute hepatitis B from chronic hepatitis B with acute exacerbation, as higher concentrations are more indicative of acute infection.[56,57]

Anti-HBs antibodies indicate natural or post-vaccination immunity. Testing anti-HBs level is not necessary for screening (see above). Measurement of anti-HBs antibodies can be considered to document anti-HBs seroconversion following HBsAg loss. Additionally, it may help assess the risk of HBVr in patients undergoing immunosuppressive therapy.

New viral biomarkers

Recently, emerging non-invasive biomarkers reflecting the intrahepatic pool of transcriptionally active HBV covalently closed circular DNA (cccDNA) have been proposed, comprising quantification of serum hepatitis B core-related antigen (HBcrAg) and HBV RNA.[36] They all require sophisticated technology for quantification and are not yet implemented in routine clinical practice for initial screening or diagnosis. However, HBcrAg has recently been shown to be a useful serologic marker to indicate high viraemia in treatment-naïve, HBV-infected patients.[58] A rapid point-of-care HBcrAg test proved to be a reliable tool to identify highly viraemic patients, in low- and middle-income countries (LMICs),[59] thus helping in guiding treatment when HBV DNA or HBeAg assays are not available.

Moreover, quantitative anti-HBc is gaining attention as a potential biomarker reflecting HBV-specific immune responses and has been associated with disease activity[60,61] and HBVr risk.[62]

The potential role of these emerging biomarkers in monitoring the natural course of HBV infection, predicting disease progression, and stratifying patients for stopping NA therapy is discussed in detail in sections “Treatment indications” and “Treatment”.

Assessment of relevant coinfections

Hepatitis D, also known as Delta hepatitis, is a special form of viral hepatitis, as it is always a coinfection with HBV. Infection with the hepatitis D virus (HDV), a small RNA virus, occurs exclusively in patients with HBV infection, as HDV requires the HBV envelope (HBsAg) to infect hepatocytes and egress from hepatocytes. An acute HDV infection leads to a superinfection or coinfection with HBV.[63] The interaction between HDV and HBV can significantly promote the progression of liver disease. Chronic HBV/HDV infection is therefore considered the most severe form of chronic viral hepatitis, as it is associated with an increased risk of developing cirrhosis and hepatic complications, including the development of HCC.[63,64] Worldwide, approximately 4-5% of individuals chronically infected with HBV are also coinfected with HDV. However, the prevalence of hepatitis D varies worldwide and there are regions with high prevalence, including parts of Africa, Asia and the Mediterranean.[65,66] It is assumed that a large proportion of HDV coinfections worldwide are still undetected. Thus, all HBsAg-positive individuals should be screened for HDV at least once.[64] The risk groups for HBV/HDV infection include people from endemic areas with a high HDV prevalence, such as people with a migration background from Asia, Africa, South America and people from corresponding risk groups, as HDV is mainly transmitted parenterally, predominantly sexually or through contaminated blood (*e.g.* drug use) or blood products.[65] HDV testing should be repeated in case of persistent risk factors or unexplained ALT elevation.

The detection of anti-HDV antibodies is carried out by immunoassays,[67] but testing for serum/plasma HDV RNA is needed to confirm an ongoing HDV infection.[68]

In resource-limited countries where routine HDV serology is not available, an HDV antibody RDT could be used,[69] though its real-world diagnostic performance requires further validation.

Reliable commercial HDV RNA tests are available; however, variability in RNA extraction methods, primer/probe design, lack of automation, and limited standardisation across laboratories affect test performance. These inconsistencies make comparability between different HDV RNA tests challenging, particularly when interpreting quantitative HDV RNA values.[68,70,71]

In addition, it is essential to screen for coinfections with HCV and HIV, as the infections affect the same risk groups.[32] Furthermore, the inclusion of HIV testing is important if antiviral therapy is necessary,[72] since tenofovir (tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF]) is also an HIV-active medication.

In resource-limited settings, HIV[73] and HCV antibody RDTs,[74] which have demonstrated excellent diagnostic performance, can be used to detect coinfection in HBsAg-positive individuals.

Given that locally acquired hepatitis E virus (HEV) is now one of the most common causes of acute viral hepatitis in many countries, HEV test (anti-HEV IgM or HEV RNA) should be considered to rule out HEV coinfection in the event of an increase in transaminases of unclear aetiology.[75] Additionally,

testing for anti-hepatitis A virus IgG/IgM is recommended. If the anti-hepatitis A virus IgG result is negative, hepatitis A vaccination may be offered, especially to patients with advanced chronic liver disease.

What additional investigations are recommended for disease assessment in HBsAg-positive individuals?

Recommendations

- Baseline liver disease assessment should be performed in all HBsAg-positive individuals **(strong recommendation, strong consensus).**
- Abdominal ultrasound should be performed at diagnosis in all HBsAg-positive individuals **(strong recommendation, strong consensus).**
- Non-invasive methods should be used to assess liver fibrosis and stage liver disease in all HBsAg-positive individuals **(strong recommendation, strong consensus).**
- Liver biopsy can be performed in case of diagnostic uncertainty, discordant non-invasive test results or the presence of liver-related comorbidities **(weak recommendation, strong consensus).**

Clinical biochemical laboratory tests are crucial for a comprehensive assessment of liver inflammation and potential liver function impairment. This evaluation includes measuring liver inflammation markers (aspartate aminotransferase [AST], ALT), synthetic liver function parameters (total bilirubin, albumin), and coagulation status (*e.g.* prothrombin time expressed as international normalised ratio [INR]) and full blood count.

Ultrasound examination of the abdomen is recommended to detect potential liver tumours, identify coexisting conditions (*e.g.* hepatic steatosis), and look for signs of portal hypertension. For details on using ultrasound for HCC surveillance see section “HCC surveillance”.

Non-invasive methods of fibrosis assessment, such as liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), shear wave elastography (SWE), and acoustic radiation force impulse imaging (ARFI), as well as serum-based tests (*e.g.* AST-platelet ratio index [APRI], Fibrosis-4 [FIB-4], FibroTest), should be preferred over liver biopsy for evaluating liver fibrosis and its progression. However, the accuracy, availability, and reliability of these non-invasive tests can vary depending on factors such as underlying liver disease, inflammation, and operator expertise. In an optimal setting, liver fibrosis is assessed using LSM, with defined cut-off values for VCTE indicating significant fibrosis (7.2-7.9 kPa), advanced fibrosis (8.8-9.4 kPa) and cirrhosis (≥11.7-12.2 kPa), as shown in two systematic reviews and meta-analyses focused on individuals with HBV infection.[76,77] Another systematic review reported slightly different thresholds: 7.0 [6.5–7.4] kPa for significant fibrosis, 8.0 [7.6–8.4] kPa for advanced fibrosis, and 11.0 [10.0–11.9] kPa for cirrhosis.[78] The most recent meta-analysis, focused exclusively on individuals with HBV infection, proposes thresholds of 6.0–8.0 kPa for significant fibrosis (with a cut-off of >7.0 kPa identifying most cases), >8.0–11.0 kPa for advanced fibrosis, and >11.0–14.0 kPa for cirrhosis.[79] These minor differences in thresholds can be attributed to variations in study composition, analysis periods, and slight differences in selection criteria across the meta-analyses. Despite these discrepancies, the sensitivity and specificity of the thresholds remained comparable in the two most recent meta-analyses, ranging from 69% to 89%. Additionally, a small subset of patients in the analysed studies was receiving antiviral treatment, which may have influenced the diagnostic accuracy of LSM. However, detailed subgroup analyses comparing treated and untreated patients are not available.[79] Table 6 shows LSM thresholds that are approximated for practical application.

The Baveno VI consensus introduced the term “compensated advanced chronic liver disease (cACLD)” to describe patients with advanced fibrosis or early cirrhosis who remain asymptomatic but are at risk of developing clinically significant portal hypertension (CSPH) and disease progression.[80] Liver stiffness values <10 kPa were proposed as a safe cut-off for excluding cACLD and values >15 kPa as highly suggestive of cACLD. However, in a multicentre study of real-world data involving 5,648 patients with liver disease (including 716 patients with chronic HBV infection, representing 13% of the cohort),[81] the sensitivity of the <10 kPa cut-off for ruling out cACLD was lower in patients with chronic HBV infection compared to those with other aetiologies.

Besides the estimation of liver fibrosis stage, LSM can be useful to rule out the presence of CSPH and high-risk varices in patients with cirrhosis. Indeed, the Baveno VI guidelines recommend avoiding oesophagogastroduodenoscopy (EGD) for patients with VCTE-LSM <20 kPa and platelet counts >150,000 (favourable Baveno VI status) as the probability of high-risk varices (and bleeding) is low.[80]

NA therapy can modulate or even reverse CSPH in patients with HBV-related cirrhosis.[82] In a meta-analysis including 39 studies and 14,212 patients with ACLD, NA treatment was associated with reduced risks of overall hepatic decompensation events, such as variceal bleeding. Nonetheless, the Baveno VI criteria were also validated in the presence of viral suppression during NA antiviral treatment.[83]

The challenge with the Baveno VI criteria is that patients often fail to meet one of the two criteria (either LSM or platelet levels). To address this, the Baveno VII consensus[84] introduced spleen stiffness measurement as a supplementary tool to assess the risk of high-risk varices, thereby helping to avoid unnecessary EGDs in these cases. The cut-off of spleen stiffness measurement of ≤40 kPa was also validated in a cohort of 504 patients with HBV-related cirrhosis.[85] This strategy avoided more EGDs than Baveno VI criteria, with a comparable rate of missing high-risk varices.

Table 6. VCTE-based LSM thresholds.

Fibrosis stage	Thresholds
Significant fibrosis (F2 or F3 or F4 Metavir)	>7 kPa
Advanced fibrosis (F3 or F4 Metavir)	>8 kPa
Cirrhosis (F4 Metavir)	>11 kPa

LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.
The values derived from the literature[76–79] are approximated for practical application. The lower end of these thresholds is used as a precautionary measure to minimise the risk of underestimating fibrosis severity.
The sensitivity and specificity values for the thresholds are between 69–89%.

As a limitation, VCTE hardware is costly and thus not available everywhere. Serum-based tests such as APRI and FIB-4 are widely available, but their accuracy in chronic HBV infection is limited.[86–89] The SONIC–B study (analysis of global clinical trial data) advises against using standard APRI and FIB-4 cut-offs for managing chronic HBV infection due to frequent misclassification.[88] Despite this and because other non-invasive tests may not be universally accessible, particularly in resource-limited settings, the recently updated World Health Organization (WHO) guidelines suggest the use of an APRI score of >0.5 to detect significant fibrosis, but acknowledge a high rate of false-positive results.[90] Other tests such as FibroTest[91] require specialised lab facilities.

Liver biopsy is an important diagnostic tool for assessing inflammatory activity, liver fibrosis, and comorbidities such as steatosis. However, the decision to perform a liver biopsy should primarily be based on whether the biopsy results will directly influence treatment decisions. In cases of advanced cirrhosis, a careful risk-benefit analysis is essential, as the procedure carries an increased risk of bleeding. Moreover, treatment indications can often be determined from the clinical findings of cirrhosis alone.[92] Biopsy may still be valuable for determining the aetiology in cases with unclear or negative serological results or when additional or alternative aetiologies of liver disease are suspected. For assessing fibrosis, non-invasive methods should be prioritised.

How should individuals be monitored after initial diagnosis of chronic HBV infection if they are not receiving antiviral therapy?

Recommendations

- For individuals newly diagnosed with chronic HBV infection, monitoring (ALT and HBV DNA) should be performed every 3-6 months for the first year after diagnosis or until treatment is initiated. After this initial phase, the monitoring frequency should be adjusted to every 6-12 months, depending on the disease phase **(strong recommendation, strong consensus).**
- HBsAg levels should be determined every 12 months. If a quantitative determination of HBsAg is not possible, a qualitative HBsAg test is the minimum requirement **(strong recommendation, strong consensus).**
- HBeAg and anti-HBe should be tested in HBeAg-positive individuals every 12 months or when ALT levels or HBV DNA levels change significantly **(strong recommendation, strong consensus).**
- Non-invasive methods should be used to assess liver fibrosis progression. The frequency and intervals should be individualised based on factors such as disease phase and presence of comorbidities **(strong recommendation, consensus).**

For individuals diagnosed with chronic HBV infection who are not yet on antiviral therapy, regular follow-up is critical to ensure optimal management and timely interventions. Monitoring should include a comprehensive approach tailored to the clinical status of the individual.

The basis for assessing the stage of infection is the determination of serum ALT and the quantification of HBV DNA. ALT levels are a measure of liver inflammation and disease activity. ALT determination should be performed at every monitoring visit. HBV DNA levels are a measure of viral replication and can be used to support treatment decisions. After the initial diagnosis of chronic HBV infection, HBV DNA determination should be performed every 3-6 months in the first year post-diagnosis to define the phase of the infection or until the treatment indication has been confirmed. Initial monitoring is crucial to detect fluctuations in HBV DNA and ALT levels, particularly in HBeAg-negative individuals who initially present with very low HBV DNA levels,[93,94] as they may be overlooked for treatment indications. Long-term studies on individuals with HBeAg-negative infection (inactive HBV carriers)[94,95] or individuals afer spontanous HBeAg/anti-HBe seroconversion[96] indicate that while most remain in remission, reactivation to hepatitis can occur in approximately 15-33% over a follow-up of up to 11.5 years, with a higher risk in individuals with HBV DNA >2,000 IU/ml,[94] and those who undergo HBeAg/anti-HBe seroconversion at an older age (particularly >40 years).[97] Studies assessing the risk of disease progression, including HCC, in individuals with low HBV DNA levels (<20,000 IU/ml) have identified elevated ALT during follow-up as a key predictor of progression.[94,98–100]

If ALT values are below the upper limit of normal (ULN), HBV DNA is <2,000 IU/ml, quantitative HBsAg is <1,000 IU/ml in genotype D individuals and <100 IU/ml across all HBV genotypes, and there is no evidence of fibrosis, the positive predictive value for the diagnosis of HBeAg-negative chronic HBV infection is high.[9,46] In these cases, following the initial assessment, monitoring intervals may be extended.

Although spontaneous HBsAg seroclearance is unusual in chronic HBV infection, its likelihood increases with age and annual HBsAg monitoring is recommended to detect such events. Integrating quantitative HBsAg measurement into diagnostic protocols post-diagnosis improves the identification of the phase of infection and allows for more precise patient management strategies.[9]

Monitoring of HBeAg and anti-HBe is important in HBeAg-positive individuals as seroconversion can occur sporadically and represents a change in the phase of infection. Spontaneous HBeAg/anti-HBe seroconversion can occur at any time up to the age of 30-40 years (mean age 31 years), thereafter occuring less frequently.[101] After HBeAg/anti-HBe seroconversion, monitoring of HBV DNA and ALT remains important, as mutations in the precore or basal core promoter region that affect HBeAg expression lead to immunologic escape and HBeAg-negative hepatitis.[102] In contrast, spontaneous HBeAg/anti-HBe seroconversion without need for subsequent antiviral therapy is associated with a high rate of future HBsAg seroclearance (38-45% in 25 years).[103,104]

HCC risk prediction models consider factors such as age, sex, HBeAg status, serum HBV DNA levels, ALT, quantitative HBsAg levels.[105] Therefore, routine monitoring should systematically include these parameters, as outlined in Table 7. Besides ALT and viral markers, monitoring should also include non-invasive measurements to detect fibrosis progression. The frequency and intervals of fibrosis progression monitoring depend on the phase of infection. Patients with a stable condition may have LSM repeated at 2-3 year intervals to assess liver fibrosis progression.[106] Controlled attenuation parameter for hepatic steatosis is available simultaneously with LSM in the same VCTE examination. Controlled attenuation parameter is useful to diagnose coexisting steatotic liver disease (SLD), yet it is not as prognostically important as LSM to predict hepatic decompensation[107] or HCC.[108]

Notably, HBsAg-positive patients with compensated cirrhosis who are not receiving therapy because their HBV DNA levels remain persistently below the LOD require close monitoring at least every 6 months, including comprehensive HCC surveillance (Table 7).

By following a structured monitoring protocol, healthcare providers can effectively track disease progression, detect complications early, and adjust interventions to improve patient outcomes. When determining monitoring intervals, it is essential to consider potential phase transitions, which may be triggered by factors such as steroid use or aging-related comorbidities like changes in host immunity. Prolonged intervals between clinical visits can delay detection, as these risks often go unnoticed due to unreliable records, patient non-disclosure, or limited awareness among non-specialists. Educating individuals with chronic HBV infection about their risks and the importance of regular follow-up empowers them to take an active role in their care. Effective collaboration between healthcare providers and hepatology specialists is essential to optimise patient management and ensure timely adjustments to monitoring as well as treatment strategies.

Treatment goals

What are the goals of antiviral therapy for chronic HBV infection?

Statement

- The clinical goal of treating chronic HBV infection is to reduce morbidity (cirrhosis, hepatic decompensation, liver failure, HCC) and improve survival.

Since clinical endpoints such as cirrhosis, end-stage liver disease and HCC manifest over a longer period of time, surrogate markers are instrumental in defining treatment success **(strong consensus):**

- Persistent suppression of HBV DNA (preferably undetectable HBV DNA) is the primary goal of antiviral therapy.
- HBsAg loss is the ultimate goal of therapy.
- Normalisation of ALT is an additional endpoint.

Additional goals of antiviral therapy are **(strong consensus):**

- Confirmed loss of HBeAg and seroconversion to anti-HBe antibodies (for HBeAg-positive patients) in combination with HBV DNA <2,000 IU/ml can serve as an intermediate treatment endpoint.
- Improvement of liver fibrosis
- Improvement of HBV-associated extrahepatic manifestations
- Improvement of health-related quality of life and patient-reported outcomes
- Prevention of HBV transmission
- Prevention of HBV reactivation and/or hepatitis

HBV DNA suppression

HBV DNA >2,000 IU/ml is associated with an increased risk of developing liver cirrhosis, end-stage liver disease and HCC.[109,110] The relationship between serum HBV DNA level and HCC risk is a non-linear dose-response relationship, with a more significant increase in HCC risk at serum HBV DNA levels >200,000 IU/ml compared to the risk observed between 2,000 IU/ml and 200,000 IU/ml, while the risk is very low at levels <2,000 IU/ml.[111,112]

Sustained HBV DNA suppression after a finite treatment course of interferon-alfa (IFNα) or PEG-IFNα, or maintained HBV DNA suppression with NAs, is associated with the prevention or reduced risk of cirrhosis, hepatic decompensation, HCC, liver transplantation and death.[113]

Caucasian patients with chronic HBV infection and compensated liver disease treated with long-term entecavir (ETV) or tenofovir showed excellent overall and liver-related 8-year survival, which was similar to that of the general population. HCC was the main factor affecting their overall mortality and the only factor affecting their liver-related mortality.[114] Sustained suppression of HBV DNA is associated with an improvement in liver histology. After 5 years of treatment with ETV or tenofovir, improvement in liver fibrosis was observed in most patients and there was even reversal of Ishak F5/6 fibrosis/cirrhosis in some patients.[115,116]

The strongest evidence for the effect of HBV DNA suppression by NA therapy compared to no treatment on the prevention of HCC and death is available for patients with cirrhosis.[113,117]

In patients without cirrhosis, while antiviral therapy has been shown to reduce the risk of cirrhosis,[118] many studies with follow-up periods of around 5 years likely had insufficient duration and sample sizes to demonstrate a significant effect on preventing HCC and death.[118] However, one retrospective study with a follow-up of 8 years showed that TDF was associated with an HCC risk reduction of 73% in patients without cirrhosis.[119]

Even if the effects of therapy on clinical outcomes cannot be consistently demonstrated for all subgroups to the highest standard of evidence to date, the solid data demonstrating the positive effects of antiviral therapy make future prospective, placebo-controlled trials ethically untenable and impractical.

However, there is no conclusive evidence for a specific HBV DNA threshold that should be reached during therapy. Ideally, HBV DNA levels should be reduced to undetectable levels (<20 IU/ml) during or after antiviral therapy. It is widely accepted that only partial suppression of HBV DNA – due to poor adherence or non-response – increases the risk of viral resistance, progression

Table 7. Monitoring intervals for HBsAg-positive individuals who are not receiving antiviral treatment*.

Population	Monitoring
HBeAg-positive infection[1]	• ALT every 6 months[2] • HBV DNA every 6 months • HBsAg quantitative every 12 months • HBeAg//anti-HBe every 6-12 months • Non-invasive fibrosis assessment every 12-24 months based on clinical assessment
HBeAg-negative infection (HBV DNA <2,000 IU/ml) [1]	• ALT every 12 months[3] • HBV DNA every 12 months[4] • HBsAg quantitative every 12 months[4] • Fibrosis assessment every 2-3 years
HBeAg-negative infection (HBV DNA ≥2,000–20,000 IU/ml) [1]	• ALT every 6 months • HBV DNA every 6 months • HBsAg quantitative every 12 months • Fibrosis assessment every 12-24 months based on clinical assessment • If stable for ≥3 years, monitoring intervals can be extended
HBeAg-negative infection (patients with compensated cirrhosis, undetectable HBV DNA and normal ALT) [1]	• ALT every 6 months • HBV DNA every 6 months • HBsAg quantitative every 12 months • HCC surveillance every 6 months • Fibrosis assessment is not required but LSM and platelet count can be used to assess the risk of clinically significant portal hypertension and the need for EGD surveillance[85]

ALT, alanine aminotransferase; EGD, oesophagogastroduodenoscopy; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

*Patients with a strong indication for treatment (see section "Treatment goals") are not discussed here. Monitoring intervals may be influenced by each country's healthcare policies and available resources. While the recommended monitoring intervals are based on expert panel consensus, the evidence for specific timeframes remains limited.

[1]After the initial diagnosis of chronic HBV infection, monitoring should be performed every 3-6 months in the first year post-diagnosis to define the phase of the infection.

[2]In individuals >30 years (if not yet on treatment) consider closer monitoring every 3-6 months.

[3]Monitoring intervals may be adjusted based on individual risk factors, with shorter intervals recommended in uncertain situations, particularly for patients at risk of phase transition.

[4]Monitoring interval can be extended in cases where the HBeAg-negative infection phase is clearly defined.

of liver disease and HCC.[120,121] Achieving undetectable HBV DNA levels is particularly important in patients with advanced fibrosis and especially cirrhosis. Patients with compensated cirrhosis and low-level viraemia (HBV DNA 20-2,000 IU/ml) may be at a higher risk of HCC and hepatic decompensation than those with undetectable levels of HBV DNA (regardless of whether they are on antiviral therapy or untreated).[122–126] However, some studies documented conflicting results. A Korean study of 567 untreated patients with compensated cirrhosis demonstrated that episodic low-level viraemia did not increase the risk of disease progression compared to those with undetectable HBV DNA.[127] Similarly, another study involving over 2,300 multi-ethnic patients with compensated cirrhosis from Korea, Singapore, and Japan showed that untreated patients with low-level viraemia had similar outcomes (hepatic decompensation, HCC) compared to those with undetectable HBV DNA (either spontaneous or during NA treatment).[128]

HBsAg loss

Loss of HBsAg (post therapy) is the ultimate goal of treatment, is the defining feature of functional cure of HBV infection,[55] and is associated with an improved prognosis. In Asian studies, loss of HBsAg has been associated with a lower risk of HCC, especially when it occurs before the age of 50, compared to individuals who do not achieve HBsAg loss.[129–131] A systematic review also showed that HBsAg loss correlates with lower rates of incident cirrhosis, hepatic decompensation, and overall and liver-related mortality, though there was substantial heterogeneity across studies for all outcomes.[132]

However, a study from Alaska found no association between HBsAg seroclearance and reduced HCC risk. Notably, the four patients with HBsAg loss who developed HCC were older at study entry (median age 52.7 years) compared to those who did not develop HCC (median age 28.8 years),[133] underscoring the importance of achieving HBsAg loss at a younger age.

An additional benefit of HBsAg loss is the possibility of discontinuing NA therapy. Achieving confirmed HBsAg loss (HBsAg loss is confirmed by repeated measurement on two occasions 6 months apart) after therapy, with or without the development of anti-HBs, and undetectable HBV DNA, represents a functional cure.[55,134] At the 2022 American Association for the Study of Liver Diseases (AASLD)/EASL Endpoint Conference, it was recommended to define functional cure of HBV as HBV DNA levels below the LOQ (<10 IU/ml), while acknowledging that occasional "blips" in HBV DNA detection may still occur, even after HBsAg loss.[55] Consistent with the AASLD/EASL recommendations, the panel emphasised that anti-HBs is not required to define functional cure, as HBsAg loss is maintained in over 90% of patients with or without anti-HBs during long-term follow-up with currently approved therapies.[129,135,136]

HBeAg/anti-HBe seroconversion

HBeAg/anti-HBe seroconversion following IFNα therapy has been associated with a favourable prognosis, comparable to that of individuals with HBeAg-negative chronic infection.[137] A long-term Asian cohort study with 15 years of follow-up reported a lower incidence of cirrhosis and HCC in patients who achieved IFNα-induced HBeAg/anti-HBe seroconversion compared to both IFNα-treated patients who did not achieve seroconversion and untreated controls.[138] However, some studies have not demonstrated improved outcomes with HBeAg/anti-HBe seroconversion compared to untreated controls. In one study, 89%

of patients remained HBV DNA-positive post-seroconversion, though HBV DNA levels were not quantified, and precore/basal core promoter mutations were not analysed, leaving the potential progression to HBeAg-negative hepatitis unaddressed.[139] Therefore, HBeAg/anti-HBe seroconversion should be accompanied or followed by sustained HBV DNA suppression to <2,000 IU/ml, or ideally below the LOD. During NA treatment, HBeAg/anti-HBe seroconversion can be used as a criterion for discontinuing therapy if HBV DNA is undetectable, but relapses (often severe) are common.

Additionally, low HBsAg levels can further refine this endpoint. The 2022 AASLD/EASL Endpoint Conference proposed a sustained HBsAg level of <100 IU/ml, combined with HBV DNA <LOQ after 24 weeks without therapy, as an alternative intermediate endpoint or "partial cure" for emerging finite therapies.[55] HBsAg levels <100 IU/ml are associated with subsequent HBsAg loss and a reduced risk of relapse after discontinuing NA therapies, and could be particularly relevant in this context.

ALT

Achieving persistent virological suppression usually leads to normalisation of ALT levels. Real-world studies of large patient cohorts, consisting of 21,182[140] and 4,639[141] patients receiving TDF or ETV, respectively, have shown that early ALT normalisation during NA treatment is linked to a reduced risk of hepatic events and HCC, regardless of baseline steatosis, cirrhosis, or virological response during treatment. If ALT levels remain elevated despite undetectable HBV DNA, it is important to investigate other potential causes, such as steatohepatitis or chronic HDV infection. Patients with undetectable HBV DNA, but who continue to have elevated ALT levels, are less likely to have fibrosis regression.[142] It is important to note that a subset of treatment-naïve individuals with normal ALT levels may still have significant or advanced fibrosis.[143] Therefore, a normal ALT level should not exclude the possibility of antiviral therapy or substitute for a thorough fibrosis assessment.

HBV-associated extrahepatic manifestations

HBV infection can lead to extrahepatic manifestations such as mixed cryoglobulinemia vasculitis, serum sickness-like syndrome, non-rheumatoid arthritis, rheumatoid arthritis, panarteritis nodosa, glomerulopathies, or non-Hodgkin lymphoma that influence morbidity, quality of life, and mortality.[144–147] However, the frequency of extrahepatic manifestations in HBV infection is considerably lower than that observed in HCV infections.

Thus, the goal of antiviral treatment is to improve extrahepatic symptoms. However, there are no established threshold values for HBV markers that predict improvement in extrahepatic manifestations, and evidence remains limited on whether antiviral therapy alone can fully reverse these conditions. Immunomodulatory and immunosuppressive agents (such as high-dose IgG, rituximab, high-dose corticosteroids and plasmapheresis) are usually required (in addition to antiviral therapy) to treat the major renal, neurologic and haematologic manifestations observed.[144–146] Therefore, NA therapy should always be employed to address HBV-related extrahepatic manifestations and at the same time prevent reactivation when immunosuppressive therapy is used.

Impact on health-related quality of life and patient-reported outcomes

Reducing the clinical burden of chronic hepatitis B, such as hepatitis and fibrosis, and preventing cirrhosis and HCC through antiviral treatment will also improve the health-related quality of life (HRQoL) of individuals with chronic hepatitis B.[148] HRQoL encompasses the physical, psychological, and social aspects of well-being directly related to health conditions and their management. Studies have also explored the broader patient-reported outcomes (PROs) associated with chronic HBV infection. PROs represent the subjective experiences and perceptions of patients, including their psychological and social well-being, which extend beyond measurable clinical parameters. Recent research has specifically highlighted the significant psychosocial burden of HBV, demonstrating its profound effects on HRQoL and PROs, extending beyond the direct clinical impact.[149–152] However, the influence of social and religious backgrounds on these outcomes remains insufficiently studied and requires further investigation.

Discriminatory experiences can manifest at different stages of life and affect education, employment opportunities, sexual life and choice of partner. Individuals living with chronic HBV infection are often afraid of potentially transmitting the virus to their families, partners and friends, which can jeopardise their relationships and trigger fears of rejection. These psychosocial factors contribute to the overall burden of disease and significantly negatively impact both HRQoL and PROs.

In one small study, workplace discrimination and limited career choices were documented as contributing factors to diminished HRQoL among individuals with HBV infection. Even treated patients reported lower scores in general health perception and limitations in daily activities due to chronic HBV infection, reflecting the broad impact on both HRQoL and PROs.[153]

Nevertheless, patients and physicians should also be aware that extending the indication of therapy with the idea of improving HRQoL and PROs is based on little evidence to date and patients and physicians should weigh the potential benefits of therapy against its limitations, such as socioeconomic burden, drug-related side effects (*e.g.* bone and kidney disease in the case of TDF), the emergence of resistant mutations (albeit low) and the need to take medication daily, especially considering that the duration of therapy in the majority patients will be long term. A recent study has highlighted the importance of functional cure, which is rarely achieved with current therapies, in reducing social stigma and self-stigma and significantly improving the HRQoL of individuals living with HBV.[149]

While improving HRQoL and PROs is a desirable goal of the management of chronic HBV infection, evidence to support initiating therapy solely for this purpose remains limited.

Prevention of transmission

Minimising HBV transmission is a key treatment goal to prevent new infections. For individuals at risk of HBV transmission, such as healthcare workers, HBV DNA levels should be suppressed to <2,000 IU/ml, and to <200 IU/ml for those involved in exposure- or injury-prone activities for optimal prevention of transmission.[154] However, one study suggested that HBV transmission by needlesticks is unlikely to occur with HBV DNA levels <2 million IU/ml[155]

To prevent MTCT, HBV DNA levels at birth should ideally be <200,000 IU/ml, provided the newborn receives appropriate active-passive immunisation. If vaccination cannot be ensured, lower HBV DNA thresholds should be considered as a precautionary measure. Addressing the fear of transmitting HBV to close contacts and family members is crucial, and treatment aimed at preventing transmission can help alleviate these concerns. More important, however, is the dissemination of information and education about HBV prevention through vaccination and the interpretation of laboratory results, noting that the risk of transmission is low when HBV DNA is low (<2,000 IU/ml).[156]

Prevention of reactivation

HBVr, a risk for both HBsAg-positive and HBsAg-negative/anti-HBc-positive individuals due to persistent cccDNA, is increased under immunosuppression but can be effectively prevented with antiviral therapy (for details, see section "Prophylaxis of HBV reactivation").

Treatment indications

Which patients with chronic HBV infection should be treated?

Statement

- In principle, all HBsAg-positive individuals with detectable HBV DNA are candidates for antiviral therapy. The indication for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage and risk of liver disease progression and HCC **(strong consensus).**

Recommendations

- Patients with HBeAg-positive or HBeAg-negative chronic hepatitis B, HBV DNA level ≥2,000 IU/ml and elevated ALT (>ULN) and/or significant fibrosis should receive antiviral therapy **(LoE 1, strong recommendation, strong consensus).**
- Patients with cirrhosis should be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT **(LoE 3, strong recommendation, strong consensus).**
- Patients with advanced liver disease (corresponding to Metavir fibrosis score ≥F3 on liver histology or defined by a LSM > 8 kPa) can be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT **(LoE 5, weak recommendation, strong consensus).**
- Patients with persistently low HBV DNA (<2,000 IU/ml) and persistently elevated ALT (>ULN) can be treated. However, it should be considered that other liver diseases may also be implicated **(LoE 5, weak recommendation, consensus).**

Statement

- Individuals with HBeAg-positive or HBeAg-negative chronic HBV infection require a personalised assessment to determine the appropriate treatment indication (details see next two recommendations) **(strong consensus).**

The use of antiviral therapy to achieve long-term HBV DNA suppression leads to significant improvements in clinical outcomes, including the prevention of disease progression and HCC,[113,117,157] reversal of fibrosis and cirrhosis,[115,116] clinical recompensation in advanced liver disease,[158–160] and enhanced survival.[113] Given these findings, it seems obvious to consider antiviral therapy for all individuals with chronic HBV infection and active viral replication. Indeed, early initiation of treatment is a basic principle of infectious disease medicine, as it aims to prevent complications arising from ongoing viral replication. Expanding treatment indications to all HBV DNA-positive individuals may optimise the cascade of care and minimise missed treatment opportunities. Furthermore, current antiviral treatments with potent NAs are highly safe and widely available as generics in most countries.

However, the question of whether all HBV DNA-positive individuals should be treated is complex and still debated, as chronic HBV infection is heterogeneous and encompasses a wide range of clinical scenarios, including individuals who are not at risk of disease progression. An accumulation of data has shown that HBeAg-negative individuals with chronic HBV infection, formerly named "inactive carriers" have a very low risk of HCC.[5,161] In addition, HBsAg loss is rarely achieved with NA therapy (≤0.33% annually,[129,162]), and long-term treatment with strict adherence to daily therapy is usually required. Finally, the feasibility of a treat-all approach is uncertain, especially in settings where healthcare systems are overwhelmed with limited resources.

Therefore, prioritisation of treatment still depends on the individual's risk of disease progression and HCC, as indicated by virological and host factors. Most current evidence is indeed available for the immune-active phases (*i.e.* biochemical hepatitis) of chronic HBV infection[5,113] and decision-making in other common and sometimes difficult-to-define settings (*e.g.* individuals falling outside the defined phases, formerly called the "grey zone" or "intermediate phase") mostly depends on indirect evidence, albeit which increasingly favours earlier treatment in many situations[7].

The level of HBV replication, measured by HBV DNA, represents the most important parameter for assessing the risk of disease progression and HCC. The REVEAL studies conducted in Asia have shown that the risk of cirrhosis and HCC increases significantly in individuals with increasing HBV DNA levels >2,000 IU/ml.[109,110] While these studies primarily included individuals >30 years, predominantly HBeAg-negative, with genotypes B and C (mostly vertical transmission), their findings should be considered in therapeutic decisions, particularly

given the sizable HBV population in Europe originating from Asian countries, despite differences in genotypes and modes of transmission.

Systematic reviews confirmed a non-linear dose-response relationship between HBV DNA levels at baseline and the incidence of liver-related complications (cirrhosis and HCC) and deaths.[111] Among untreated individuals, the risk for cirrhosis and HCC is lowest if HBV DNA is <2,000 IU/ml. In HBeAg-negative individuals with low HBV DNA levels, HBsAg levels >1,000 IU/ml can serve as a marker indicating a higher risk for HCC.[9,163] In addition, HBcrAg has been suggested as a prognostic marker for occurrence and recurrence of HCC.[164,165] Other viral markers associated with HCC are distinct HBV genotypes and the presence of core promoter mutations (Table 8). The presence of HBeAg in individuals aged >30 years is consistently reported as a prognostic factor[163,166,167] and is included in the REACH-B risk score.[168] However, in both HBeAg-positive and HBeAg-negative individuals with chronic HBV infection, different clinical settings present varying risks for disease progression and HCC.

Besides viral factors that are linked to disease progression, host factors are associated with HCC risk and should be considered for treatment indication as well.

Cirrhosis is the strongest predictor of HCC,[161,167,169] even after viral suppression.[170,171] Thus, HBV DNA-positive patients with cirrhosis should receive antiviral therapy independent of HBV DNA level, although the evidence regarding whether low-level viraemia (<2,000 IU/ml) or undetectable HBV DNA makes a difference to outcomes is conflicting.[122–125,127,128] Nevertheless, due to the high risk of HCC in cirrhosis and the safety of NA therapy, treating all patients with detectable HBV DNA and cirrhosis is recommended, especially as this can prevent ALT flares in the event of possible HBV DNA fluctuations.

In cases of uncertainty, *e.g.* non-invasive fibrosis assessments indicate high values that have not yet reached cirrhotic levels (LSM thresholdssee Table 6), and presence of additional risk factors for disease progression, treatment should be considered for any patient with advanced liver fibrosis (equivalent to Ishak ≥F4 or Metavir ≥F3) with detectable HBV DNA <2,000 IU/ml. A study of US veterans with chronic hepatitis B (albeit on therapy) showed that in multivariate analysis, only baseline FIB-4 was consistently associated with long-term risk of cirrhosis or HCC.[172]

The most recent WHO guideline recommends treating patients with significant fibrosis (equivalent to Ishak ≥F3 or Metavir ≥F2), regardless of HBV DNA levels. However, the evidence for this recommendation in patients with low viraemia (<2,000 IU/ml) is weak. A prospective Danish study documented a very low risk of disease progression over 5 years in individuals with chronic HBV infection and LSM <10 kPa.[173] However, in uncertain situations, especially when additional risk factors are present (Table 8), treatment may be warranted, particularly when LSM is not available and fibrosis determination is based on other markers (*e.g.* FIB-4 or APRI).

Elevated ALT levels are associated with an increased risk of HCC.[163,166,167] Evidence suggests that antiviral therapy is warranted even in patients with minimally elevated ALT, when combined with HBV DNA ≥2,000 IU/ml, owing to its potential benefits in reducing fibrosis progression, as demonstrated in the prospective TORCH-B study.[174] Therefore, antiviral treatment is recommended when serum ALT is elevated and HBV DNA ≥2,000 IU/ml. ALT values ≥40 U/L are generally considered elevated irrespective of sex and age.[5] A study demonstrated that using lower ALT cut-offs (30 U/L for men and 19 U/L for women) significantly enhances the prediction of liver-related adverse outcomes, including mortality, HCC, and decompensating liver events, in the general population.[175] Of note, ALT reference ranges vary between laboratories due to differences in chemical analysers and methods used to establish reference intervals.[176] While a universal normal value has not been defined herein, where local labs differentiate ULN thresholds by sex, these should be considered accordingly.

However, normal ALT levels (especially a single assessment) *per se* do not justify withholding treatment, owing to laboratory variabilities and individual fluctuations, particularly in HBeAg-negative individuals, and because they may misrepresent the severity of underlying liver disease.[177] Thus, normal serum ALT alone does not preclude the need for antiviral therapy.

In individuals with low HBV DNA levels (<2,000 IU/ml) and no signs of liver fibrosis but persistently elevated ALT (>ULN), treatment may be justified in uncertain situations. However, it is crucial to investigate other potential causes of ALT elevation, such as steatotic liver disease or coinfections with other hepatitis viruses like HCV or HDV.

The impact of cancer risk factors such as obesity,[178,179] metabolic syndrome,[180–182] type 2 diabetes mellitus (T2DM),[179,183] excessive alcohol consumption,[161] and cigarette smoking[181,184–187] on HCC risk in chronic HBV infection has been described but is still not always conclusive and sometimes even contradictory (Table 8). It is unclear if these factors independently increase the risk of HCC or accelerate the risk of HBV infection and whether antiviral treatment would reduce this risk, *e.g.* if HBV DNA is already low. The most conflicting data relate to SLD, with some data suggesting an increased risk of HCC,[188] while others report a lower risk and even a higher rate of spontaneous HBsAg loss.[180,189] Notably, SLD without systemic metabolic dysfunction may have a distinct impact. A recent study of over 8,700 individuals showed that while SLD was associated with a lower overall mortality risk, cumulative cardiometabolic risk factors increased the risk of all-cause, liver-related, and cardiovascular mortality in a dose-dependent manner among patients with chronic HBV infection and SLD. Additionally, the development of diabetes mellitus, hypertension, and weight gain during follow-up further exacerbated these risks.[182] This is consistent with previous studies showing that a higher metabolic risk factor burden is associated with increased risks of HCC, non-HCC cancers, and all-cause mortality in patients with chronic HBV infection.[180,181,190]

Age is another important risk factor for HCC. HCC risk increases in individuals over the age of 30-35[163,166] and varies by sex and ethnicity,[191] with men being generally at higher risk than women.[166,169]

Multiple studies have identified a positive family history of HCC as an independent risk factor for both the development and recurrence of HCC in all phases of chronic HBV infection. Therefore, individuals with a family history of HCC require more intensive HBV management.[192,193]

The association between family history and HCC risk suggests that genetic factors may play a role in HCC susceptibility. Ethnicity itself may therefore act as an additional risk factor due to inherited genetic predispositions. For example, birth in regions such as Africa and Oceania is linked to very early-onset

HCC.[194] However, sub-Saharan Africans with chronic HBV infection who relocate to Europe show a lower incidence of HCC, with risk factors resembling those of the general population.[195] After adjusting for age, studies indicate no significant differences in HCC incidence between Western and Eastern populations.[161] Therefore, additional factors may increase the risk of HCC in certain ethnic groups, including certain HBV genotypes[196,197] and environmental exposures such as aflatoxin or air pollution, which, when present in combination with HBV, has been shown to significantly increase the risk of HCC.[198–201]

In terms of genotype, genotype C has been associated with a higher risk of HCC than genotype B in individuals with chronic HBV infection in Asia.[105,196] In individuals from Africa (*e.g.* The Gambia), HBV genotype A has been identified as a risk factor for liver fibrosis[202] and HCC[199] compared with genotype E. In Alaska, genotype F was associated with the highest HCC risk.[197]

Africans and Asians may have a higher risk of HCC than Caucasians, likely due to a combination of factors, such as environmental factors, longer duration of infection due to higher rates of vertical transmission, and/or different HBV genotypes.

Antiviral therapy not only prevents disease progression but also helps reduce transmission, improve extrahepatic manifestations, and lower the risk of viral reactivation. Additionally, chronic HBV infection has been associated with a higher risk of developing extrahepatic malignancies.[203,204]

As a result, additional factors should be considered when determining the need for antiviral therapy, ultimately expanding the criteria for its use. Finally, a shared decision-making approach[205,206] is essential in hepatitis B treatment, encouraging collaboration between clinicians and patients to make joint decisions that combine clinical evidence with patient concerns and preferences. This process also considers the impact on HRQoL and PROs. Crucially, open discussions about the benefits and limitations of therapy are fundamental for addressing patient concerns, building trust, and promoting informed decisions that improve adherence and overall outcomes. Additionally, patients should be informed about the importance of addressing modifiable factors, such as smoking cessation, reducing excessive alcohol consumption, and managing relevant comorbidities, including metabolic dysfunction, to optimise long-term health.

In areas with limited access to HBV DNA testing, the WHO recommends, with low evidence, antiviral treatment with NAs for all HBsAg-positive individuals with persistently elevated ALT levels, with the benefit of reducing complications being deemed to outweigh the potential side effects. However, EASL strongly advocates the implementation of HBV DNA testing, preferably using reflex HBV DNA viral load testing in resource-limited settings, but recognises the WHO's practical approach when access to treatment is unlimited. However, it should be considered that this approach may pose challenges in settings where access to NAs remains limited, as prioritisation may not be possible.

Should patients with HBeAg-positive chronic HBV infection be treated?

Statement

- In young individuals (<30 years) with HBeAg-positive chronic HBV infection, persistently normal ALT levels, no significant liver fibrosis, no family history of HCC and no immunosuppressive condition, current clinical evidence does not support immediate antiviral treatment. However, the potential benefits of early therapy – such as reducing HBV DNA integration and clonal expansion – should be balanced against the need for strict adherence to long-term daily treatment and the difficulty of achieving rapid and complete viral suppression in patients with high viral loads **(strong consensus).**

Recommendations

- Individuals with HBeAg-positive chronic infection and an increased HCC risk should be treated **(LoE 3, strong recommendation, strong consensus).**
- Individuals with HBeAg-positive chronic infection and HBV-related extrahepatic manifestations should be treated **(LoE 4, strong recommendation, strong consensus).**
- Individuals with HBeAg-positive chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral treatment to prevent hepatitis **(LoE 2, strong recommendation, strong consensus).**
- Selected individuals with HBeAg-positive chronic infection can be treated to prevent HBV transmission **(LoE 3, weak recommendation, strong consensus).**
- In pregnant women with HBV DNA ≥200,000 IU/ml, antiviral therapy should be administered to prevent mother-to-child transmission (for a specific recommendation see "What are the treatment recommendations for pregnant HBsAg-positive women?") **(LoE 1, strong recommendation, strong consensus).**

Given that the level of HBV DNA has been identified as an independent risk factor for the development of cirrhosis and/or HCC, it is reasonable to consider that individuals with HBeAg-positive chronic HBV infection (formerly defined as "immunotolerant") might also benefit from antiviral therapy. Moreover, studies have shown that HBV DNA integration and immune dysregulation are key mechanisms of HBV-related liver carcinogenesis.[220] Furthermore, several studies have reported clonal hepatocyte expansion and T cell activity in individuals with HBeAg-positive chronic infection, including those aged <30 years.[220,221] Antiviral therapy has been shown to reduce the number of HBV DNA integrations and clonal hepatocyte expansion in patients who have achieved HBV DNA suppression with tenofovir.[222,223]

However, currently, there is limited clinical evidence that antiviral therapy reduces the incidence of cirrhosis or HCC, or provides a survival benefit in young individuals with HBeAg-positive chronic infection. The REVEAL study cohort was not representative of this population: all patients were older than 30 years, with 67% over 40, and 85% were HBeAg-negative.[109,110] The ATTENTION trial investigated whether individuals with moderate to high HBV DNA (4-8 $\log_{10}$ IU/ml) and normal ALT would benefit from antiviral NA therapy. Among 127 HBeAg-positive participants, no HCC cases were observed in the NA-treated group, while three cases occurred in the observation group. However, 22-24% of participants had a family history of HCC, and the median age (52 years in the NA group, 54 years in the control group) does not align with the typical "immunotolerant" phase.[224] While age is a key risk factor for HCC, evidence of increased risk in individuals under 30 years remains limited (Table 8).

Studies examining liver histology in young individuals with HBeAg-positive chronic infection and low-normal ALT levels show that significant histological changes are only observed in a minority.[225–227] A systematic review and meta-analysis of 11 studies reported that among HBeAg-positive individuals with chronic infection, 16.9% had significant liver fibrosis, 5.4% had advanced fibrosis, and 0% had cirrhosis, though there was notable heterogeneity among the studies.[228]

When starting NA treatment in HBeAg-positive individuals with a high viral load, achieving optimal viral suppression (HBV DNA <LOD) is a challenge[229] and strict treatment adherence is critical, as fulminant liver failure associated with ALT flares can occur in the event of uncontrolled treatment cessation. Of note, individuals with HBeAg-positive chronic infection can achieve spontaneous HBeAg/anti-HBe seroconversion without treatment, though the likelihood decreases with age.[97] In a prospective study of 240 participants, approximately 85% had developed anti-HBe by age 31, yet 15% of these individuals subsequently developed HBeAg-negative chronic hepatitis.[230] Another study found that individuals who achieved HBeAg/anti-HBe seroconversion before the age of 30 had a very low cumulative incidence of cirrhosis and HCC. In contrast, seroconversion after the age of 40 was associated with a significantly higher incidence of HBeAg-negative hepatitis, cirrhosis, and HCC over a mean follow-up of approximately 12 years. However, there was no significant difference in the frequency of HBeAg-negative hepatitis between individuals who seroconverted between 31 and 40 years of age and those who seroconverted before the age of 30.[97]

Importantly, the risk of HCC in HBeAg-positive individuals is highest among those with a moderate baseline viral load[207] and a new HCC risk score, PAGED-B, which incorporates moderate baseline HBV DNA levels (5-8 $\log_{10}$ IU/ml), has shown improved predictive accuracy over previous risk scores for HBeAg-positive individuals.[218] On the other hand, individuals with very high HBV DNA levels (>8 log IU/ml), usually individuals in the earlier phase of infection, exhibit the lowest HCC risk.[207] In line with this, HBV DNA levels correlate inversely with both APRI and FIB-4 scores in HBeAg-positive individuals.[231] With increasing age, HBV DNA levels may decline due to immune responses, but without spontaneous HBeAg/anti-HBe seroconversion, potentially leading to disease progression.

The different pretreatment baseline HBV viral load was also significantly associated with HCC risk despite antiviral treatment, with HBV DNA ≥8 log being associated with the lowest HCC risk.[232] The authors hypothesised that initiating antiviral treatment at an earlier point when patients have high baseline viral load would maintain the lowest risk of HCC over the duration of treatment. However, the available evidence has not clearly proven this hypothesis. One study showed that untreated individuals with HBeAg-positive chronic infection were at a significantly higher risk of HCC and death or need for liver transplantation than NA-treated patients with HBeAg-positive hepatitis. However, the average age of individuals with HBeAg-positive chronic infection in this study was 38 years, an age at which treatment would generally be considered, making its classification as an "immune-tolerant phase" inconsistent.[233]

Notably, when interpreting studies on HBeAg-positive infection, besides age, it is essential to consider comprehensive fibrosis assessment, as some studies included participants with low platelet counts. Additionally, family history of HCC and duration of follow-up should be taken into account, as these factors can influence disease progression and outcomes, potentially impacting the generalisability of the findings.

Several studies have identified key risk factors for disease progression and/or HCC in patients previously classified within the "intermediate" or "grey" zone.[7] These factors include age, sex, coinfection with HCV and/or HDV, excessive alcohol consumption, cigarette smoking, obesity, T2DM, HBV genotypes, or aflatoxin exposure (Table 8). As mentioned above, it remains unclear whether antiviral treatment would significantly reduce the risk of HCC in this population if the modifiable factors are still present. Several studies have shown that elevated ALT levels and low platelet counts are associated with disease progression in these cases. However, these factors are considered clear indications for treatment in this population. Several analyses also showed that HBeAg-positive individuals with ALT values in the upper normal range (men >30 U/L, women >19 U/L) are more likely to have significant histological changes that may justify antiviral therapy, especially if other risk factors are present.[6,226,234,235]

Extrahepatic manifestations have been documented in HBeAg-positive individuals[236–239] and this should be an indication for treatment regardless of the ALT level, especially as the treatment of extrahepatic manifestations usually requires additional immunosuppressive therapy.[144–146]

HBeAg-positive chronic HBV infection typically presents with HBV DNA levels ≥20,000 IU/ml. Given the correlation between viral load and transmission risk, antiviral therapy should be considered to prevent transmission, notably in pregnant women and healthcare workers (see above).

Pregnant women with HBeAg-positive chronic infection and HBV DNA >200,000 IU/ml should be treated to prevent MTCT (details see "What are the treatment recommendations for pregnant HBsAg-positive women?").

Antiviral therapy is indicated to suppress HBV replication in individuals with HBeAg-positive chronic infection who otherwise could be excluded from occupational activities (*e.g.* medical practitioners, nurses) so that continued employment is possible. Transmission has mainly been reported during exposure- or injury-prone procedures (*e.g.* thoracic surgeons, oral surgeons and gynecologists) and has almost always occurred at HBV DNA levels >20,000 IU/ml (see above).[154,155] Transmission of HBV, particularly in the healthcare sector, is thus considered unlikely at HBV DNA

Table 8. Risk factors that have been associated with HCC risk in individuals with chronic HBV infection.

Risk factor	Comments and references
Viral factors	
HBV DNA*	Non-linear risk starting with >2,000 IU/ml[111,161,163] Highest risk in HBeAg-positive individuals with 6-7 log_{10} IU/ml (lower risk if HBV DNA is ≥8 log_{10})[207]
HBsAg	High HBsAg (≥1,000 IU/ml) in HBeAg-negative individuals[163]
HBeAg*	In overall analyses, positive HBeAg (in individuals older than 30 years) is associated with HCC[163,166,167]
HBcrAg	Prognostic marker for occurrence and recurrence;[164,165,208] importance of HBcrAg in HBeAg-negative infection[209]
HBV genotype	Genotype C,[197] genotype A (*e.g.* in The Gambia[199]), genotype F in Alaska native persons,[197] genotype D in India[210]
Core promoter mutations	Present[169,211]
Viral coinfections	HDV,[212,213] HCV,[167,184,214] HIV[215]
Host factors	
Cirrhosis	Strongest risk factor for HCC[161,167,169] HCC risk remains after viral suppression[170,171]
Low platelets*	Indicator for cirrhosis[195]
Family history of HCC	Independent risk factor in all phases of chronic HBV infection[192,193,216]
Age*	HCC risk increases with age, with most studies focusing on individuals older than 30 years.[161,185] Evidence increases with age ≥35,[166] ≥40,[163] ≥50.[167] HCC risk varies in different age groups for men and women and for different ethnic groups[191]
Sex*	Higher risk among males[161,166,169,185]
ALT*	Elevated (or in the upper normal range)[163,166,167,185]
Type 2 diabetes mellitus (T2D)	T2D is independently associated with HCC.[183,217,218] Glycaemic burden is associated with HCC.[219] T2D is included in HCC risk scores[168,218] However, one analysis showed that T2D was not independently associated with HCC in chronic HBV infection[179]
Steatotic liver disease (SLD)	Conflicting data: - Increased risk of HCC and cirrhosis[188] - Lower risk of HCC, cirrhosis, and mortality[180,182,189]
Body mass index (BMI)	High BMI ≥30,[179] HR stronger in females[178]
Metabolic syndrome	Multiple (≥3) metabolic risk factors or increasing burden of metabolic dysfunction are associated with HCC[180–182,190]
Cigarette smoking	Present[181,184–187]
Alcohol consumption	Heavy alcohol intake ≥60 g/d[161]
Ethnicity	Evidence low or absent: - Birth in Africa/Oceania: linked to very early-onset HCC[194] - Sub-Saharan Africans with HBV in Europe: lower HCC incidence, similar risk factors to general population[195] - Western *vs.* Eastern studies: no significant age-adjusted differences in HCC incidence[161]
Environmental factors	
Aflatoxin B1 (AFB1)	In high-exposure areas, AFB1 and HBV synergistically increase HCC risk; reducing aflatoxin exposure could lower HCC cases by 23%[198]
Air pollution	Association between fine particulate matter and HCC[200,201]

ALT, alanine aminotransferase; EGD, esophagogastroduodenoscopy; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.
*Part of the REACH-B score.

levels <2,000 IU/ml and in particular <200 IU/ml for exposure-prone procedures, and thus should not justify a ban from the profession.

Social aspects, such as stigmatisation of the infected person or sexual practices (multiple sexual partners), which are associated with an increased risk of transmission, may also justify antiviral therapy.

Should patients with HBeAg-negative chronic infection be treated?

Statement

- Patients with HBeAg-negative chronic infection (persistent HBV DNA <2,000 IU/ml, persistently normal ALT, no signs of liver fibrosis) have a low risk of disease progression and transmission and usually do not require immediate antiviral treatment **(strong consensus).**

Recommendations

- Individuals with HBeAg-negative chronic infection and a high risk of HCC should be treated **(LoE 3, strong recommendation, strong consensus).**
- Individuals with HBeAg-negative chronic infection and HBV-related extrahepatic manifestations should be treated **(LoE 4, strong recommendation, strong consensus).**
- Individuals with HBeAg-negative chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral therapy to prevent HBV reactivation/hepatitis **(LoE 2, strong recommendation, strong consensus).**
- Selected individuals with HBeAg-negative chronic infection can be treated to prevent HBV transmission **(LoE 4, weak recommendation, consensus).***

Individuals with chronic HBeAg-negative infection who generally do not require treatment are those with persistently low viral replication, previously referred to as "inactive HBsAg carriers." These individuals are characterised by persistently low HBV DNA levels (<2,000 IU/ml), normal ALT levels, and absence of significant fibrosis, placing them at minimal risk for HBV-related morbidity and mortality.[34,240,241]

Notably, individuals meeting these criteria exhibit a relatively high cumulative rate of spontaneous HBsAg loss – the ultimate endpoint of HBV infection – over the natural course of the disease.[104,242,243] The annual incidence of HBsAg loss in this population is approximately 2%, increasing further (up to 7%) in older individuals and those with low HBsAg levels (<100 or <250 IU/ml).[242,244] This rate is significantly higher than in NA-treated patients with chronic HBV infection, where the reported average annual rate is ≤0.33%.[129,162] However, direct comparisons between these groups remain challenging, and it is still unclear whether NA treatment influences the rate of HBsAg loss.

HBeAg-negative individuals with HBV DNA levels between 2,000–20,000 IU/ml who maintained persistently normal ALT levels for at least 3 years typically exhibit minimal evidence of significant liver fibrosis or disease progression.[245] A systematic review, mainly based on Asian data, found that among individuals with viral loads of 2,000-20,000 IU/ml and normal ALT, the HCC incidence rate was low.[7] A cohort study from West Africa reported a very low risk of liver complications and an age-standardised mortality rate similar to that of the general population among individuals with chronic HBV infection and low median viral load and normal ALT levels.[241]

Thus, patients meeting these criteria may not initially require immediate antiviral treatment. However, monitoring intervals (HBV DNA, ALT) should be more frequent than in patients with HBV DNA levels persistently <2,000 IU/ml.

HBeAg-negative individuals with an HBV DNA of ≥20,000 IU/ml and normal ALT should be considered for antiviral therapy. Data from the Asian REVEAL study group support the association of HBV DNA and HCC or cirrhosis risk, especially in HBeAg-negative patients with HBV DNA ≥20,000 IU/ml[109,110] as confirmed by two meta-analyses.[111] The prospective ATTENTION trial evaluated whether individuals with HBV DNA levels between 4 and 8 $\log_{10}$ IU/ml (83% HBeAg-negative) and normal ALT would benefit from antiviral NA therapy. The study demonstrated that NA treatment significantly reduced the incidence of serious liver-related events.[224] Data from the WHO Africa region are limited; however, one longitudinal study from The Gambia found that, among treatment-naïve individuals with chronic HBV infection, an HBV DNA level >20,000 IU/ml was a predictor of liver disease progression, even after adjusting for sex and age.[241]

Certain subgroups of individuals with HBeAg-negative chronic infection, reported mainly in Asian cohorts, may have an increased risk of HCC compared to HBsAg-negative individuals, regardless of HBV DNA levels. Risk stratification may be conducted using quantitative HBsAg measurements. An HBsAg level of ≥1,000 IU/ml was associated with an increased risk of HCC in both HBeAg-negative individuals with HBV DNA <2,000 IU/ml and those with HBV DNA between 2,000 and 20,000 IU/ml. However, it is not clear from the studies whether these individuals had persistently normal ALT levels.[163,185,246] Moreover, this association has not yet been documented in European patients.[247] Also, the impact of antiviral treatment on reducing HCC risk in individuals with HBsAg ≥1,000 IU/ml and HBV DNA <2,000 IU/ml remains uncertain, since NA therapy has minimal effect on lowering HBsAg levels.[9] Novel biomarkers, such as HBcrAg, may help improve HCC risk prediction in individuals with chronic HBV infection. In treatment-naïve individuals in Japan, HBcrAg levels >2.9 $\log_{10}$ U/ml were identified as an independent predictor of HCC, outperforming HBV DNA levels for predicting HCC development.[248] Another study from Asia found that HBcrAg levels >4 $\log_{10}$ U/ml were an independent risk factor for HCC in individuals with intermediate viral loads (HBV DNA between 2,000 and 20,000 IU/ml).[208] Consistently, a large multicentre cohort study showed that an HBcrAg cut-off of 3.14 log10 U/ml effectively distinguished HBeAg-negative chronic hepatitis from HBeAg-negative chronic infection.[47] In summary, lower HBcrAg levels are generally favourable; however, a definitive cut-off for HBcrAg to guide antiviral therapy recommendations in the guidelines is not yet justified. Additionally, the assay's low detection sensitivity, particularly in HBeAg-negative individuals, remains a concern.

Assessment of liver fibrosis, preferably by non-invasive methods, is critical to determine whether significant or advanced fibrosis is present, which can be an indication for treatment in HBeAg-negative chronic infection despite normal ALT, although the supporting evidence is limited. In individuals with HBV DNA <2,000 IU/ml, normal ALT and significant fibrosis, other reasons for chronic liver disease should be ruled out. In untreated patients with minimal fibrosis, fibrosis status should be reassessed regularly based on their risk profile (LSM thresholds see Table 6).

As with HBeAg-positive individuals, additional HCC risk factors must be considered in HBeAg-negative patients (Table 8).

In addition to the increasing risk of HCC with age,[185] individuals aged ≥30 years have been identified as more likely to experience ALT elevation in HBeAg-negative chronic HBV infection.[249] It is important to note, however, that there is limited evidence on whether further viral suppression in HBeAg-negative individuals effectively reduces the risk of HCC if concomitant modifiable risk factors are not adequately managed. An increasing subgroup within this population are individuals with concomitant SLD. However, the evidence on SLD as an additional risk factor for HCC is controversial (Table 8), with the data even suggesting that SLD may be associated with a higher likelihood of HBsAg loss.[188,189]

Extrahepatic manifestations have rarely been documented in HBeAg-negative infections,[250] but if suspected, they should lead to treatment, especially since additional immunosuppressive treatment is usually required.[144–146]

In addition, prevention of reactivation of HBV replication and hepatitis is an important treatment indication in immunosuppressed patients with HBeAg-negative chronic infection (details see section "Prophylaxis of HBV reactivation").

The absence of HBeAg is usually associated with lower HBV DNA levels and thus a 10-fold reduction in the risk of transmission; however, it does not exclude the possibility of transmission. Cases of HBV transmission have been reported in this setting.[154,251] Therefore, treatment to prevent HBV transmission may be warranted in individuals with chronic HBeAg-negative infection, particularly healthcare workers who are often required to maintain HBV DNA levels <2,000 IU/ml or <200 IU/ml when performing exposure-prone procedures.

From a health equity perspective, antiviral treatment for individuals with chronic HBV infection living in LMICs should be based on at least one of the following tests: HBV viral load, ALT level, or liver fibrosis. While the CPG group recognises the challenges in accessing these tests in LMICs, there is currently insufficient evidence to recommend a universal test-and-treat strategy for all HBsAg-positive individuals in these settings.

Simplified treatment algorithm

To support clinical decision-making, we have developed a simplified treatment algorithm (Fig. 1) that avoids categorizing patients according to HBeAg status or traditional disease phases. It does not take into account the strength of individual recommendations and is intended to supplement the more detailed, phase-based guidance. This pragmatic approach is intended to facilitate the timely initiation of antiviral therapy, particularly in non-specialized settings.

Treatment

Which treatment options are recommended for patients with chronic HBV infection?

Statement

- Two different therapeutic options are recommended for the treatment of chronic HBV infection: NAs or PEG-IFNα **(strong consensus).**

Recommendation

- When choosing between NAs and PEG-IFNα as first-line treatments, the distinct characteristics of each treatment option (Table 9) and individual patient preferences should be comprehensively considered **(LoE 1, strong recommendation, strong consensus).**

NA therapy

NAs integrate into viral DNA during HBV replication, causing premature termination of the DNA chain and effectively

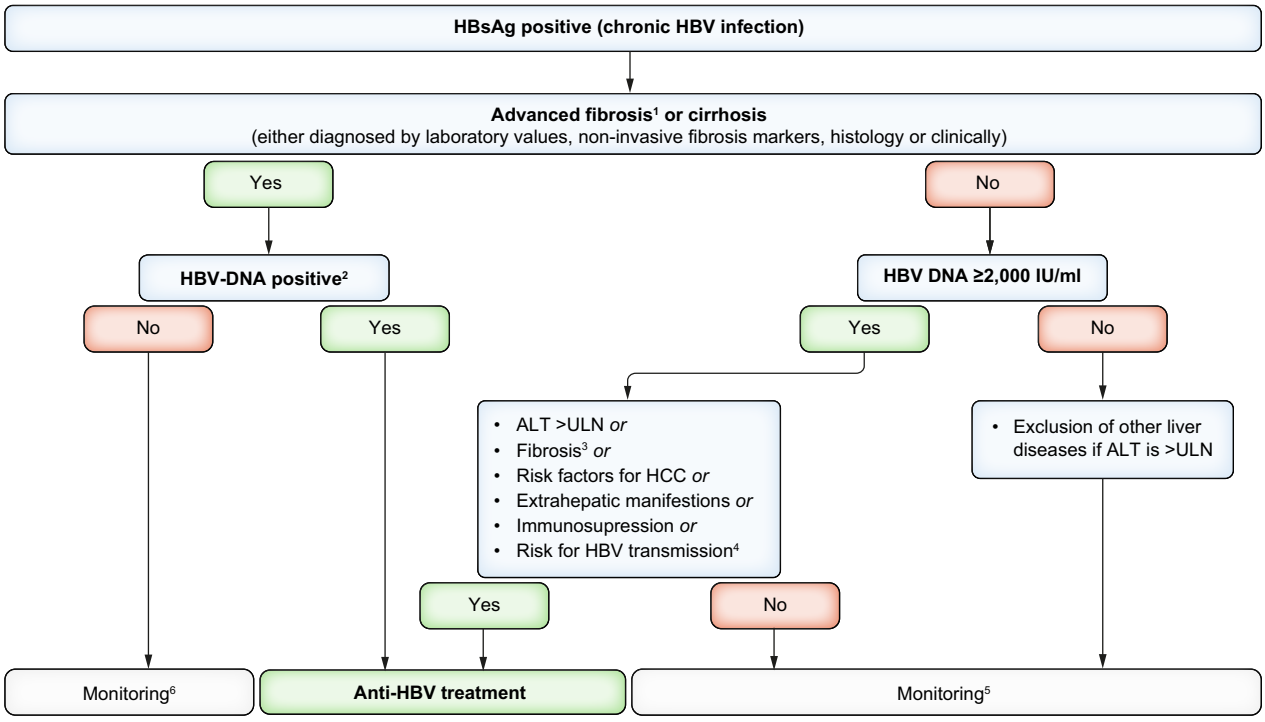

Fig. 1. Treatment indication for chronic HBV infection. [1]Equivalent of ISHAK F ≥4/Metavir F ≥3 (non-invasive assessment is preferred, LSM > 8 kPa). [2]Sensitive NAT assay (lower limit of detection <20 U/L). [3]Equivalent of ISHAK ≥F3/Metavir ≥F2 (non-invasive assessment is preferred, LSM > 7 kPa). [4]The threshold values for HBV DNA vary depending on the activity and risk of transmission. Important: Tenofovir in pregnant women with HBV DNA ≥200,000 IU/ml. [5]Anti-HBV treatment in HCC, HIV co-infection, extrahepatic manifestations, immunosuppression. [6]Anti-HBV treatment in immunosuppression. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LSM liver stiffness measurement; ULN, upper limit of normal.

preventing further viral replication. This inhibition reduces HBV DNA levels in the bloodstream. Approved NAs for the treatment of chronic HBV infection include lamivudine, adefovir dipivoxil, ETV, telbivudine, TDF, and TAF. These drugs are categorised by their resistance profiles into low-barrier NAs (lamivudine, adefovir dipivoxil, telbivudine) and high-barrier NAs (ETV, TDF, TAF). ETV, TDF, and TAF offer predictable, long-term antiviral efficacy, along with a favourable safety profile and the convenience of oral administration.[5]

The antiviral efficacy of NAs has been proven in numerous studies[113] and long-term data over more than 5 years are available for ETV, TDF and TAF (Table 10). The virological response (HBV DNA <LOD) in naïve patients with these NAs increases over time and is ≥85% after 5 years of treatment, with HBeAg-negative patients showing a higher response of ≥90% (Table 10).

Since NAs do not directly affect the HBV cccDNA transcriptional template, a modest decrease in cccDNA is observed after long-term NA therapy, most likely due to the indirect impact of NAs on *de novo* infections and intracellular replenishment coupled with the gradual dilution of the cccDNA pool through cell division.[253,254] Low rates of HBsAg loss on NA treatment are ascribed to the limited effect of NAs on the cccDNA template and to the significant contribution of HBV integration to HBsAg production, especially in HBeAg-negative individuals.[255,256]

The long-term suppression of HBV DNA by NA therapy can reduce liver inflammation and fibrosis, which ultimately helps to prevent disease progression, the development of cirrhosis and liver cancer and improves survival rates.

Histological improvement: prolonged NA therapy (3-5 years) can lead to improvement of liver histology, including regression of cirrhosis.[115,116,268]

Risk of HCC development: NA treatment significantly reduces the risk of HCC, in particular in patients with cirrhosis. This protective effect becomes apparent after maintained HBV DNA suppression for over a year.[113,117,157] In patients without cirrhosis, longitudinal studies have also shown that long-term viral suppression reduces the risk of HCC,[118,119] but the evidence in this case is less conclusive, mainly due to short follow-up and the low incidence rate in this setting. Risk scores can assist in determining appropriate surveillance intervals for patients on NA therapy (see section “HCC surveillance”).

Recompensation: in patients with decompensated cirrhosis, NA therapy can lead to significant clinical improvement, including reduced risk of HCC. Notable outcomes include decreases in MELD (model for end-stage liver disease) and Child-Pugh scores, along with enhanced survival rates.[158–160]

Improvement of survival: multiple studies, as summarised in a meta-analysis, have demonstrated a 50% reduction in mortality in patients with cirrhosis achieving viral suppression on NA therapy.[113]

Due to their excellent safety profiles, NAs are suitable for various HBsAg-positive populations, including those with fulminant or decompensated liver disease, liver transplant recipients, patients with extrahepatic manifestations, and for the prevention of HBVr in immunocompromised patients (see below). In addition, NAs are critical for preventing HBV transmission in individuals with high level viraemia, even if they do not meet urgent indications for treatment initiation.

PEG-IFNα therapy

The aim of PEG-IFNα therapy is to achieve long-term off-treatment HBV suppression following a finite treatment duration. Its therapeutic effects in HBV infections are multifaceted. One key aspect is its immune modulatory effect, enhancing the host immune response by impacting various immune cells, such as natural killer cells, T cells, and B cells.[269] This immune activation can have cytolytic and non-cytolytic effects, leading to suppression of HBV replication and clearance of infected hepatocytes. Thus, in contrast to NAs, PEG-IFNα affects the HBV life cycle through multiple mechanisms of action, including inhibition of HBV RNA stability, translation, encapsidation and reverse transcription, destabilisation of viral capsids and decreased transcriptional activity of cccDNA through epigenetic silencing.[269] The serological surrogate parameters HBeAg/anti-HBe seroconversion and HBsAg loss (even in HBeAg-negative patients) are achieved more frequently with IFNα or PEG-IFNα-based therapy than with NA therapy of the same duration (usually 48 weeks).[270–273] Although the cumulative HBeAg/anti-HBe seroconversion rates with long-term NA therapy are comparable to those achieved with finite PEG-IFNα therapy, the seroconversion rates following PEG-IFNα treatment appear to be more sustained than those observed after discontinuation of NA therapy.[274] Despite the slightly higher HBeAg/anti-HBe seroconversion rates, the overall rate of HBsAg loss after PEG-IFNα therapy is still low.

Meta-analyses and several long-term longitudinal studies have documented improvements in clinical endpoints, such as ALT levels, HBV DNA levels, liver histology, and the incidence of HCC, following IFNα or PEG-IFNα treatment for both HBeAg-positive and HBeAg-negative chronic hepatitis B, compared to untreated patients.[275–278] However, one analysis did not show a preventive effect of IFNα on HCC in a European study cohort, which had a lower incidence of HCC in untreated patients and a smaller proportion of HBeAg-positive individuals.[275]

Two retrospective cohort studies from Asia reported a lower cumulative incidence of HCC in PEG-IFNα-treated patients compared to those on NA therapy over 5 years.[279,280] However, these studies had limitations, including potential selection bias, as certain groups (*e.g.* older patients or those with comorbidities) were less likely to receive PEG-IFNα due to side effects. While matching or propensity score methods were used, key factors such as genotype, quantitative HBsAg, and alcohol consumption were not considered. Notably, the type of NA used as a comparator may have significantly influenced outcomes. One study did not specify which NAs were used as comparators,[280] limiting interpretability.

The variable response rates and unfavourable safety profile of PEG-IFNα treatment are major drawbacks that limit patients’ eligibility or prompt patients to decline this treatment option. Predictors of response and early discontinuation criteria help personalise PEG-IFNα therapy by identifying patients with a high likelihood of response and limiting treatment duration.

Table 9. Differences between PEG-IFNα and NA therapy.

Features	ETV, tenofovir (TDF, TAF)	PEG-IFNα
Strategy	Preventing disease progression through persistent HBV suppression	Induction of an off-treatment response through finite treatment
Administration	Oral, once daily	Subcutaneous, once weekly
Treatment duration	Long-term	Finite (48 weeks)
Response guided treatment	Criteria for stopping long-term therapy before HBsAg loss (see "When can antiviral therapy for hepatitis B with NAs be stopped?")	Stopping rules after 12-24 weeks of therapy (see "How should therapy with PEG-IFNα be administered in patients with chronic HBV infection?")
Side effects	Very low	Moderate to high
Contraindications	Very few (*e.g.* ETV in pregnancy)	Numerous
Level of viral suppression	High	Low to high, depending on patient profile
HBeAg/anti-HBe seroconversion rates	Initially low, moderate during long-term treatment	Low to high, depending on patient profile
HBsAg loss	Very low	Low, higher compared to NAs
Risk of viral resistance	Very low	Absent

ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NAs, nucleos(t)ide analogues; PEG-IFNα, pegylated interferon-alfa.

Table 10. Key data from pivotal studies with treatment response to entecavir and tenofovir (TDF, TAF).

Nucleos(t)ide analogue	HBeAg-positive	HBeAg-negative
Entecavir (ETV)		
ETV 48 weeks n = 715 HBeAg-positive[257] n = 648 HBeAg-negative[258]	HBV DNA <LOD: 67% HBeAg/anti-HBe sc: 21% HBsAg loss: 2%	HBV DNA <LOD: 90% HBsAg loss: <1%
ETV 96 weeks (n = 354 HBeAg-positive)[259]	HBV DNA <LOD: 80% HBeAg/anti-HBe sc: 31% HBsAg loss: 5%	n.a.
ETV 7 years (n = 222)[260] n = 90 HBeAg-positive n = 132 HBeAg-negative	HBV DNA <LOD: 96.8%	HBV DNA <LOD: 100%
ETV 10 years (n = 1,094) n = 458 HBeAg-positive[261]	HBeAg loss: 16%, 23%, 30%, 35%, 37% and 38% at years 1–6, respectively; 38% at year 10	
Tenofovir disoproxil (TDF)		
TDF 48 weeks[262] n = 176 HBeAg-positive n = 250 HBeAg-negative	HBV DNA <LOD: 76% HBeAg/anti-HBe sc: 21% HBsAg loss: 3.2%	HBV DNA <LOD: 93% HBsAg loss: 0%
TDF 48 weeks n = 292 HBeAg-positive[263] n = 140 HBeAg-negative[264]	HBV DNA <LOD: 67% HBeAg/anti-HBe sc: 8% HBsAg loss: <1%	HBV DNA <LOD 93% HBsAg loss: 0%
TDF 96 weeks (n = 432)[265] n = 290 HBeAg-positive n = 142 HBeAg-negative	HBV DNA <LOD: 75% HBeAg/anti-HBe sc: 12% HBsAg loss: 1%	HBV DNA <LOD: 91% HBsAg loss:0%
TDF 7 years (n = 437)[266]	HBV DNA <LOD: 99.4% HBeAg/anti-HBe sc: 39.6% HBsAg loss: 11.8%	HBV DNA <LOD: 99.3%
TDF 10 years (n = 203)[267]	HBV DNA <LOD: 98% HBeAg/anti-HBe sc: 27%	HBV DNA <LOD: 100%
Tenofovir alafenamide (TAF)		
TAF 48 weeks n = 581 HBeAg-positive[263] n = 285 HBeAg-negative[264]	HBV DNA <LOD: 64% HBeAg/anti-HBe sc: 10% HBsAg loss: 1%	HBV DNA <LOD: 94% HBsAg loss: 0%
TAF 96 weeks (n = 866)[265] n = 569 HBeAg-positive n = 297 HBeAg-negative	HBV DNA <LOD: 73% HBeAg/anti-HBe sc: 18% HBsAg loss: 1%	HBV DNA <LOD: 90% HBsAg loss:<1%
TAF 5 years (n = 741)[252] n = 492 HBeAg-positive n = 249 HBeAg-negative	HBV DNA <LOD: 80.9% HBeAg/anti-HBe sc: 23.6% HBsAg loss: 0.8%	HBV DNA <LOD: 92.4% HBsAg loss:1.2%

ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LOD, limit of detection (cut-offs vary between assays from 20-80 IU/ml); sc, seroconversion; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

In summary, healthcare providers should thoroughly assess the efficacy, safety profile, potential side effects, treatment duration of the available treatment options, and patient-specific factors such as comorbidities and treatment preferences when making the decision to treat. Engaging patients in shared decision-making processes and providing adequate information about the available treatment options can help align treatment choices with patient preferences and optimise treatment outcomes.

How should NA therapy be administered and what should be considered during long-term therapy?

Recommendations

- ETV, TDF, or TAF should be used as first-line NA therapy. When selecting between ETV, TDF and TAF, comorbidities (especially renal insufficiency and reduction in bone density) and concomitant circumstances (*e.g.* women of child-bearing age, pregnancy, age) as well as previous therapies should be taken into account **(LoE 1, strong recommendation, strong consensus).**
- Determination of HBV DNA and ALT levels should be carried out every 3-6 months until a virological response (see Box 1) is achieved. Thereafter, the monitoring interval can be extended to 6-12 months for therapy with ETV or tenofovir (TDF or TAF) **(LoE 2, strong recommendation, strong consensus).**
- HBsAg status should be tested every 12 months. Ideally, a quantitative determination of HBsAg should be performed **(LoE 3, strong recommendation, strong consensus).**
- It is suggested to test HBeAg and anti-HBe in HBeAg-positive patients every 12 months **(LoE 2, weak recommendation, consensus).**
- Kidney function should be assessed before treatment initiation and monitored regularly during treatment to adjust the NA dose **(LoE 1, strong recommendation, strong consensus).**
- Treatment with TDF should be switched to another NA (ETV or TAF) if the glomerular filtration rate decreases, if tubulopathy occurs, and in case of hypophosphatemia or osteoporosis. Previous therapies and resistance should be taken into account when choosing the NA **(LoE 1, strong recommendation, strong consensus).**
- Non-invasive fibrosis assessment should be performed every 12-24 months **(LoE 3, strong recommendation, consensus).**

Virological efficacy of ETV and tenofovir

Antiviral resistance can significantly compromise the efficacy of NA treatment. However, resistance is rare with ETV, TDF, or TAF.[5] These NAs are the most effective in preventing resistance, ensuring superior long-term virological response rates. Consequently, their use as first-line therapy is essential to minimise resistance, which is associated with increased morbidity and mortality, particularly in patients with advanced fibrosis or cirrhosis.[281–283]

Genotypic resistance to ETV is uncommon in treatment-naïve patients, with a reported rate of only 1.2% at 5 years.[284] However, in patients with prior lamivudine treatment, resistance rates increase significantly, reaching 6% after 1 year and exceeding 50% beyond 5 years.[285,286] Therefore, ETV should not be used in patients with confirmed lamivudine resistance, though it may be considered at a dose of 1 mg per day (double the usual dose) in patients with lamivudine experience.[287,288]

Resistance to tenofovir-based therapies remains exceptionally low. Both TDF and TAF have demonstrated a 0% resistance rate after 5 years of treatment.[252,289] Real-world studies have not raised significant concerns regarding clinically meaningful drug resistance, though isolated mutations with reduced antiviral efficacy have been reported.[290,291]

HBV DNA suppression rates are comparable between TDF and TAF at both 48 and 96 weeks of treatment (Table 10). However, ALT normalisation occurs more frequently with TAF at both time points, although the clinical significance of this stronger biochemical response remains uncertain.[263–265]

Given extensive resistance data and long-term efficacy studies (Table 10), there is no longer a clinical justification for using lamivudine, telbivudine, or adefovir as first-line treatments. Generic formulations of ETV and TDF are now widely available, with real-world data confirming their efficacy and safety.[292,293]

Recent meta-analyses have investigated potential differences between ETV and TDF in reducing HCC risk. Two meta-analyses, including 14 and 15 studies, respectively, primarily from Asian cohorts, demonstrated a statistically significant reduction in HCC incidence among patients receiving long-term TDF therapy compared to ETV.[294,295] Additionally, an individual patient data meta-analysis from Korea, Taiwan, and Hong Kong (11 studies) suggested that TDF was associated with a significantly lower HCC risk than ETV, particularly in HBeAg-positive patients.[296] However, another systematic review and meta-analysis, which analysed sources of heterogeneity, found no significant difference between TDF and ETV regarding HCC risk reduction.[297] Similarly, a large multicentre European cohort study reported equally low HCC rates among patients receiving long-term ETV or TDF therapy.[298] However, due to conflicting data on HCC risk reduction and the absence of a mechanistic explanation, there is currently no clear recommendation favouring TDF over ETV. Instead, treatment selection should be based on other key factors, including tolerability, prior therapies, comorbidities, cost, and drug availability. An exception is tertiary prophylaxis of HCC, see "Should patients with chronic HBV infection and HCC be treated with antiviral therapy, and if so, how?".

Treatment monitoring

When using ETV, TDF or TAF, HBV DNA levels should be monitored every 3-6 months until a virological response, defined as suppression of HBV DNA below the LOD, is achieved. The monitoring intervals can be adjusted individually depending on the importance of close monitoring (*e.g.* in advanced stages of liver disease) or the risk of poor treatment adherence. Clinical cohort studies suggest that up to 40% of virological failures are due to irregular medication adherence rather than viral resistance.[299] According to a systematic review, adherence to NA treatment is 75%, with similar rates observed in high-income countries and LMICs.[300] With consistent adherence to ETV, TDF or TAF, monitoring can be extended to 6-12 months due to low resistance risk. However, if NAs with a lower barrier to resistance are still used, quarterly monitoring should continue to promptly detect and manage resistance.

In HBeAg-positive patients, the HBeAg status (HBeAg, anti-HBe) should be monitored during therapy, *e.g.* annually, to document HBeAg/anti-HBe seroconversion, which occurs increasingly with long-term treatment (Table 10). More frequent

monitoring may be considered if ALT fluctuations occur. If HBeAg/anti-HBe seroconversion occurs in conjunction with effective HBV DNA suppression, this may prompt consideration of possible discontinuation of antiviral therapy (see below).

Additionally, HBsAg status should be checked every 12 months to monitor for HBsAg loss, which is rare but significant as treatment can be stopped. Ideally, HBsAg levels should be quantified to track declines over time. Achieving low HBsAg values during long-term therapy is associated with a higher likelihood of eventual HBsAg loss after HBeAg/anti-HBe seroconversion.[52] For HBeAg-negative patients, particularly those with HBsAg levels <1,000 IU/ml in Caucasians or <100 IU/ml in Asians, this may prompt consideration of NA treatment discontinuation[301,302] (for details see "When can antiviral therapy for hepatitis B with NAs be stopped?").

Monitoring safety

All HBV-approved NAs are primarily eliminated via the kidneys, necessitating regular monitoring of serum creatinine and estimated glomerular filtration rate (eGFR) to guide dose adjustments (see product information). ETV and TDF require adjustment based on renal function, while TAF does not, though it is not approved for patients with an eGFR <15 ml/min/1.73m^2 who are not on haemodialysis. Additionally, due to their renal clearance, NAs may pose a risk of renal toxicity. Nephrotoxicity has been observed primarily with nucleotide analogues (TDF and adefovir in particular), whereas it is less common with nucleoside analogues such as ETV.[303] Initially, nephrotoxicity was documented in HIV-infected patients and it was shown that either concomitant medication or comorbidities associated with HIV influenced the severity and frequency. For chronic HBV infection, cohort studies indicate that TDF is associated with renal complications, including declines in eGFR and serum phosphate levels, which may lead to dose adjustments or discontinuations due to safety concerns. In a pooled analysis of 535 patients with chronic HBV infection treated with TDF for up to 8 years, renal complications were minimal, with only one case of mild renal failure and 3.4% needing dose adjustments.[303] Tubular dysfunction reported with long-term TDF use is often reversible or partially reversible when therapy is discontinued or switched to ETV or TAF.[304,305] Of note, Fanconi syndrome has also been associated with TDF in HIV[306] and HBV-infected patients,[303,307] which can revert after discontinuation of TDF.[307] It has also been shown that continuation of treatment with TAF is possible in this situation.[308]

In addition to serum creatinine and eGFR monitoring, annual serum and urine phosphate levels and urine protein levels are recommended if TDF is used. Serum creatinine alone may not fully reflect renal damage and factors such as muscle mass and protein intake impact its level. Early indicators of tubular damage, such as proteinuria or fractional excretion of phosphate may be more sensitive markers.[303]

Long-term use of TDF may impair phosphate reabsorption, leading to hypophosphatemia, decreased bone mineral density (BMD), and an increased risk of osteopenia.[303] A phase III study found no significant reduction in lumbar spine BMD after 72 weeks of TDF in adolescents,[309] while an Italian study showed initial BMD declines during TDF therapy that later improved again.[310] A UK cohort study documented that TDF was associated with a lower hip T-score compared to no TDF, with age, smoking, lower BMI, and TDF exposure being independent predictors of low BMD.[311] A study from Hong Kong reported an increased risk of bone fractures associated with TDF in patients aged >60 years.[312] Since older patients with chronic liver disease often have lower BMD, monitoring bone health in aging populations, including postmenopausal women on long-term TDF therapy, is particularly important.

Notably, studies evaluating TAF for chronic HBV infection have shown that after 96 weeks, patients treated with TAF experienced significantly less decline in eGFR and BMD compared to those receiving TDF.[252,313–316] Switching from TDF to TAF has led to an improvement in BMD in some cohorts. There is now also evidence from a retrospective cohort study that treatment with TAF reduces the risk of osteoporotic fractures compared to TDF.[313–317]

Based on current evidence, EASL recommends that TAF should be preferred over TDF in patients with hypophosphatemia, osteopenia/osteoporosis, renal insufficiency or risk factors for TDF-related nephrotoxicity. Risk factors include decompensated cirrhosis, eGFR <60 ml/min/1.73m^2, poorly controlled hypertension, proteinuria, diabetes mellitus, glomerulonephritis, nephrotoxic drugs and organ transplantation. Because TAF may not be available in some countries or may not be fully reimbursed, ETV is an alternative. Cohort studies suggest that ETV is generally not associated with the development of kidney or bone damage.[303]

Of note, treatment with ETV is associated with a higher risk of resistance in patients previously treated with lamivudine.[5] In such cases, a higher dose of 1 mg ETV should be considered,[287] although even this dose may not always prevent treatment failure[318] and is therefore not the preferred option in this setting. In addition, ETV is not recommended during pregnancy.

Multiple studies, including large cohorts and meta-analyses, have consistently shown that TAF-containing regimens are associated with higher lipid levels than TDF-containing regimens in both people living with HIV (PLWH) and individuals with HBV infection.[319–321] A real-world cohort of over 6,400 PLWH who switched from TDF to TAF (with no other medication changes) demonstrated a steady rise in LDL over approximately 9 months, while triglycerides increased for 9–16 months before plateauing.[322] Notably, several studies have linked TDF use to reductions in lipid levels, suggesting that TDF may exert a mild lipid-lowering effect.[319,321] Nevertheless, a meta-analysis comparing HBV treatments showed that TAF worsens lipid profiles more than TDF as well as ETV, further highlighting its role in dyslipidaemia.[321] Additionally, weight gain is a well-documented effect after switching to TAF and is believed to contribute to deteriorating lipid profiles.[319,323] In individuals with chronic HBV infection, previous diabetes and hypertension were identified as risk factors for worsening lipid profiles in TAF-treated individuals.[321] Thus, clinicians should closely monitor lipid profiles and consider cardiovascular risk when transitioning patients from TDF to TAF, particularly in those with pre-existing metabolic risk factors.

Severe lactic acidosis is a potential adverse event documented during NA treatment in patients with significantly impaired liver function (*e.g.* MELD score >20).[324,325] NAs can contribute to this condition by inhibiting mitochondrial DNA

polymerase-γ and disrupting aerobic metabolism. However, larger studies and meta-analyses involving patients with liver failure or decompensated cirrhosis have not shown an increased incidence of lactic acidosis associated with NA treatment, suggesting that this is a rare event.[303,326]

Monitoring fibrosis by non-invasive measures

For patients with chronic HBV infection undergoing antiviral therapy, regular non-invasive assessment of liver fibrosis, preferably using LSM, is recommended. This allows for the early detection of significant fibrosis and monitoring its regression or progression. Long-term studies have generally shown significant regression of liver fibrosis stage as measured by LSM in patients on NA therapy.[327,328] LSM assessment helps to assess the risk of liver-related complications, especially HCC, and thus provides information to guide the appropriate HCC surveillance strategy (see section "HCC surveillance"). Studies have shown that incorporating on-treatment LSM values significantly improves the accuracy of HCC risk prediction, especially for patients with a virological response to treatment.[329–331] The recommended interval for LSM assessment ranges from 1 to 2 years, depending on the patient's profile and their risk factors for HCC development. However, caution is required when assessing fibrosis changes during NA treatment, as LSM values may be overestimated during hepatitis flares,[332] and one study suggested that LSM is unreliable for estimating fibrosis regression during NA therapy.[333]

What is the procedure in case of partial virological response or virological non-response to NA therapy or development of resistance?

Recommendations

- In the event of a partial virological response or virological non-response (Box 1), the patient's adherence to treatment should be assessed in the first instance **(LoE 1, strong recommendation, strong consensus).**
- A test for HBV variants associated with NA resistance can be performed if treatment adherence is confirmed **(LoE 2, weak recommendation, strong consensus).**
- In the event of a partial virological response, virological non-response or virological resistance (Box 1), the following treatment adjustments are recommended **(LoE 1-2, strong recommendation, strong consensus)**:
  - Switch to tenofovir (TDF or TAF) if a nucleoside analogue was previously used **(LoE 1).**
  - Switch to ETV or tenofovir (TDF or TAF) if adefovir was previously used **(LoE 1).**
  - Switch to or add-on ETV if tenofovir (TDF or TAF) was previously used **(LoE 2).**
- In case of persistent low-level HBV DNA (<2,000 IU/ml) or blips during treatment with tenofovir (TDF or TAF) or ETV, treatment does not need to be immediately adjusted in the absence of advanced liver fibrosis and when resistance has been excluded **(LoE 4, weak recommendation, strong consensus)**. Potential explanations, such as poor adherence to treatment or reduced absorption in the intestine, should be considered.
- In patients with cirrhosis, the goal is to achieve undetectable HBV DNA ideally after 12 months of treatment. If this is not achieved, treatment adjustment should be considered **(LoE 3, strong recommendation, strong consensus).**

The aim of NA treatment is the suppression of HBV DNA (ideally below the LOD). This is particularly important in patients with cirrhosis, in whom undetectable HBV DNA should be achieved after 12 months of treatment, as this leads to a reduced risk of developing HCC. However, in patients without advanced fibrosis treated with ETV, TDF, or TAF, evidence on the clinical significance of HBV DNA not reaching the LOD and the persistence of low-level viraemia (HBV DNA 20-2,000 IU/ml) remains limited.[334] Nevertheless, existing data suggest an association between low-level viraemia and fibrosis progression, and progression of liver disease. However, available studies often included mixed cohorts with a significant proportion of patients with cirrhosis or identified alcohol intake as a strong additional risk factor for disease progression, making it challenging to isolate the specific impact of low-level viraemia.[126,335] Additionally, viral mutants may emerge in response to suboptimal NA treatment.[336] Of note, achieving optimal viral suppression can be challenging in patients with very high pre-treatment HBV DNA levels. In HBeAg-positive individuals with chronic HBV infection characterised by high HBV DNA and normal ALT levels, only 55% achieved HBV DNA suppression <LOD after 4 years of treatment with TDF. The addition of emtricitabine to TDF treatment increased the response rate to 76%.[229] Thus, in cases of high baseline viraemia, complete suppression of HBV DNA can take an extended period. If a plateau is reached without further reduction in HBV DNA levels, the response to treatment should be considered inadequate. Before modifying treatment regimens, it is important to consider that 30–40% of virologic breakthroughs in clinical cohorts are attributed to poor adherence. Poor adherence to medication is associated with a higher mortality and greater risk of HCC and cirrhosis-associated complications.[337] Notably, a retrospective study initially associated low-level viraemia during ETV treatment with an increased risk of HCC, liver-related death, and cirrhotic complications, but when adherence (≥90%) was accounted for, low-level viraemia was not a predictive factor for these outcomes.[338] Previously known risk factors for forgetting to take medication for ≥1 day include a shorter period after diagnosis and younger patient age.[299,339,340] Another possible explanation for low-level viraemia or intermittent viral "blips" (HBV DNA increase <1 $\log_{10}$) despite consistent medication intake is reduced intestinal

Box 1. Definition of treatment response in NA-treated adherent patients.

- **Complete virological response** is defined as undetectable HBV DNA measured with a sensitive assay (<20 IU/ml).
- **Partial virological response** is present if HBV DNA does not decline steadily and remains >2,000 IU/ml.
- **Virological non-response** is defined by a decline <1 $\log_{10}$ at 6 months of NA treatment.
- **Virological resistance** is assumed if HBV DNA increases to ≥1 $\log_{10}$ above nadir.

HBV, hepatitis B virus; NA, nucleos(t)ide analogue.

absorption of the drug. TDF can have reduced intestinal permeability due to its highly charged phosphonate group. This limited absorption can impair drug efficacy and contribute to suboptimal viral suppression.[341] Note that tenofovir (TDF, TAF) should be taken with food and ETV on an empty stomach.

In selected cases, identifying polymerase gene mutations associated with HBV resistance may aid treatment planning, particularly when prior therapies are unclear or in cases of virological breakthrough (defined as an HBV DNA increase of ≥1 $\log_{10}$). Virological breakthrough due to HBV resistance typically precedes biochemical relapse by several weeks. Treatment adjustments should be made promptly once virological relapse is confirmed; however, waiting for resistance test results should not unnecessarily delay treatment modification.

In cases of primary virological non-response or resistance during treatment with nucleoside analogues (lamivudine, telbivudine, ETV), it is recommended to switch to tenofovir (TDF or TAF), as monotherapy with tenofovir is generally effective in these situations.[5,314] In patients who fail treatment with lamivudine, a higher dose of 1 mg ETV can be considered as an alternative,[287] although this is suboptimal because of the increased risk of viral breakthrough, which can rise to 72% over time.[318] The nucleotide analogue adefovir is no longer recommended as first-line therapy. However, if a patient is still treated with adefovir and does not achieve a sufficient response, it is recommended to switch to ETV (if lamivudine was not previously used) or tenofovir (TDF or TAF). If the response to tenofovir is inadequate and reasons related to drug non-adherence have been ruled out, switching to or adding ETV may be beneficial. This is supported by data from case series, cohort studies and some tenofovir registration studies.[342]

When can antiviral therapy for hepatitis B with NAs be stopped?

Recommendations

- Antiviral therapy with NAs should only be discontinued after consultation with a physician experienced in the treatment of hepatitis B and if close monitoring is guaranteed. HBsAg levels, HBeAg status, comorbidities, duration of HBV DNA suppression, stage of liver fibrosis in addition to patient understanding and preference should be taken into account **(LoE 2, strong recommendation, strong consensus).**
- Antiviral therapy with NAs should be stopped after confirmed HBsAg loss with or without anti-HBs seroconversion in the absence of coexisting risk factors **(LoE 2, strong recommendation, consensus).**
- When considering NA discontinuation in HBsAg-positive individuals, HBsAg levels should be used to select patients **(LoE 2, strong recommendation, strong consensus).**
- In HBeAg-positive patients without advanced liver disease, antiviral therapy with NAs can be stopped 12 months after confirmed HBeAg/anti-HBe seroconversion and undetectable HBV DNA if close monitoring is guaranteed after the end of therapy **(LoE 2, weak recommendation, consensus).***
- In selected HBeAg-negative patients without advanced liver disease, NA therapy can be discontinued before HBsAg loss if HBV DNA has been undetectable for at least 3-4 years, HBsAg level is low (for values see comments below), and close monitoring is guaranteed after the end of therapy **(LoE 1-2, weak recommendation, consensus).***
- In addition to HBsAg level, HBcrAg and HBV RNA level can be used to further improve the patient stratification before discontinuing therapy **(LoE 3, weak recommendation, consensus).***

Stopping NAs after HBsAg loss

Although loss of HBsAg is rare with NA therapy (Table 10), it is clinically significant, as it may indicate effective control of HBV infection, which is associated with the best long-term prognosis.[5,55,134,343,344] However, HBsAg seroreversion remains possible due to the persistence of cccDNA in the liver.[11] If HBsAg loss is confirmed on two occasions 6 months apart, the risk of post-treatment relapse is very low. In the largest study of 4,080 patients from Asia, over 95% of those who achieved HBsAg loss and discontinued NA treatment remained HBsAg negative (2.9% of NA-treated patients), though only 38% had detectable anti-HBs titres. Anti-HBs seroconversion has also not been shown to be a determining marker for sustained HBsAg loss in other studies.[129,135,345,346] Thus, cessation of NA therapy is generally recommended after confirmed HBsAg loss.

In patients with compensated cirrhosis, discontinuation of NA therapy is only suggested after confirmed seroconversion to anti-HBs or following HBsAg loss with at least 12 months of consolidation therapy. The primary concern is that HBsAg seroreversion with HBV DNA relapse could trigger liver decompensation. However, the recommendation to wait for anti-HBs seroconversion is based on precaution rather than strong evidence, as studies indicate that anti-HBs seroconversion is not significantly associated with the durability of HBsAg loss.[346] Notably, anti-HBs seroconversion after HBsAg loss can take several years, occurring in 58% of patients after 5 years and 78% after 10 years.[135,347] While evidence supporting extended consolidation therapy is limited,[346] a study from Hong Kong documented no cases of HBsAg seroreversion in patients who completed 12 months of consolidation therapy before stopping NAs.[135]

For patients with decompensated cirrhosis, discontinuation of NA therapy should only be considered, if at all, after confirmed seroconversion to anti-HBs. NA withdrawal should not be performed in patients undergoing immunosuppressive therapy, as even HBsAg-negative/anti-HBc-positive individuals may require continuous antiviral treatment to prevent HBVr (see section “Prophylaxis of HBV reactivation”).

Data on long-term outcomes following HBsAg loss with antiviral therapy are limited. Therefore, regular monitoring of HBV DNA and ALT levels at 3-month intervals is recommended during the first year after discontinuing NA therapy. Subsequently, monitoring should be adjusted to 6-12-month intervals, considering factors such as comorbidities, age, sex, and the degree of liver fibrosis, particularly given the risk of developing HCC.

Stopping NA therapy before HBsAg loss

Stopping NA therapy in initially HBeAg-positive patients after HBeAg/anti-HBe seroconversion

Stopping NA therapy in HBeAg-positive patients who do not achieve HBeAg/antiHBe seroconversion is not recommended even if HBV DNA is suppressed for a long time. After HBeAg/anti-HBe seroconversion, NA treatment discontinuation can be considered. However, the risk of HBeAg seroreversion and HBVr is higher in NA-induced seroconverters than spontaneous seroconverters.[348]

Comprehensive data on treatment discontinuation in initially HBeAg-positive patients after HBeAg loss and anti-HBe seroconversion were reported in a meta-analysis including a total of 1,217 HBeAg-positive patients. However, the included studies showed major heterogeneity and were conducted almost exclusively in Asia, so that the transferability to other parts of the world is limited.[349] Overall, 71.2% of patients showed virological remission (HBV DNA <2,000 IU/ml) 1 year after the end of antiviral therapy. Biochemical remission was achieved in 66.5% of 403 patients for whom corresponding data were available. HBeAg/anti-HBe seroconversion remained stable in 91.9% of patients 1 year after the end of therapy. After 2 years, the number of patients with virological remission fell to 53.4%, while HBeAg/anti-HBe seroconversion was stable in 88% of patients.

Heterogeneous data indicate that a lower HBsAg level at the time of NA discontinuation is associated with an increased likelihood of sustained off-therapy remission. Specifically, an HBsAg level <2.5 $\log_{10}$ IU/ml (equivalent to <300 IU/ml) has been linked to sustained remission in Asian patients.[350] However, the evidence supporting the use of HBsAg for stratification is weaker compared to its application in HBeAg-negative patients (see below).

Some studies suggest that virological remission is more likely, and the risk of relapse is lower, if NA consolidation therapy and HBV DNA suppression are maintained for at least 12 months following seroconversion.[351–353] However, a systematic review found no clear evidence supporting the necessity of 12 months of consolidation treatment, though the findings were limited by small case numbers and variability in NA treatment regimens across studies.[349] Nevertheless, consistent with other guidelines, NA consolidation therapy is recommended for at least 12 months after HBeAg/anti-HBe seroconversion before discontinuing treatment.[354]

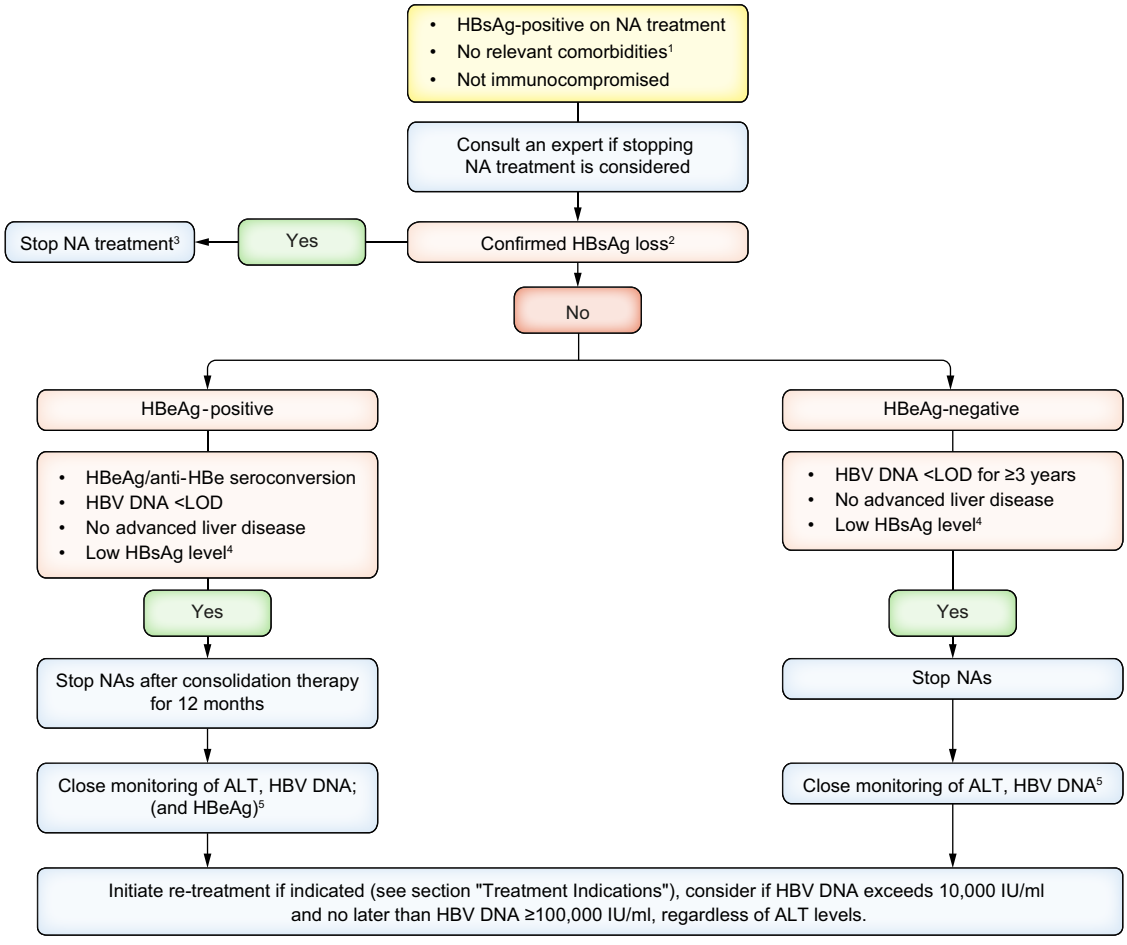

Fig. 2. Algorithm for stopping NA treatment. [1]HCC, decompensated cirrhosis, HIV. [2]HBsAg loss is confirmed on two occasions 6 months apart. [3]In patients with compensated cirrhosis, we suggest discontinuing NA therapy only after confirmed seroconversion to anti-HBs or following HBsAg loss with at least 12 months of consolidation therapy. [4]HBsAg <1,000 IU/ml for Caucasians; <100 for Asians (data more robust in HBeAg-negative); HBcrAg, HBV RNA can be used to further improve stratification. [5]Monitoring at least monthly for the first 6 months, followed by every 3 months for 12–24 months, considering earlier relapse with tenofovir *vs.* entecavir.

A virological and biochemical relapse usually occurs within the first year after treatment cessation, so HBV DNA and ALT should be monitored at least every 1-3 months after the end of treatment. However, the optimal monitoring intervals after discontinuation of therapy are not yet well established and should be carried more out frequently, especially in patients with proven liver fibrosis (see below for details on monitoring). It is also recommended to assess the HBeAg/anti-HBe status after the end of treatment, as there is a significant risk of HBeAg seroreversion. If there is uncertainty as to which patients are suitable for discontinuation of therapy, continuing therapy is recommended as an alternative until HBsAg loss is achieved, particularly in patients with advanced fibrosis and always in the presence of cirrhosis.

Stopping NA therapy in HBeAg-negative patients

The possibility of stopping NAs in HBeAg-negative patients was already included in the previous guidelines.[5] There are two concepts to consider when stopping NA therapy. The first is to maintain virological remission and the second is to increase functional cure rates.

The probability of virological remission (HBV DNA <2,000 IU/ml) 1 year after discontinuation of antiviral therapy has been documented to be around 50% in HBeAg-negative patients[349,355] based on two systematic reviews, albeit which included data that overlap to a large extent and were mainly from Asia.[349,355] It is important to highlight the heterogeneity in patient selection, the retrospective nature of the studies and differences in treatment re-introduction criteria, which might have influenced clinical outcomes. The probability of a long-lasting virological remission after discontinuation was significantly increased if a virological remission had previously been maintained for at least 24 months on antiviral therapy. A study with longer follow-up showed a further reduced relapse rate (defined as HBV DNA >2,000 IU/ml) with at least 3 years of antiviral therapy compared to 2 years in a small study with HBeAg-positive and HBeAg-negative patients.[356]

Several studies have identified additional parameters associated with an increased likelihood of persistent virological remission. These include a lower initial viral load at the start of treatment (<200,000 IU/ml), lower ALT levels, younger age (<40 years), female sex, and the absence of cirrhosis. However, these findings may be subject to bias due to selection criteria. Consistent across most studies, lower HBsAg levels at the time of treatment discontinuation were associated with an increased probability of sustained remission (details see below).[349,355]

In the prospective and randomised STOP-NUC study conducted in Germany, which involved patients who had received TDF for at least 4 years, the rate of virological remission (HBV DNA <2,000 IU/ml and ALT <ULN) after 2 years of follow-up was 41%.[357]

A relatively high rate of HBsAg loss has been observed in long-term follow-up after cessation of NA therapies. In European studies, a HBsAg loss rate of 19-39% was reported.[357–361] In the prospective and randomised STOP-NUC study, the HBsAg loss rate 2 years after the end of therapy was 10% in all patients stopping NA treatment, and 28% in the subgroup of patients with an HBsAg level <1,000 IU/ml at the time of treatment discontinuation. No patient who continued NA therapy achieved HBsAg loss during this time.[357] Of note, in multicentre studies in which Asians predominated and comprised up to 80% of the cohort, reported rates of functional cure were lower and generally did not exceed 10-15% at 5-6 years after discontinuation of NA therapy.[301,362] Heterogeneity in treatment withdrawal criteria, along with demographic characteristics such as HBV genotype or treatment duration (usually lower among Asian cohorts), possibly contribute to these differences.

One possible explanation for the unusually high rate of HBsAg loss after NA cessation is that HBV DNA relapse following treatment discontinuation may trigger immune responses, although further studies are needed to fully understand the underlying virus-host interactions.[358,363,364]

Situations in which stopping NAs is not recommended

A systematic review and meta-analysis assessed the risk of severe clinical events after discontinuing NA therapy, finding that 1.21% of patients experienced severe hepatitis flares or hepatic decompensation, with significantly higher risks in patients with cirrhosis (3.63%) and a 0.37% chance of flare-related death or liver transplantation.[365] Given these risks, NA therapy should not be discontinued in patients with advanced liver disease before achieving HBsAg loss and, ideally, anti-HBs seroconversion. The risk in patients without cirrhosis was lower but not negligible (0.89%), though study heterogeneity and inconsistent reporting on monitoring and safety outcomes must be taken into account.[365] Notably, prospective studies with adequate safety measures, including monitoring and retreatment strategies, reported no serious flare-related outcomes.[357,359,366] Nevertheless, discontinuation in patients without advanced liver disease still requires caution, close monitoring (see below), and standardised retreatment protocols to ensure individualised and safe decision-making.

Patients with concomitant liver diseases or those receiving immunosuppressive treatment were usually excluded from studies on NA treatment discontinuation or not included in the analysis, resulting in a lack of reliable data for these populations. In the case of pronounced comorbidities or immunosuppression, discontinuation of HBV therapy is generally not recommended due to the high risk of reactivation.

In patients with HIV coinfection, tenofovir (TDF or TAF) is usually the cornerstone of antiretroviral therapy. Therefore, switching to a non-tenofovir-based regimen would be similar to the stop-NA concept, which is generally not recommended. If switching is necessary, ETV is the preferred alternative. To date, there is a lack of systematic data on the cessation of NA in the context of HIV coinfection, which could be a focus of future research. Until such evidence is available, this strategy cannot be generally recommended in this setting.

Monitoring and follow-up after stopping NAs

Virologic relapse, defined as HBV DNA ≥2,000 IU/ml, typically occurs within 6–12 months after discontinuing NA therapy but is earlier and more frequent with TDF, with 70% of patients relapsing within 12 weeks, compared to <10% for those stopping ETV in the same period.[367–369] Patients who discontinue TAF also experience higher and earlier relapse rates than those stopping ETV, and even TDF,[370] highlighting the need for individualised monitoring, particularly in the first months post-withdrawal.

Following viral relapse, ALT flares typically occur after a delay, with most emerging within the first year after stopping

NA therapy.[371] ALT flares tend to occur earlier and be more severe after tenofovir discontinuation compared to ETV,[372] with off-TDF flares peaking within the first 6 months, whereas off-ETV flares appear later.[367] A study suggests that switching from TDF to ETV before NA cessation may reduce or delay clinical relapse,[373] reinforcing the evidence that different NAs exhibit distinct post-treatment relapse kinetics and offering a potential strategy to mitigate off-treatment flares.

While flare severity may decrease over time, late ALT flares, though less frequent, can still be clinically significant, with ALT levels reaching ~10× ULN. Physicians should remain vigilant for signs of hepatic decompensation or liver dysfunction.[371,374,375]

Frequent monitoring after NA discontinuation is essential, with assessments at least monthly for the first 6 months, followed by every 3 months for 12–24 months. HBV DNA typically rises within 2-24 weeks, often preceding ALT elevations, necessitating close surveillance of both markers. As relapse occurs earlier and more frequently with TDF/TAF than ETV, monitoring should be adjusted accordingly: every 4 weeks for the first 6 months after stopping tenofovir (TDF/TAF), while longer intervals may be considered after stopping ETV, but vigilance at later time points remains crucial.

If retreatment is required, it should follow the standard recommendations for starting antiviral therapy for hepatitis B, using ETV, TDF, or TAF (see section "Treatment indications"). It is assumed that restarting NA therapy too early could prevent positive immune responses and that it is beneficial to undergo a prolonged episode of ALT elevation after discontinuing NAs. However, evidence supporting this strategy remains limited. A prospective study exploring this concept was insufficiently powered to draw definitive conclusions, although a significant benefit was observed with delayed treatment initiation in patients with HBsAg <1,000 IU/ml at the end of treatment.[366]

Until stronger evidence emerges, patient safety should remain the priority. Retreatment should be considered if HBV DNA exceeds 10,000 IU/ml, regardless of ALT levels, and initiated no later than when HBV DNA reaches ≥100,000 IU/ml to prevent severe liver injury. Data from the large multicentre RETRACT-B study indicate that patients with HBV DNA >5 $\log_{10}$ IU/ml within 12 weeks after stopping treatment face the highest risk of subsequent ALT flares (44% within the first 12 weeks). Approximately 30% of patients with HBV DNA >4 $\log_{10}$ IU/ml experienced flares after 3 months, though some with HBV DNA between 4 and 5 $\log_{10}$ IU/ml showed spontaneous viral decline, avoiding the need for retreatment.[371] When therapy was re-initiated with ETV or tenofovir, viral suppression was successfully restored.[358] Current evidence does not indicate reduced efficacy upon reintroducing antiviral therapy or the emergence of resistance, though long-term data remain limited.

Clinical endpoints after stopping NAs

There is a growing body of data evaluating clinical outcomes after discontinuation of NA treatment before HBsAg loss, but these data are retrospective and should still be evaluated with caution. Asian studies did not document higher rates of clinical endpoints, including HCC, after discontinuation of therapy according to APASL stopping rules. The observation period was 12-60 months and even patients with compensated cirrhosis were included.[376–378] In a study of HBeAg-negative patients with HBV-related cirrhosis from Taiwan, finite NA therapy (n = 494) was not only associated with increased HBsAg loss, but even with a significantly lower incidence of HCC and improved survival after a 10-year follow-up compared to continuous therapy (n = 593). The study employed propensity score matching to control for biases related to HCC risk factors.[379] A multicentre study including European patients showed that discontinuation of effective long-term NA therapy in patients without cirrhosis was not associated with increased HCC risk.[380] Data from other parts of the world (*e.g.* Africa and South America) are currently not available.

Stratification of patients to determine NA discontinuation

Given the risks of ALT flares associated with discontinuation of antiviral therapy and the absence of reliable predictors of significant ALT flares or liver dysfunction, it is crucial to carefully assess factors linked to favourable outcomes, such as off-treatment viral control or HBsAg loss. This thorough evaluation enables informed discussions with patients about the potential risks and benefits of discontinuing therapy. Consequently, reliable biomarkers for patient stratification are essential.

Most data predicting favourable outcomes after stopping NA treatment, including subsequent HBsAg loss, emphasise the importance of low HBsAg levels at the time of treatment discontinuation. Stronger evidence for defined HBsAg thresholds is available in HBeAg-negative patients. It is noteworthy that the predictive thresholds for HBsAg levels are different for Asians and Caucasians: for Asians, an HBsAg value <100 IU/ml is associated with a favourable outcome, whereas for Caucasians, the threshold is <1,000 IU/ml.[301,302] Of note, HBsAg levels at the end of treatment do not seem to be associated with the timing or severity of ALT flares.[381]

In addition to HBsAg, the ability of other markers like HBcrAg,[382–389] anti-HBc,[390,391] HBV RNA,[385,389,392] soluble inflammatory markers[393] and immune markers[394,395] to predict responses after discontinuing NA therapy has been explored.[396] Growing evidence supports the use of HBcrAg and HBV RNA for improving risk stratification in patients who are candidates for stopping NA therapy.[382–384,386,387,397] Generally, lower or undetectable levels of HBcrAg, particularly when combined with low HBsAg values, are associated with a reduced risk of relapse.[384,387,389,397] An Asian multicentre study[387] developed the SCALE-B risk score, which includes HBsAg, HBcrAg, age, ALT, and tenofovir use, to predict off-treatment response, and this model has been validated in other cohorts.[382,398]

However, the cohorts were heterogeneous with respect to HBeAg status, and the score could only be validated for predicting HBsAg loss, but not for predicting relapse in a Caucasian HBeAg-negative cohort.[399]

The evidence supporting HBV RNA as a biomarker is still limited. While some studies associate HBV RNA negativity with favourable outcomes,[385,392] others have not demonstrated its predictive value for relapse.[400] These conflicting results suggest that differences in study design, as well as variability in

assay characteristics and sensitivity, may influence findings. Combining HBV RNA with HBsAg may enhance predictive accuracy.[389]

Though limited, data for HBeAg-positive patients undergoing HBeAg/anti-HBe seroconversion during NA therapy suggest that relapse rates after discontinuing NA therapy are low when HBV RNA is undetectable and HBcrAg levels are low at the end of treatment, especially when HBsAg levels are <100 IU/ml.[388,389,401] A *post hoc* analysis of a 2-year multicentre randomised-controlled trial showed that HBeAg-positive patients who tested negative for both HBV DNA and RNA at the end of treatment maintained a sustained virological response for ≥4 years after stopping therapy.[402]

Data on the association of new viral markers and functional cure for patients undergoing NA discontinuation are emerging. A multicentre cohort study including 1,216 HBeAg-negative patients showed that HBcrAg levels at the end of treatment were significantly associated with the probability of subsequent HBsAg loss.[403] Data for HBeAg-positive patients are limited. Despite the added value of both HBcrAg and HBV RNA in stratifying patients for treatment discontinuation, definitive cut-offs for these markers have not been established.

Data on immune markers as predictors of response, although promising, still await standardisation and consolidation.[396]

Fig. 2 outlines an algorithm to guide cessation of NA therapy in selected patients, providing practical criteria for safe treatment discontinuation.

How should therapy with PEG-IFNα be administered in patients with chronic HBV infection?

Recommendations

- Predictive factors should be used to guide the decision to initiate PEG-IFNα treatment. In addition, PEG-IFNα-associated side effects should be considered, and the patient's treatment preferences should be taken into account to support the decision-making process **(LoE 2, strong recommendation, strong consensus).**
- PEG-IFNα should be administered once a week, typically for a duration of 48 weeks. The dose of PEG-IFNα-2a should be 180 μg weekly (s.c.) **(LoE 1, strong recommendation, strong consensus).**
- Stopping rules should be considered based on the quantitative determinations of HBV DNA and HBsAg at treatment week 12 and 24 **(LoE 2, strong recommendation, strong consensus).**
- *De novo* combination therapy with PEG-IFNα and NAs cannot be generally recommended. PEG-IFNα as an add-on therapy can be considered in selected HBeAg-negative patients undergoing NA therapy with low HBsAg levels **(LoE 2, weak recommendation, consensus).***
- During and after therapy with PEG-IFNα, regular safety-related blood tests should be carried out and adverse reactions should be monitored **(LoE 1, strong recommendation, strong consensus).**

Prediction of response

Baseline predictors of PEG-IFNα response in HBeAg-positive patients include a low viral load, elevated serum ALT (2-5× ULN), high histological inflammatory activity, younger age, female sex, and HBV genotypes A and B, which are associated with higher rates of HBeAg/anti-HBe seroconversion and HBsAg loss compared to genotypes D and C, respectively.[404,405] A scoring system evaluated in HBeAg-positive Asian patients with genotypes B/C revealed that age <40 years, female sex, ALT >4x ULN, HBsAg <25,000 IU/ml, and HBV DNA <6 $\log_{10}$ IU/ml were predictive of treatment response.[406] Additionally, a simple scoring system based on demographic and baseline biomarkers from 1,363 patients, including 408 HBeAg-negative individuals, predicts virological response to PEG-IFNα, irrespective of HBeAg status and HBV genotypes, by considering age, sex, HBsAg and HBV DNA levels, and ALT ratio (ALT divided by the ULN of the local laboratory).[407] However, predictive accuracy remains low, and the fluctuating patterns of HBV DNA and ALT in serum may make it challenging to predict responses based solely on these variables. Consequently, the dynamics of HBsAg and HBV DNA during treatment offer better predictability for response to PEG-IFNα. Hence, stopping rules based on HBsAg and HBV DNA kinetics have been established (see section "Stopping rules").

Dose and duration of PEG-IFNα

Data from a prospective randomised study showed that 48 weeks of therapy with 180 μg PEG-IFNα-2a once a week (approved treatment duration and dose) was superior to a shorter therapy (24 weeks) or a lower dosage (90 μg once a week) in terms of durable anti-HBe seroconversion.[408] However, this study included relatively few patients from Europe.

The optimal duration of therapy for HBeAg-negative patients has not been well studied. In HBeAg-negative patients, a longer duration of therapy (*e.g.* 72 or 96 weeks) appears to be associated with higher long-term response rates.[409]

PEG-IFNα -2a and PEG-IFNα -2b[410,411] demonstrate comparable efficacy as monotherapy or when combined with NAs. However, PEG-IFNα -2b is typically less favoured due to its requirement for dosing adjustment based on body weight and potential challenges in patients with renal impairment, in contrast to the fixed dosage regimen of PEG-IFNα -2a.

Stopping rules

HBeAg-positive chronic hepatitis B

A combined retrospective cohort of HBeAg-positive patients (n = 803) identified HBsAg serum concentrations >20,000 IU/ml or the lack of a drop in HBsAg levels after 12 or 24 weeks of PEG-IFNα therapy as a robust negative predictor of treatment response (Fig. 3)[412].

In the study, response was defined as the combined endpoint of HBeAg/anti-HBe seroconversion and HBV DNA <10,000 copies/ml (equivalent to <2,000 IU/ml) 24 weeks after the end of PEG-IFNα treatment. These results were confirmed for patients receiving PEG-IFNα monotherapy or a combination of PEG-IFNα and NAs. By including predominantly Caucasian and Asian HBV cohorts, the identified predictor could be successfully applied to patient subgroups with HBV genotypes A, B, C and D.

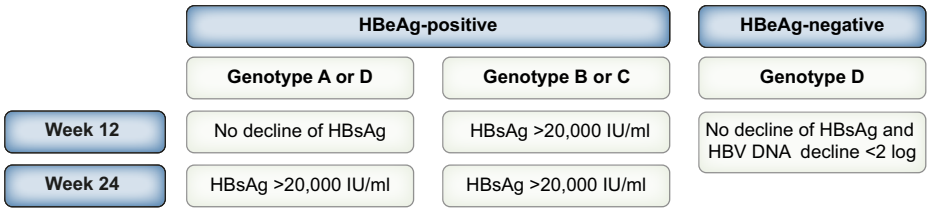

Fig. 3. Rules for discontinuing PEG-IFNα therapy at treatment week 12 and 24 for HBeAg-positive and -negative patients. These rules are based on the viral genotype, HBsAg and HBV DNA levels (no change to CPG 2017[5]). CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG-IFNα, pegylated interferon-alfa.

HBeAg-negative chronic hepatitis B

Studies evaluating predictors of treatment response in HBeAg-negative patients have shown a high negative predictive value (>95%) for treatment response when established stopping rules are applied. In the largest retrospective study (n = 262), treatment response was defined as the combined endpoint of normalisation of ALT and HBV <2,000 IU/ml at 24 weeks after the end of PEG-IFNα treatment. The highest predictive value for treatment non-response was observed in patients with HBV genotype D, where the absence of HBsAg decline and an HBV DNA reduction of <2 $\log_{10}$ after 12 weeks of therapy predicted non-response with 100% accuracy.[413]

Notably, the only patient who achieved a treatment response despite meeting the stopping criteria was infected with HBV genotype A. Based on these findings, the identified predictors are strongly recommended as decision-making criteria for the premature discontinuation of PEG-IFNα therapy at week 12, particularly in patients with HBV genotype D infection, where treatment efficacy is unlikely.

The additional value of HBcrAg in refining stopping rules and predicting response to PEG-IFNα therapy has been suggested. HBcrAg decline at week 24, combined with HBsAg-based stopping rules, may more effectively identify non-responders among HBeAg-positive patients.[414] In the ANCHOR study, HBcrAg <4 $\log_{10}$ U/ml in combination with anti-HBs >2 $\log_{10}$ IU/L at the end of treatment predicted sustained response with 100% positive predictive value.[415] Additionally, in HBeAg-negative patients, high baseline levels of HBsAg (>3.4 $\log_{10}$ IU/ml) and HBcrAg (>3.7 $\log_{10}$ U/ml) demonstrated high negative predictive values for virological response (90%) and HBsAg clearance (100%).[416] However, no definite cut-offs have been defined.

Combination therapy PEG-IFNα and NA

A systematic review concluded that there is no evidence for an advantage of PEG-IFNα/NA combination therapy over PEG-IFNα monotherapy.[417]

However, most studies were conducted with lamivudine. One randomised-controlled trial in HBeAg-positive and HBeAg-negative patients compared primary combination therapy with PEG-IFNα-2a plus TDF for 48 weeks to PEG-IFNα-2a monotherapy (48 weeks) or TDF monotherapy (120 weeks). The primary endpoint, HBsAg loss at week 72, was achieved in relatively few patients overall. At 48 weeks, the combination group showed a significantly higher HBsAg loss rate compared to the PEG-IFNα monotherapy group (9.1% *vs.* 2.8%). The highest response rates were observed in HBV genotype A and HBeAg-positive patients, but the small subgroup sizes limit definitive conclusions.[418]

Based on this study, no general recommendation for *de novo* combination therapy can be made. However, in individual HBeAg-positive cases where PEG-IFNα treatment appears appropriate (*e.g.* genotype A or other favourable predictive factors), a 48-week combination of PEG-IFNα and TDF may be considered to increase the likelihood of HBsAg loss and achieve durable immunological control of HBV infection. It should be noted that this therapy is not technically licensed, and "off-label use" is likely subject to varying regulations across different countries.

Numerous studies analysed the effectiveness of a switch from ongoing treatment with NAs to PEG-IFNα for 48-52 weeks or an additional ("add-on") treatment with PEG-IFNα (usually for 24-48 weeks) to ongoing treatment with NAs *vs.* continued NA monotherapy. HBsAg loss rates can be improved by PEG-IFNα therapy. However, overall HBsAg loss rates were only 8% for the "add-on" therapy and 14% for the "switch" therapy. Higher HBsAg loss rates in the "switch" studies may be explained by the selection of patients with more favourable conditions, making it difficult to compare treatment outcomes.[419] Tolerance and acceptance of add-on PEG-IFNα may be a concern as a recent multicentre, open-label, randomised-controlled trial in France found this regimen to be poorly tolerated, leading to early discontinuation of PEG-IFNα in 20% of patients but no significant increase in HBsAg clearance.[420]

Based on the available evidence from mainly non-randomised studies, treatment of selected individuals with low HBsAg levels with NAs plus PEG-IFNα (*e.g.* as add-on therapy) may be a viable option to achieve HBsAg loss. Patients with low HBsAg levels (*e.g.* <1,500 IU/ml), HBeAg-negative status, and HBV DNA negativity may benefit from this therapy, regardless of prior IFNα treatment. Predictive factors for a positive treatment response include younger age (≤40 years) and low baseline or week 12 HBsAg levels.[421] Notably, a randomised-controlled trial demonstrated that in HBeAg-negative patients with HBV DNA <60 IU/ml for ≥2.5 years, switching from NAs to PEG-IFNα for 48 weeks significantly reduced virological relapse rates (7.8% *vs.* 20.9%) and increased HBsAg loss (21.5% *vs.* 9.0%) compared to NA cessation alone,[422] suggesting an optimised strategy for NA cessation.

Monitoring for safety

A decline in leukocytes and platelets is common during PEG-IFNα-based therapy.[423]

The blood count should be checked and the PEG-IFNα dose adjusted in accordance with the prescribing information. PEG-IFNα therapy can trigger autoimmune thyroid disease. This has

been shown in particular in patients with chronic hepatitis C[424] and there is limited evidence that this also occurs in HBV infection. Nevertheless, thyroid stimulating hormone should be checked before and during therapy (every 8 weeks). ALT flares can also occur during treatment despite suppression of HBV DNA, particularly in the early treatment phase[425] ALT levels should be determined every 8-12 weeks during treatment. Psychiatric side effects, including depression, are significant concerns with PEG-IFNα treatment and should be carefully considered both during patient selection and throughout therapy to ensure proper management.[426]

HCC surveillance

Which patients with chronic HBV infection should undergo HCC surveillance and how should HCC surveillance be undertaken?

Recommendations

- The inclusion of patients at risk of HCC in surveillance programmes is recommended. The strength of this recommendation for HCC surveillance is based on the individual risk level **(LoE 2, strong recommendation, strong consensus).**
- Individual risk assessment can be enhanced by applying HCC risk scores **(LoE 2, weak recommendation, strong consensus).**
- HCC surveillance should involve abdominal ultrasound performed every 6 months by an experienced operator in all at-risk populations **(LoE 2, strong recommendation, strong consensus).**
- HCC surveillance should be continued in at-risk patients irrespective of effective antiviral therapy or HBsAg loss **(LoE 2, strong recommendation, strong consensus).**
  - Other imaging modalities (contrast-enhanced CT, MRI) should be used if abdominal ultrasound cannot provide reliable information **(LoE 3, strong recommendation, strong consensus).**
  - Tumour biomarkers (*e.g.* alpha-fetoprotein [AFP]) can be used in addition to imaging for HCC surveillance **(LoE 2 (for AFP), weak recommendation, consensus).***

Cancer surveillance programmes are a key public health initiative aimed at reducing liver-related and overall mortality, as recommended by the WHO in its viral hepatitis elimination plan. However, in most LMICs, programmes for the early diagnosis of cirrhosis and HCC surveillance remain scarce. Addressing this gap should be a priority for health policymakers and research institutions.

HCC surveillance involves regular diagnostic testing for patients with chronic HBV infection at risk of developing HCC (Table 11). Its effectiveness depends on factors like HCC incidence in the population, access to accurate, affordable diagnostics, and availability of effective treatments. In high-risk groups with elevated HCC incidence, surveillance is cost-effective, often meeting thresholds such as $50,000 per life year saved by enabling early detection and treatment.[427] HCC surveillance is suggested to be cost-effective when the annual HCC incidence exceeds 0.2% in individuals with chronic HBV infection.[428] Importantly, robust evidence, including meta-analyses of cohort studies and a large randomised-controlled trial in patients with chronic HBV infection, has shown that HCC surveillance significantly improves clinical outcomes, including reduced HCC mortality.[429–431] Of note, HCC surveillance may also cause harms, primarily due to false-positive or indeterminate test results, occurring in approximately 10% of patients, but the benefits outweigh these risks.[432]

Risk groups

Patients with cirrhosis have the highest risk of HCC and require HCC surveillance regardless of antiviral therapy. This is because the risk of HCC is not eliminated even with effective antiviral treatment and HCC can still develop several years after treatment.[433] However, in patients with cirrhosis and life-threatening comorbidities and decompensated cirrhosis (*i.e.* Child-Pugh C), where treatment options for HCC are limited or no longer available unless transplantation is possible, HCC monitoring is not cost-effective and is not recommended.[427,432]

For HBsAg-positive individuals without cirrhosis, multiple risk factors influence the risk of developing HCC, and these factors have been incorporated into various risk scores. Numerous prediction models have been developed to enhance the accuracy of HCC risk assessment in both untreated and treated patients[218,434,435] (Table 12).

These models can play an important role in risk stratification, enabling prioritisation of high-risk patients for HCC surveillance. Most of these models were initially developed in treatment-naïve Asian patients with chronic HBV infection before antiviral therapies became widely available.[436] In the era of effective antiviral treatments for HBV, an increasing number of prognostic models have been developed and validated specifically for patients receiving these therapies.

Table 11. Recommendation for HCC surveillance in HBsAg-positive individuals (adapted from[427]).

Patients at risk of developing HCC	Recommendation	Evidence
Patients with cirrhosis (Child-Pugh A and B and Child-Pugh C who are candidates for liver transplantation)	Surveillance is recommended	LoE 2
HBsAg-positive individuals without cirrhosis (under NA therapy) at intermediate or high risk of HCC (*e.g.* PAGE-B ≥10, family history of HCC, chronic hepatitis delta and advanced fibrosis [64])	Surveillance is recommended	LoE 3
HBsAg-positive individuals without cirrhosis at low risk of HCC	Surveillance is not suggested but the risk of HCC should be regularly re-evaluated	LoE 2

HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

Table 12. Available HCC risk scores (adapted from[218,434,435]).

Score	Variables	Comments and risk cut-offs
REACH-B	Age, sex, HBeAg, HBV DNA, ALT	Developed for treatment-naïve patients, Low: 0-7; Intermediate: 8-12; High: ≥13
mREACH-B	Age, sex, HBeAg, ALT, LSM	Tailored to antiviral therapy, Low: 0-5; Intermediate: 6-11; High: ≥12
PAGE-B	Age, sex, platelets	Simple risk score for NA therapy: Low: 0-9; Intermediate: 10-17; High: ≥18
mPAGE-B	Age, sex, platelets, albumin	Modified version of the original PAGE-B score: Low: 0-8; Intermediate: 9-12; High: ≥13
PAGED-B	Age, sex, platelets, HBV DNA (5-8 $\log_{10}$ IU/ml), diabetes	Modified for HBeAg-positive individuals: Low: <7; High: ≥7
CAGE-B	Age (at year 5#), baseline cirrhosis, LSM (year 5#)	Low: 0-5; Intermediate: 6-10; High: ≥11
SAGE-B	Age (at year 5#), LSM (year 5#)	Low: 0-5; Intermediate: 6-10; High: ≥11
HCC-RESCUE	Age, sex, cirrhosis	Low: 18-64; Intermediate: 65-84; High: ≥85
CAMD	Age, sex, cirrhosis, T2DM	Low: 0-7; Intermediate: 8-13; High: ≥14
AASL-HCC	Age, sex, cirrhosis, albumin	Low: 0-5; intermediate: 6-19; High: ≥20
aMAP	Age, sex, albumin, bilirubin, platelets	Low: 0-49.9; Intermediate: 50-59.9; High: ≥60
REAL-B	Age, sex, cirrhosis, platelets, alcohol, T2DM, AFP	Low: 0-3; Intermediate: 4-7; High: 8-13
GAG-HCC	Age, sex, HBV DNA, core promoter mutations, cirrhosis	Low: 0-100; High: >100
CU-HCC	Age, albumin, bilirubin, HBV DNA, cirrhosis.	Low: 0-4; Intermediate: 5-19; High ≥19
LSM-HCC	Age, serum albumin, HBV DNA, LSM	Modified version of the CU-HCC: Low: 0-10; High: 11-30
RWS-HCC	Age, sex, cirrhosis, AFP	Low: <4.5; High: ≥4.5
NGM1-HCC, NGM2-HCC	Age, sex, family history of HCC, alcohol consumption habit, ALT, HBeAg, HBV DNA, HBV genotype	Nomograms, no cut-offs

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; NA, nucleos(t)ide analogue; T2DM, type 2 diabetes mellitus.
#at year 5 of antiviral treatment.

In general, almost all models include age and sex as one of the variables, emphasising the importance of increasing age and male sex as important factors associated with HCC in untreated and treated patients.[434] Models that include HBeAg, HBV DNA and ALT may be less accurate in patients on NA therapy as these factors can change during long-term treatment.[434] Such models (*e.g.* the REACH-B score) may be more suitable for identifying untreated patients who would benefit from antiviral therapy (see section "Treatment indications"). Models that incorporate liver function or fibrosis-related parameters, such as LSM, tend to be more accurate for treated patients,[437–439] who are the target of HCC surveillance programmes, as untreated patients at risk of HCC should be treated accordingly.

Given the increasing prevalence of T2DM in patients with chronic HBV infection, its impact on HCC risk prediction has been carefully assessed. The inclusion of T2DM as a variable in risk models could improve their predictive accuracy.[440] In a systematic review of the available HCC scores, the REAL-B model, which also includes T2DM as a variable, showed the best discrimination and calibration.[434] For clinical practice, however, the PAGE-B and mPAGE-B scores are simpler, as they do not require a precise diagnosis of cirrhosis by histology or LSM (Table 13).

Of note, the PAGE-B score, originally developed in European patients[441] and further validated in other European cohorts[442] and in European HIV/HBV-coinfected patients,[443] appears to perform differently in Asian and Caucasian populations, likely due to different factors such as age at HBV transmission and genotype distribution.

Thus, it is suggested to use the PAGE-B score in Caucasian patients where it has shown higher predictive accuracy. For

Table 13. HCC risk assessment using PAGE-B and mPAGE-B scores.[441,446]

PAGE-B: Low risk: 0-9; intermediate risk: 10-17; high risk: ≥18							
Age (years)	**Points**	**Sex**	**Points**	**Platelets (μmol/L)**	**Points**		
16-29	0	Female	0	>200	0		
30-39	2	Male	6	100-199	6		
40-49	4			<100	9		
50-59	6						
60-69	8						
≥70	10						
mPAGE-B: Low risk: 0-8; intermediate risk: 9-12; high risk: ≥13							
Age (years)	**Points**	**Sex**	**Points**	**Platelets (μmol/L)**	**Points**	**Albumin (g/dl)**	**Points**
16-29	0	Female	0	>250	0	≥4.0	0
30-39	3	Male	2	200-250	2	3.5-4.0	1
40-49	5			150-200	3	3.0-3.5	2
50-59	7			100-150	4	<3.0	3
60-69	9			<100	5		
≥70	11						

HCC, hepatocellular carcinoma.

Asian populations, alternative models may be more appropriate owing to demographic and genetic factors. Nevertheless, in a large study from Hong Kong involving over 32,000 individuals receiving ETV or TDF treatment, the PAGE-B and mPAGE-B scores effectively identified low-risk patients who may not require routine 6-monthly HCC surveillance, thus optimising resource allocation.[444] The SAGE-B and CAGE-B models that include age and LSM at 5 years of NA treatment might be better than the PAGE-B model in predicting HCC development after 5 years of NA treatment.[445] In the absence of specific screening recommendations and validated risk assessments for patients of African descent, and until population-specific models are developed and validated, a more conservative screening strategy should be considered. Further studies are essential to refine risk stratification and optimise surveillance strategies for African patients.

There is ongoing debate about whether HBsAg-negative/anti-HBc-positive individuals face a high enough risk of HCC to justify routine surveillance. A meta-analysis of 16 cohort and 10 case-control studies demonstrated an increased HCC risk in HBsAg-negative/anti-HBc-positive individuals with chronic liver disease, independent of geographic region, disease stage, or aetiology. The highest risk was seen in those with isolated anti-HBc.[447]

However, the HCC risk may vary across three clinical scenarios, which must be considered separately: 1) chronic hepatitis B with HBsAg seroclearance, 2) past HBV infection without a history of chronicity, and 3) occult HBV infection (HBsAg-negative, anti-HBc positive or negative, low-level HBV replication).

For individuals with chronic hepatitis B who have lost HBsAg, studies indicate that HCC risk may remain above the surveillance threshold (≥0.2% per year), particularly in those who are older (>50 years) at HBsAg loss, have cirrhosis, or have a family history of HCC.[448] Therefore, HCC surveillance is justified when these risk factors are present.

For individuals with resolved HBV infection (HBsAg-negative, anti-HBc-positive) without prior chronic HBV infection, routine HCC surveillance is generally not recommended, unless other risk factors are present. In the Taiwanese NBNC (Non-B, Non-C) population, wherein 87% of individuals were anti-HBc positive, the HCC incidence was 47.2 per 100,000 person-years, which is below the threshold needed to justify a surveillance programme.[449]

Occult HBV infection has been implicated in liver disease progression, but its role in cirrhosis and HCC development remains debated. Some studies – particularly in HCV-related liver disease – show a significant association, while others do not.[11] While occult HBV infection retains oncogenic mechanisms similar to overt HBV – such as viral DNA integration and pro-oncogenic protein production – further research is needed to clarify its precise impact on HCC pathogenesis.[11] Routine HCC surveillance for patients with occult HBV infection is not currently recommended, unless they have additional risk factors – such as cirrhosis, metabolic liver disease, or coinfections – that increase their estimated annual HCC risk to ≥0.2% per year.

Optimal surveillance intervals

The 6-month screening interval recommended in the guidelines is initially based on the average doubling time of the tumour volume in HCC, which is around 4 to 5 months.[450] However, based on expert opinion, the Asian guidelines recommend shortening the screening interval for high-risk groups to 3-4 months.[24–26] Indeed, one study from Taiwan showed that regular ultrasound screening with intervals less than 6 to 12 months may be associated with early detection of HCC, especially in patients with chronic hepatitis B.[451] Another study from Taiwan comparing ultrasound screening intervals of 4 months *vs*. 12 months in patients with chronic hepatitis B or C found that although the shorter interval led to earlier cancer detection, there was no significant difference in 4-year survival rates between the groups.[452] The analysis of the Italian Liver Cancer database showed that a 3-month interval in high-risk patients with chronic viral hepatitis did not further improve survival.[453] A multicentre randomised trial showed that HCC surveillance every 3 months detected more small focal lesions than ultrasound surveillance every 6 months, but did not improve detection of small HCCs.[454] The NICE guidelines contain systematic reviews and meta-analyses on the frequency of surveillance (ultrasound in combination with AFP) and conclude that a 6-month interval is optimal. Shorter intervals of 3-4 months showed no additional benefit, while longer intervals of 9-12 months were associated with disadvantages in early detection.[455] A further meta-analysis showed that the sensitivity of the 6-month examination was 20% better than that of the 12-month examination.[456] Based on this evidence, EASL recommends a 6-month interval for HCC surveillance.

Imaging techniques for HCC surveillance

Ultrasound is the method of choice for HCC surveillance and shows acceptable diagnostic accuracy as a monitoring tool, with a sensitivity of 58% to 89% and a specificity of over 90%, although its performance certainly depends on the expertise of the examiner and the quality of the equipment.[427,432] The widespread use of ultrasound is also due to its safety, acceptance by patients, and relatively low cost, and the ability to detect the occurrence of other complications of cirrhosis, such as subclinical ascites or portal vein thrombosis, which also require rapid treatment. However, if ultrasound is difficult to perform or provides inadequate results due to patient factors such as obesity, intestinal gas or chest wall deformities, contrast-enhanced CT or MRI may be considered. Cohort studies from Asia demonstrated that both CT and hepatobiliary contrast-enhanced MRI have superior sensitivity for early-stage HCC detection compared with ultrasound-based surveillance.[457,458] However, CT or MRI, while offering high diagnostic sensitivity, are generally not cost-effective for routine HCC surveillance and validation in European cohorts are lacking. These modalities have high false-positive rates and require contrast agents to achieve adequate sensitivity, contributing to their limitations.[427] A high rate of false-positive findings from advanced imaging may lead to unnecessary follow-up investigations and higher costs. Long-term use is debatable due to the cumulative risks of radiation exposure (CT), high costs (MRI), and potential complications from contrast agents, such as allergic reactions or gadolinium deposition in the brain.[427]

Biomarker integration in surveillance

Some international guidelines recommend combining serum AFP with liver ultrasound for HCC surveillance.[432,459] However, AFP is not produced in approximately 10-20% of HCC cases

due to biological variability, limiting its utility in some patients.[427,460] Despite this, a meta-analysis of 32 studies involving 13,367 patients with cirrhosis showed that combining ultrasound with serum AFP improves sensitivity for early-stage HCC detection (63%) compared to ultrasound alone (45%).[460] A cost-benefit analysis showed that ultrasound and AFP is more cost-effective for HCC surveillance than ultrasound alone or no surveillance in patients with compensated cirrhosis.[461]

Combining AFP with novel biomarkers may further enhance HCC detection sensitivity.[460] Newer biomarkers and models, such as the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), des-γ-carboxy-prothrombin (DCP or PIVKA-II), and the GALAD (Gender, Age, AFP-L3, AFP and DCP) score, are being used more frequently in the diagnosis and prognosis of HCC.[460] The GALAD score consistently outperformed AFP alone in detecting HCC across various studies including a phase III study.[462] Sensitivities range from 54% to 91% and specificities from 73% to 98%, with even better results when combined with ultrasound (*e.g.* GALADUS).[459,460] GALAD and GAAD (GALAD without AFP-L3) performed comparably across disease stages, aetiologies and ethnicities.[463] However, limitations include high false-positive rates, reduced sensitivity with stricter adjustments, and challenges in automation.[459]

Treatment in special patient populations

Should patients with acute HBV infection be treated with antiviral therapy?

Statement

- Given the high spontaneous clearance rate of HBsAg during acute HBV infection in adults, antiviral treatment is not required in this clinical setting as long as synthetic liver function is not impaired **(strong consensus).**

Recommendation

- Patients with acute hepatitis B and impaired synthetic liver function should be treated with NAs and should be managed in cooperation with a transplant centre **(LoE 2, strong recommendation, strong consensus).**

Acute hepatitis B usually resolves spontaneously in most adults, with HBsAg clearance in over 95% of cases.[5] Thus, further improving the HBsAg loss rate through antiviral therapy is unlikely and has not been documented. A randomised, placebo-controlled study in India demonstrated no advantage of lamivudine over placebo in acute hepatitis B.[464] Conversely, a study from Asia reported improved clinical outcomes, including reduced mortality, with lamivudine in 80 patients with severe cases, including patients with impaired coagulation.[465] A European placebo-controlled study in patients with severe hepatitis without liver failure could not be completed due to insufficient recruitment. However, the available data did not demonstrate any survival or transplant benefit in severe cases (defined as prothrombin time >50%, corresponding to an INR <1.5), although this conclusion is based on a low number of cases.[466] A meta-analysis covering different degrees of severity of acute HBV infection concluded that antiviral therapy is not generally recommended for acute HBV infection at present.[467]

However, case reports and case series suggest that early antiviral NA therapy in patients with fulminant hepatitis B (characterised by signs of liver dysfunction and occurring in 0.1–0.5% of adult cases) significantly reduces the need for transplantation. This is in contrast to historical controls, where 50–80% of untreated patients required transplantation.[468–470] Of note, patients with fulminant hepatitis B were underrepresented in the aforementioned meta-analysis.[467]

In this setting, treatment should be initiated promptly, as liver transplantation or death can no longer be prevented by antiviral therapy in patients with advanced liver failure.[469] Patients with symptomatic hepatitis B should therefore be closely monitored for liver function to ensure early intervention.

The impact of early NA therapy on the HBV-specific immune response and its potential role in HBsAg loss remains a subject of ongoing debate. While an Asian study suggested it might reduce HBsAg seroconversion rates,[465] this was not confirmed by other studies.[466,469] Overall, the available evidence, including the benefit-risk ratio, supports NA therapy for acute severe hepatitis B with signs of impaired synthetic liver function. In cases of impaired hepatic synthesis (*e.g.* prothrombin time ≤50% corresponds to an INR ≥1.5), immediate NA therapy is indicated to prevent fulminant liver failure. In addition, prompt referral to a liver transplant centre is essential.

Antiviral therapy should be continued until confirmed HBsAg loss. Although most studies were conducted with lamivudine, more recent data suggest that ETV and tenofovir are equally effective and safe.[469]

When selecting NAs, comorbidities (especially renal insufficiency and reduced BMD) and concomitant circumstances should be taken into account (see section “Treatment”).

What are the treatment recommendations for pregnant HBsAg-positive women?

Recommendations

- In pregnant women on antiviral therapy, tenofovir (TDF, TAF) should be continued, ETV or adefovir should be switched to tenofovir (TDF, TAF). Treatment with PEG-IFNα should be discontinued and switched to tenofovir (TDF, TAF) **(LoE 2, strong recommendation, strong consensus).**
- Untreated pregnant women should receive antiviral therapy during pregnancy in the following cases **(LoE 1, strong recommendation, strong consensus):**
  - Chronic hepatitis, in accordance with the recommendations for non-pregnant women.
  - HBV DNA levels ≥200,000 IU/ml, to prevent mother-to-child transmission of HBV.
  - Positive HBeAg irrespective of HBV DNA level, in areas where HBV DNA testing is unavailable, to prevent mother-to-child transmission.
- Treatment to prevent mother-to-child transmission should ideally be started before the last trimester of pregnancy. Tenofovir (TDF, TAF) should be used during pregnancy **(LoE 2, strong recommendation, strong consensus).**

- Maternal antiviral prophylaxis with tenofovir can be continued long-term post-delivery to maintain viral suppression **(LoE 2, weak recommendation, strong consensus).**
- During maternal antiviral prophylaxis with tenofovir, the newborn can be breastfed **(LoE 4, weak recommendation, strong consensus).**

When assessing the benefits and risks of antiviral therapy during pregnancy, it is essential to differentiate potential risks to the newborn from those affecting the pregnant woman. For women with chronic HBV infection, whether known or newly diagnosed, the indication for treatment should be carefully reassessed.

Safety of antiviral therapy in pregnancy

There are limited data on the safety of PEG-IFNα in pregnancy and there is a possibility of potential risks to the foetus as the effect on pregnancy and foetal development is not fully known, although one systematic review did not find an increased risk of major malformation, miscarriage, stillbirth or preterm delivery compared to general population rates.[471] PEG-IFNα is not recommended during pregnancy due to the availability of safer alternative therapies.

Lamivudine, ETV, and adefovir are classified by the FDA as "Category C" drugs, indicating that side effects have been observed in animal studies. In contrast, tenofovir and telbivudine are classified as "Category B" drugs, meaning that while no evidence of adverse effects on the foetus has been observed in animal studies, controlled human studies are lacking. Despite this, sufficient clinical data from studies and large pregnancy registries support the safety of lamivudine, telbivudine, and tenofovir (both TDF and TAF). No increased risk of foetal malformations has been found with these medications, even when used in the first trimester.[472–478] Therefore, tenofovir is the recommended antiviral drug during pregnancy and treatment should be continued (or started) if the treatment indications are met and to prevent MTCT.

Prevention of MTCT

MTCT can still occur in highly viraemic mothers despite the newborn receiving appropriate simultaneous active-passive immunisation. The risk of MTCT rises with higher HBV DNA concentrations in pregnant women, reaching up to 30% when HBV DNA levels exceed 6-8 $\log_{10}$ IU/ml.[479,480] This risk can be mitigated by reducing the viral load to <200,000 IU/ml as early as possible through antiviral therapy (tenofovir recommended).[472,473,481,482] Even though a placebo-controlled study with 147 patients in each group (placebo *vs*. TDF) showed no significant difference in transmission risk in this setting, all (three) cases of MTCT occurred in the placebo group.[483] A systematic review and meta-analysis of 31 studies involving 2,588 highly viraemic mothers who received TDF, 280 who received TAF, and 1,600 who received no treatment showed that both TDF and TAF were effective in reducing MTCT of HBV, with no safety concerns recorded for either mothers or infants.[478] However, to date, there is no evidence suggesting that MTCT of HBV occurs when HBV DNA levels are <200,000 IU/ml, as long as the newborn receives timely active-passive birth dose vaccination.[472,480] Therefore, antiviral therapy to prevent MTCT does not need to be started if the HBV DNA level is <200,000 IU/ml, provided that postpartum vaccination is guaranteed.

Timing of maternal antiviral prophylaxis

To minimise the risk of MTCT, antiviral therapy can be initiated at any stage of pregnancy, including the first trimester.[472,477] Most studies have started treatment between weeks 28 and 32.[472,473,481,482] Notably, one study demonstrated that an 8-week prenatal course of TAF, starting at week 33, was also effective, with 97% of treated women achieving HBV DNA levels <200,000 IU/ml at delivery.[484] However, another study found that when treatment was initiated at 30-32 weeks, 31 out of 97 mothers still had HBV DNA levels ≥200,000 IU/ml at delivery, leading to five cases of MTCT.[482] One modelling study based on real-world data suggests that pregnant women with chronic HBV infection and HBV DNA levels >8 $\log_{10}$ IU/ml should begin antiviral prophylaxis before 25 weeks of gestation.[485] A recent randomised-controlled trial demonstrated that initiating TDF at gestational week 16 in high-viraemic mothers (HBV DNA >8.2 $\log_{10}$ IU/ml) was non-inferior to starting at week 28, provided that both active and passive birth dose vaccination were administered.[486] The authors of the study suggest that early initiation of treatment, such as at week 16, may be important for preventing MTCT of HBV in settings where HBIG is unavailable.

Continuation or discontinuation of maternal antiviral therapy postpartum

Decisions regarding postpartum continuation of NA therapy depend on multiple factors. If a mother plans another pregnancy, had a preexisting treatment indication (*e.g.* chronic hepatitis or fibrosis), or wishes to continue therapy, treatment should be maintained. Conversely, if there was no treatment indication beyond MTCT prevention (*e.g.* HBeAg-positive chronic infection), treatment can be stopped shortly after delivery, provided close monitoring is ensured. The Chinese Medical Association recommends that pregnant women who have no other indications for treatment (*e.g.* HBeAg-positive chronic infection) can stop taking NAs immediately postpartum or 1-3 months after delivery.[487] A systematic review showed no significant differences in the efficacy of maternal antiviral prophylaxis when discontinued at the time of childbirth compared to 4-8 weeks postpartum.[488] A recent prospective study further demonstrated that stopping tenofovir at delivery, compared to prolonged treatment, did not increase the risk of virological relapse, need for retreatment, or transmission of the virus to the infant.[489] ALT flares have been reported after treatment cessation, with pooled analyses indicating no significant difference in frequency between patients who

discontinued TDF treatment and those who were not treated during pregnancy.[478,488] However, one prospective study suggested a slightly higher occurrence after antiviral withdrawal.[490] These ALT flares were generally mild and did not progress to fulminant hepatitis.[472,473,490,491] Postpartum ALT flares can be associated with spontaneous HBeAg/anti-HBe seroconversion but the evidence remains inconclusive.[490,492–494] Pooled analyses showed that the severity or frequency of ALT flares was not affected by the timing of cessation of TAF or TDF therapy.[478]

Breastfeeding and antiviral therapy

Concerns about potential drug transfer through breast milk often influence the decision to initiate breastfeeding postpartum. However, lamivudine, TDF, and TAF concentrations in breast milk are very low, with infant exposure to TDF during breastfeeding being lower than *in utero*.[495–497] A study showed no detectable TAF in breast milk, while TDF was present at low levels in both breast milk and cord blood.[498] Data from women using TDF for HIV treatment or pre-exposure prophylaxis have raised no safety concerns.[499,500] Based on current evidence, breastfeeding should not be discouraged if tenofovir (TDF, TAF) therapy is continued. If therapy is stopped immediately after birth, HBV transmission risk through breastfeeding remains negligible, provided that newborns receive proper active-passive immunisation.[501] A systematic review of 10 studies found no difference in HBsAg status between breastfed and non-breastfed infants of vaccinated HBsAg-positive mothers. However, breastfeeding should be avoided in cases of bloody skin lesions.[502] One study suggested non-breastfeeding may slightly reduce MTCT risk in HBeAg-positive mothers with very high HBV DNA (>8 $\log_{10}$ IU/ml) who do not receive antiviral therapy,[503] though the absolute risk reduction was modest, with 65 women needing to abstain to prevent one additional MTCT case.[504] This reinforces the importance of early antiviral therapy in pregnancy to minimise HBV DNA levels and MTCT risk from the outset.

Role of caesarean section in preventing MTCT

The question of whether a caesarean section reduces the risk of MTCT remains debated.[504] A systematic review of 30 studies (9,906 cases) found that elective caesarean delivery may lower the relative risk of MTCT compared to vaginal birth, though data were highly heterogeneous.[505] Another review (18 studies, 11,446 cases) did not confirm this finding but noted a possible benefit for mothers with high HBV DNA levels (≥200,000 IU/ml).[506] Another study of 1,409 cases supported that caesarean section has a benefit when HBV DNA is ≥200,000 IU/ml.[507] Most studies were conducted in China, with limited data on newborn vaccination timing. Timely active-passive immunisation, ideally within 12 (the eralier the better) hours of birth, remains critical. Given the lack of generalisable evidence, routine caesarean section for MTCT prevention is not recommended. However, if maternal HBV DNA is ≥200,000 IU/ml at birth, caesarean section may be considered after a thorough risk-benefit discussion with the patient. A prospective cohort study and meta-analysis found that while caesarean section may modestly reduce MTCT risk in cases of high maternal viral load without antiviral therapy,[503] 23 women would need to undergo a caesarean section to prevent one MTCT case.[504]

How should patients with HBV infection and decompensated cirrhosis or acute-on-chronic liver failure be managed?

Recommendation

- HBsAg-positive patients with decompensated cirrhosis or acute-on-chronic liver failure should be treated with ETV or tenofovir (TDF, TAF), irrespective of HBV DNA levels. PEG-IFNα should not be used in patients with decompensated cirrhosis or ACLF **(LoE 1, strong recommendation, strong consensus).**

NA therapy is highly effective and safe in patients with decompensated liver disease, leading to clinical improvements such as reduced HCC risk, lower MELD and Child-Pugh scores, and improved survival.[158–160] Antiviral therapy often stabilises the condition, with transplant-free survival rates exceeding 80% and up to one-third of initially decompensated cirrhosis cases regressing to a compensated stage.[113,117,508,509] In a study of 320 patients with decompensated cirrhosis (ascites-related) treated with ETV for 120 weeks, more than 50% achieved recompensation per Baveno VII criteria. Predictors of stable improvement included MELD scores <10 and/or Child-Pugh class A,[510] highlighting the importance of early intervention. A study from Hong Kong, analysing 4,701 patients with cirrhosis treated with ETV, TDF, or TAF using a territory-wide database, confirmed that antiviral treatment promotes hepatic recompensation, leading to improved transplant-free survival and reduced mortality.[511] Although early treatment is important, treatment should be considered at all stages of cirrhosis, especially if liver transplantation is being considered, as antiviral therapy before transplantation can reduce the risk of HBV recurrence afterwards.[512]

A meta-analysis has documented that NA treatment of patients with acute-on-chronic liver failure (ACLF) improves survival, liver function and virological response.[513] ETV, TDF and TAF demonstrate comparable efficacy and safety for both the short- and long-term treatment of patients with ACLF.[513,514] However, a study of 272 patients with HBV-related ACLF showed that TAF was more effective than ETV in lowering viral load and improving survival, and the risk of worsening renal function was lower; however, the study was not randomised, so selection bias may have influenced the results.[515] Overall, there is currently no recommendation to select one NA (ETV, TDF, TAF) over another, except when considering factors discussed in the section "Treatment", especially renal function, which is particularly important in patients with ACLF and high MELD scores. Additionally, the risk of developing lactic acidosis should be considered[324,325,516] (see "How should NA therapy be administered and what should be considered during long-term therapy?").

Notably, ETV was initially recommended at a dosage of 1 mg, as the pivotal study used this dose because of the inclusion of lamivudine-resistant patients.[158] However, other studies have demonstrated that 0.5 mg of ETV is equally effective in patients with both compensated and decompensated liver disease.[159] Furthermore, one study confirmed that viral suppression is comparable between the 0.5 mg and 1 mg doses in this setting.[517]

Although data on TAF in decompensated cirrhosis and ACLF are available,[515,518] official approval for its use in these conditions is pending. Importantly, in patients with ACLF or decompensated cirrhosis at Child-Pugh stages B and C, treatment with PEG-IFNα is contraindicated as it can lead to further deterioration in liver function.[519]

Finally, there is debate about whether HBsAg-positive individuals with decompensated cirrhosis or ACLF should receive treatment if HBV DNA is undetectable. Currently, no evidence suggests that antiviral therapy reduces the risk of death or HCC in patients with HBV-related decompensated cirrhosis and undetectable HBV DNA.[520] However, if HBV DNA results are not immediately available, treatment should not be delayed. In addition, patients with decompensated cirrhosis are considered immunocompromised, which makes them susceptible to HBVr. Therefore, close monitoring of HBV DNA levels is essential, and if this is not guaranteed, NA treatment may be justified.

Should patients with chronic HBV infection and HCC be treated with antiviral therapy, and if so, how?

Recommendations

- HBsAg-positive patients with HCC should be treated with NAs, irrespective of HBV DNA levels **(LoE 2, strong recommendation, strong consensus).**
- TDF is suggested as the preferred NA for tertiary prophylaxis after curative treatment (*e.g.* surgery or locoablative therapy) for HCC **(LoE 2, weak recommendation, strong consensus).**

Several studies have demonstrated the benefits of antiviral therapy in HBsAg-positive patients with HCC. In patients who have undergone curative HCC resection, antiviral treatment reduces recurrence rates and improves overall survival. Similarly, patients with initially non-resectable HCC experience slower tumour progression and improved survival when treated with antivirals.[521–529]

Combining ETV or TDF with transarterial chemoembolisation (TACE) has been shown to improve HCC response rates (higher disease control rate, longer progression-free survival) compared to TACE alone.[530]

While both ETV and tenofovir (TDF, TAF) are effective as tertiary prophylaxis for HCC, evidence from randomised-controlled trials and multiple observational studies, as synthesised in systematic reviews and meta-analyses, suggests that TDF may be superior to ETV. Specifically, TDF has been associated with a significantly lower risk of tumour recurrence and improved survival following curative treatments such as surgical resection, ablation, or liver transplantation.[531–536] However, whether TAF confers the same advantage as TDF remains inconclusive. Notably, most of these findings originate from Asian cohorts, raising uncertainty about their applicability to non-Asian populations. Additionally, potential selection bias cannot be ruled out and fewer TDF-treated patients had long-term follow-up compared to those treated with ETV. For example, one study[534] reported superior HCC recurrence prevention with TDF, but median follow-up durations differed substantially (ETV: 4.4 years *vs.* TDF: 2.6 years, both pre- and post-matching). Despite these limitations, the available data consistently favour TDF in this specific setting, prompting a weak recommendation for its use over ETV. This contrasts with the general (non-HCC) population, where no clear preference has been established.

What should be considered when treating patients with HBV/HIV coinfection?

Recommendations

- HBsAg-positive individuals living with HIV should receive anti-HBV treatment regardless of ALT or HBV DNA levels **(LoE 2, strong recommendation, strong consensus).**
- HBV therapy should be given as part of antiretroviral HIV therapy. In HBsAg-positive individuals living with HIV, the antiretroviral therapy should contain tenofovir (TDF or TAF) **(LoE 1, strong recommendation, strong consensus).**
- Treatment monitoring and adjustments should be carried out in accordance with the recommendations for HBV-monoinfected patients, taking into account the HIV coinfection **(LoE 5, strong recommendation, strong consensus).**
- Anti-HBV-containing antiretroviral therapy should not be discontinued in HBV/HIV coinfection due to the risk of HBV rebound and biochemical relapse **(LoE 2, strong recommendation, strong consensus).**

More than three million people worldwide are coinfected with HIV and HBV.[537] Current HIV guidelines recommend antiretroviral therapy for all individuals with HBV/HIV coinfection because of an increased risk of fibrosis progression and HCC. According to these guidelines, HBV infection should be treated with antiviral therapy regardless of ALT or HBV DNA levels.[5,72,538,539] The risk of developing HCC increases time-dependently with HBV DNA levels of ≥200 IU/ml in HIV/HBV coinfection.[215]

In PLWH coinfected with HBV, treatment for HBV should be coordinated with antiretroviral therapy, as several HIV nucleos(t)ide reverse transcriptase inhibitors, including lamivudine, emtricitabine, and tenofovir (TDF, TAF), are also effective against HBV. Switching from TDF to TAF is recommended if side effects like renal insufficiency or bone metabolism disorders occur (see section “Treatment”). In patients with suppressed HIV and HBV viral loads, transitioning from a TDF-based to a TAF-based antiretroviral regimen has been shown to improve renal function and BMD markers.[540–542]

After initiating antiretroviral therapy in patients with a low CD4 count, immune reconstitution inflammatory syndrome may occur, which can increase the risk of a hepatic flare and liver decompensation. However, in some cases, this process can also lead to HBsAg loss.[543,544] These patients require close monitoring in the first few months. Interruption of therapy with TDF or TAF should be avoided due to possible reactivation of the HBV infection with the risk of a hepatic flare and hepatic decompensation. If TDF or TAF are contraindicated or not available, it is possible to administer ETV in individuals receiving fully suppressive antiretroviral therapy. Previous treatment with lamivudine or emtricitabine must be considered, as prior exposure may increase the risk of ETV resistance and

treatment failure (see section "Treatment"). When switching from TDF/TAF to agents with a lower genetic barrier there is a risk of viral breakthrough. In individuals coinfected with HBV/HIV, lamivudine or emtricitabine are not recommended as sole anti-HBV agents in antiretroviral therapy because of the higher risk of resistance developing. If the conditions are favourable (HBV genotype A, high ALT, low HBV DNA), therapy with PEG-IFNα can be considered.

The monitoring of HBV therapy in HIV-coinfected patients does not differ from patients with HBV monoinfection. Maintained virological suppression in individuals with HBV/HIV coinfection is usually associated with favourable outcomes, while detectable HBV replication is associated with the risk of HCC.[215,545] If liver disease progresses, liver transplantation may be considered as a therapeutic option.

What should be considered when treating patients with HBV/HDV coinfection?

Recommendations

The main recommendations for the treatment of chronic hepatitis delta (including LoE and grade of recommendation) are taken from the EASL clinical practice guidelines on hepatitis D[†] .[64]

- All patients with chronic HBV/HDV coinfection (hepatitis delta) should be considered for anti-HDV treatment (LoE 3, strong recommendation)[†].
- Patients with decompensated cirrhosis should be evaluated for liver transplantation (LoE 3, strong recommendation)[†].
- All patients with chronic HBV/HDV coinfection (hepatitis delta) and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PEG-IFNα or bulevirtide (LoE 2 for PEG-IFNα and LoE 3 for bulevirtide, strong recommendation)[†].
- The combination of PEG-IFNα and bulevirtide may be considered in patients without PEG-IFNα intolerance or contraindications (LoE 5, weak recommendation)[†].
- NAs should be given in patients with compensated or decompensated cirrhosis (LoE 5, strong recommendation)[†].
- NAs should be given in patients without cirrhosis if HBV DNA levels are ≥2,000 IU/ml (LoE 5, strong recommendation)[†].
- Patients with decompensated liver disease may be treated with bulevirtide monotherapy depending on the individual's risk benefit assessment. If decompensation occurs during therapy with bulevirtide monotherapy, therapy can be continued **(LoE 4, weak recommendation, strong consensus).**

The main recommendations for the treatment of chronic hepatitis delta are taken from the EASL CPGs on hepatitis D (for details see[64]). However, a recommendation for treatment with bulevirtide in patients with decompensated cirrhosis was not given. Currently, no randomised clinical trials have assessed the use of bulevirtide in decompensated cirrhosis, and its use in this context is not EMA-approved. However, given its mechanism of action, significant liver function deterioration due to therapy is unlikely. Published individual case reports indicate that bulevirtide therapy does not worsen liver function in patients with cirrhosis and portal hypertension. In some cases of advanced but not decompensated cirrhosis, improvement in liver function has been observed, and increases in bile acids were asymptomatic.[546] In a small German case series, patients with decompensated cirrhosis (Child-Pugh B, MELD score 9-17) treated with bulevirtide showed virological responses similar to those reported in studies on compensated cirrhosis, with 47% improving from Child-Pugh B to A.[547] Data from a French multicentre study further support these findings. In this small cohort of patients with decompensated cirrhosis awaiting liver transplantation, bulevirtide treatment demonstrated comparable virological and biochemical efficacy, leading to improved liver function in some patients. This improvement enabled one patient with HCC to undergo chemoembolisation and resulted in the delisting of 15% of patients. Moreover, bulevirtide treatment was associated with a higher 3-month transplant-free survival rate (76.9% *vs.* 36.7%) compared to no treatment, though untreated patients had more advanced liver disease.[548]

Importantly, while bulevirtide treatment appears to be beneficial for some patients with decompensated cirrhosis, its role in more advanced stages, particularly in patients with Child-Pugh C cirrhosis, remains uncertain. Thus, current recommendations focus on treating patients with Child-Pugh B cirrhosis.

The risk of HDV RNA rebound after discontinuing bulevirtide is a major concern, particularly in decompensated patients, as virological relapse could further impair liver function. Thus, stopping or interrupting treatment due to concerns about off-label use in cases of decompensation, despite a positive response, may be detrimental. In a German real-world cohort, bulevirtide was safely continued in a patient who developed ascites, which was attributed to an unrelated cause.[549]

In general, patients with advanced or decompensated cirrhosis should be treated in specialised centres to ensure timely consideration for liver transplantation. Currently, bulevirtide treatment for decompensated cirrhosis remains off-label, and its use should be carefully considered on a case-by-case basis.

Statement

- The indications for anti-HBV treatment are generally the same as those for chronic HBV monoinfection. However, in the context of anti-HCV therapy, there are additional factors to consider **(strong consensus).**

Recommendations

- HBsAg-positive patients with chronic HCV infection should be treated with HCV-specific direct-acting antivirals **(LoE 2, strong recommendation, strong consensus).**

- All HBsAg-positive patients with cirrhosis (even if HBV DNA is undetectable) should receive NA therapy during anti-HCV direct-acting antiviral therapy to prevent HBV reactivation **(LoE 2, strong recommendation, strong consensus).**
- Prophylactic NA treatment to prevent reactivation during anti-HCV direct-acting antiviral treatment can be given in patients not meeting the indication for treatment of chronic HBV mono-infection (*e.g.* HBV DNA <2,000 IU/ml, normal ALT and absence of advanced fibrosis/cirrhosis) **(LoE 2, weak recommendation, strong consensus).**

What should be considered when treating HBsAg-positive patients with HBV/HCV coinfection?

In regions where HBV and HCV are endemic, coinfection is common due to shared transmission routes.[550,551] Studies consistently show that HBV/HCV coinfection worsens liver disease prognosis compared to HBV or HCV monoinfection. An Australian study found a 32.9-fold increased risk of liver-related death in coinfected patients, compared to 12.2-fold for HBV and 16.8-fold for HCV alone.[552] Multiple systematic reviews and meta-analyses suggest that HBV/HCV coinfection significantly increases HCC risk,[553,554] though findings vary due to study design, sample size, and population differences.[555] The latest meta-analysis (23 studies, 14,849 patients) demonstrated that coinfection raises HCC risk by more than 32-fold, exceeding the risk from HBV or HCV monoinfections combined with smoking (HR 19.81 and 24.86, respectively).[184]

In HBV/HCV coinfection, virological patterns are dynamic, with one virus often suppressing the other.[556–559] Despite this, antiviral efficacy remains unaffected: high sustained virological response rates (similar to those for HCV monoinfection) are achieved with direct-acting antivirals (DAAs),[560,561] and NAs for HBV remain effective in chronic HCV infection.[562] As recommended by the EASL clinical practice guidelines on hepatitis C,[563] all patients with chronic HCV infection, including those coinfected with HBV, should be treated.

In HBV/HCV-coinfected patients, HCV clearance can lead to HBVr, similar to what was observed with PEG-IFNα treatment.[564–566] HBVr typically occurs early during or shortly after DAA therapy,[567,568] and, in rare cases, can progress to severe hepatitis flares[569] or even liver failure requiring transplantation.[568] The risk of HBVr in HBsAg-positive patients treated with DAAs ranges from 5.9% to 24%, while hepatitis flares are less frequent, occurring in <2% to a maximum of 9%.[568–570] The different definitions of HBVr used (ranging from a >1 $\log_{10}$ to >3 $\log_{10}$ increase in HBV DNA) and the considerable heterogeneity between the studies probably contributed to the different results. Higher baseline HBsAg or HBV DNA levels increase HBVr risk,[568,571,572] while prophylactic HBV therapy can help prevent or significantly reduce this risk.[572–574] This is particularly important for patients with cirrhosis. In a study from Taiwan, four patients with HBV/HCV coinfection and cirrhosis who were treated with HCV-DAAs but did not receive anti-HBV NA therapy experienced HBVr. Three of these patients developed liver failure and two died, despite the initiation of immediate NA therapy. Importantly, two of the patients had undetectable pre-treatment HBV DNA.[573] Whether prophylactic NA therapy for HBV is necessary for all HBsAg-positive individuals undergoing HCV therapy in the absence of other indications for HBV treatment or cirrhosis is debatable.

A prospective study from Taiwan involving HBV/HCV-coinfected patients treated with sofosbuvir/ledipasvir reported an increase in HBV DNA in 39 of 74 cases. Despite this, only five patients experienced ALT elevations exceeding twice the ULN, leading to the initiation of antiviral therapy in three cases.[560] In a prospective observational study of 10 HBV/HCV-coinfected patients undergoing DAA therapy, five experienced a >1 log increase in HBV DNA levels; however, none exhibited clinical reactivation (elevated ALT levels).

Despite the generally low risk of HBVr leading to hepatitis flares, a weak recommendation that NA treatment can be initiated to prevent reactivation during anti-HCV DAA therapy in patients who do not otherwise meet the criteria for chronic HBV treatment is provided (*e.g.* HBV DNA <2,000 IU/ml, normal ALT, and no advanced fibrosis or cirrhosis). The optimal duration of NA therapy in this setting is debatable, but the EASL guidelines recommend continuing NAs for at least 12 weeks after HCV treatment.[563] A prospective randomised study from Taiwan of 56 HBV/HCV-coinfected patients showed that 12 or 24 weeks of ETV therapy prevented HBVr (0% reactivation *vs.* 50% without NA) in patients with HBV DNA <2,000 IU/ml and no cirrhosis. However, after discontinuation, reactivation occurred in over 90% of cases, though without significant hepatitis flares.[574] Thus, if NA treatment is initiated in this setting and discontinuation is anticipated, it is recommended that the discontinuation rules described in section “Treatment” be followed to ensure the safety of the patient. The recent WHO guidelines[90] suggest treating all individuals with chronic HBV/HCV coinfection who have detectable HBV DNA. While this approach could simplify management, evidence is lacking regarding the benefit of NA therapy for individuals with HBV DNA levels <2,000 IU/ml, normal ALT, and no evidence of advanced fibrosis or cirrhosis after HCV cure.

Individual case reports have documented HBVr in HBsAg-negative/anti-HBc-positive individuals undergoing DAA therapy for HCV. However, the overall risk during or after HCV treatment remains low, with different meta-analyses reporting rates between 0.16% and 2%.[567,568,570,572] When HBV DNA rebound occurred, it was usually transient, and one study reported that no patients experienced an ALT flare or HBsAg seroreversion, although HBVr occurred in 10% of cases.[575]

If HBVr is clinically suspected, *e.g.* if ALT and/or AST levels persist or rise during hepatitis C therapy, HBV DNA testing should be performed and anti-HBV antiviral therapy initiated if necessary. However, there is no evidence to support routine prophylactic NA therapy in HBsAg-negative/anti-HBc-positive individuals with chronic HCV infection treated with DAAs.

Nevertheless, caution is warranted in patients with cirrhosis, particularly those with decompensated cirrhosis, as HBVr in this setting may lead to severe liver dysfunction or failure. In these high-risk patients, NA therapy can be considered on a case-by-case basis to mitigate potential complications.

What antiviral treatments are available for children and adolescents?

Statement

- Antiviral treatments approved for children and adolescents include **(strong consensus):**
  - IFNα-2b: approved by both the FDA and EMA for children aged 1 year and older.
  - PEG-IFNα-2a: approved for children aged 3 years and older.
  - Lamivudine: approved for children aged 3 years and older.
  - Entecavir: approved for children aged 2 years and older.
  - Tenofovir disoproxil fumarate: approved by the EMA for children aged 2 years and older, and by the FDA for those 12 years and older.
  - Tenofovir alafenamide: EMA approved for children aged 12 years and older or those weighing more than 35 kg, regardless of age.

Note: adefovir is not listed as it cannot be recommended anymore. For the treatment of children and adolescents with chronic HBV infection, it is important to consult specialists experienced in managing this age group to determine the most appropriate treatment based on the individual's age and health status. This guideline does not provide further details specific to this population.

Prophylaxis of HBV reactivation

How should individuals at risk of HBV reactivation be managed?

Recommendations

- HBV reactivation risk assessment and the indication for prophylaxis is based on HBV markers (HBsAg, anti-HBc and HBV DNA status), the planned immunosuppressive regimen and the underlying disease requiring immunosuppression (Table 14). Thus, HBsAg and anti-HBc antibody status should be assessed before starting immunosuppressive therapy. HBsAg-positive individuals starting immunosuppressive therapy should undergo the same clinical evaluation recommended for all HBsAg-positive individuals. HBsAg-negative and anti-HBc-positive individuals should be tested for HBV DNA before starting immunosuppressive therapy **(LoE 1, strong recommendation, strong consensus).**

The following section is intended for HBsAg-positive individuals for whom there is otherwise no indication for antiviral therapy. The term prophylaxis is therefore used for NA therapy.

- HBsAg-positive individuals at high and moderate risk of reactivation should receive prophylactic antiviral therapy with NAs **(LoE 1, strong recommendation, strong consensus).**
- HBsAg-positive individuals at low risk of reactivation do not need to be treated if HBV DNA monitoring is performed at least every 3 months. If there are concerns about feasibility of HBV DNA monitoring, prophylactic NA therapy should be initiated **(LoE 2, strong recommendation, strong consensus).**

The following section is intended for HBsAg-negative/anti-HBc-positive individuals. The term prophylaxis is therefore used for NA therapy.

- HBsAg-negative, anti-HBc-positive and HBV DNA-positive individuals should be managed in the same way as HBsAg-positive individuals **(LoE 2, strong recommendation, strong consensus).**
- HBsAg-negative, anti-HBc-positive, HBV DNA-negative individuals should receive prophylactic NA therapy if immunosuppressive therapy associated with a high risk of HBV reactivation is planned **(LoE 2, strong recommendation, strong consensus).**
- HBsAg-negative, anti-HBc-positive, HBV DNA-negative individuals who will receive an immunosuppressive regimen with moderate or low risk of reactivation do not need to be treated and should be monitored closely (HBsAg and/or HBV DNA every 3 months). If there are concerns about feasibility of HBV monitoring, prophylactic NA therapy should be initiated **(LoE 3, strong recommendation, consensus).**

The following section is intended for all individuals who require prophylactic NA therapy

- ETV or tenofovir (TAF or TDF) should be used for the prophylaxis of HBV reactivation. The duration of NA prophylaxis is not well-defined. NA therapy should be administered for at least 6-12 months after completing immunosuppressive therapy. In high-risk settings, such as with B cell-depleting therapies, it should be continued for at least 18 months after completing immunosuppressive therapy. Ideally, NA discontinuation should follow established criteria for NA withdrawal, particularly if HBV DNA was positive before starting NA therapy (**LoE 3, strong recommendation, strong consensus).**

Risk of reactivation

HBVr refers to a sudden increase in HBV replication in HBsAg-positive individuals with an inactive profile (HBeAg-negative chronic infection) or HBsAg-negative individuals with resolved hepatitis B (HBsAg-negative, anti-HBc-positive), typically due to natural or iatrogenic loss of immune control.[576] It is commonly defined by either the reappearance of HBV DNA (>100 IU/ml) or HBsAg (HBsAg seroreversion) in individuals with previously undetectable levels, or by at least a 10-fold increase in HBV DNA levels from baseline.

HBVr is a potentially life-threatening complication of chemotherapy or immunosuppressive therapies. The incidence of HBVr during or after such treatments can range from 15-50% in HBsAg-positive individuals and exceed 75% following stem cell transplantation. Without timely recognition and management, reactivation can lead to a severe, potentially fatal outcome.[577] In HBsAg-negative/anti-HBc-positive individuals, HBVr is less common but can still exceed 10% in certain

situations, such as with B cell-depleting therapies.[578] Therefore, all individuals being considered for immunosuppressive therapy should undergo testing for HBsAg and anti-HBc antibodies. In HBsAg-negative/anti-HBc-positive individuals, baseline HBV DNA measurement is crucial to rule out active HBV replication. Additionally, anti-HBs testing is suggested in this setting to further stratify the risk of HBVr in HBsAg-negative/anti-HBc-positive individuals (see below) and to identify candidates for vaccination among those who are negative for both HBsAg and anti-HBc (see section "Prevention of HBV infection").

The risk of HBVr is commonly classified into three levels: high (>10%), moderate (1–10%), and low (<1%).[577,579–581] Assessing the risk of HBVr requires a comprehensive evaluation of the individual's serological markers, HBV DNA levels, and the type and intensity of the planned immunosuppressive therapy (Table 14).

For HBsAg-negative/anti-HBc-positive individuals, the levels of anti-HBs and anti-HBc antibodies can further refine the risk assessment. Higher levels of anti-HBc antibodies in HBsAg-negative individuals may indicate an increased risk of reactivation,[62] while high levels of anti-HBs antibodies (≥100 IU/L) might offer protection.[25,582,583] However, the effectiveness of anti-HBs titres can be reduced under immunosuppressive conditions, such as during B cell-depleting treatments,[584] so anti-HBs status is generally excluded from risk assessment. An exception may apply to corticosteroids: at ultra-high doses (>40 mg/day), the HBVr risk can exceed 5% in this population when anti-HBs is negative, and appears lower when anti-HBs is positive[585] - which may justify a more cautious approach in anti-HBs-negative individuals (*e.g.* NA prophylaxis similar to high-risk category). In addition to these factors, individual host characteristics such as age, the type of underlying disease or tumour (*e.g.* haematologic malignancies, some solid tumours), coexisting conditions (*e.g.* HIV infection), the combination and duration of immunosuppressive therapies, and any concurrent liver diseases (*e.g.* cirrhosis) can also impact the HBVr risk.[578]

Numerous systematic reviews and meta-analyses have investigated HBVr risk, considering both the individual's serological status and the potency of the immunosuppressive regimens.[577,580,584,586]

The risk classifications presented in Table 14 are based on this data and additional studies, largely aligning with recommendations from other international guidelines.[579,581,587,588] There are some discrepancies, for example, in the classification of risk between our guidelines and the recently published AGA (American Gastroenterological Association) guidelines.[581] This is partly due to the challenge of precisely defining the boundaries between the 1–10% and >10% risk categories. In cases of uncertainty, patients are classified into the higher risk group as a precautionary measure. Importantly, these discrepancies rarely lead to different clinical management, as the AGA recommends NA prophylaxis for moderate-risk HBsAg-negative/anti-HBc-positive patients, whereas EASL favours monitoring when feasible.[581]

Furthermore, it is important to note that for many newer immunomodulatory agents, evidence on actual reactivation risk remains limited. For example, ustekinumab (anti-IL-12/23) has been linked to a 19% HBVr risk in HBsAg-positive individuals and a 3% risk in HBsAg-negative/anti-HBc-positive individuals, though these estimates are based on only 4 out of 21 cases and 2 out of 67 cases of HBVr, respectively.[586] As these drugs become more widely used and additional data emerge, earlier estimates of HBVr risk may prove to be overestimates, primarily due to reliance on reported cases or retrospective cohorts. Thus, HBVr risk assessments for most biologic therapies should be regularly updated, and prospective registries should ideally be used for accurate risk evaluation.

As an example, methotrexate was initially classified with a moderate HBVr risk based on a single retrospective study reporting up to 5% reactivation in 24 HBsAg-positive individuals.[587] However, a subsequent meta-analysis reclassified methotrexate as a low-risk immunosuppressive agent.[580]

While a systematic review and meta-analysis reported a 1.4% risk of HBVr in HBsAg-negative/anti-HBc-positive individuals receiving anti-TNF treatment like infliximab,[586] a prospective observational study of patients with rheumatologic diseases on long-term biologic therapies found no HBVr among 179 HBsAg-negative/anti-HBc-positive individuals, including 146 patients on anti-TNF therapy.[589]

Classifying the reactivation risk for current personalised cancer and immune therapies is challenging due to their increasing complexity and the use of combination therapies involving various drug classes. For instance, steroids are often administered alongside cancer-directed immunotherapies, which further elevates the risk of HBVr.[590]

Immune checkpoint inhibitors (ICIs) present a unique case. While they have been linked to HBVr,[577,591] they also have the potential to enhance the HBV-specific immune response and are being investigated as part of novel therapeutic approaches for achieving HBV functional cure.[592] Consequently, the risk of HBVr in these cases may be influenced by factors such as the cancer setting, concomitant cancer medications, or steroids used to manage immune-related adverse events associated with ICIs.[577] Nevertheless, it is still possible that immune-modulating effects of checkpoint inhibitors could contribute to an increased risk of HBVr.[591]

Importantly, hepatitis occurring in the context of ICI therapy is presumably more often an immune-related adverse event (ICI-hepatitis) rather than true HBVr. Distinguishing between these conditions is critical to ensure appropriate management, as misdiagnosis could lead to delayed initiation of corticosteroid therapy, which is essential and potentially life-saving in cases of ICI-hepatitis.

At the same time, because corticosteroids or other immunosuppressive therapies are frequently needed for ICI-hepatitis, the risk of HBVr increases, making proactive NA therapy essential for HBV-infected patients. To prevent treatment delays, NA therapy should be initiated preemptively, ensuring that immunosuppressive treatment is not compromised because of uncertainty about the aetiology of hepatitis.

An additional challenge in HBVr risk classification is the varying definitions used across studies. In one study evaluating HBVr in patients with HCC receiving tyrosine kinase inhibitor therapy, 27.7% experienced reactivation based on definition A (an increase in HBV DNA by at least 1 $\log_{10}$), 14% according to definition B (a ≥2 $\log_{10}$ increase in HBV DNA from baseline), and 2.6% according to AASLD definitions.[593]

The risk classification for HBsAg-positive individuals is increasingly influenced by the widespread use of prophylactic NA therapy, which has become standard practice. A systematic review and meta-analysis examining HBVr in patients with rheumatoid arthritis treated with anti-IL-6 therapy reported an overall HBVr risk of 6.7% among HBsAg-positive individuals. However, this risk increased significantly to 37% in patients who did not receive antiviral prophylaxis.[594]

As prophylactic NA therapy is now routinely recommended for HBsAg-positive individuals undergoing immunosuppressive treatments, HBVr risk classification is increasingly relevant for HBsAg-negative/anti-HBc-positive individuals. This group generally has a lower reactivation risk, and not all require prophylactic NA therapy. However, variability in data complicates the clear categorisation of therapies into high, moderate, or low risk. For instance, while some studies report HBVr rates of approximately 11% for B cell-depleting therapies,[595,596] others indicate rates below 10%, highlighting the challenge in defining consistent risk thresholds.[590,597]

To prioritise patient safety, therapies have been classified as higher risk in cases of uncertainty. However, this cautious approach may lead to overtreatment, particularly if NA prophylaxis is recommended for intermediate-risk therapies in HBsAg-negative/anti-HBc-positive individuals. Most therapies in this group are associated with an HBVr risk of approximately 1%.

NA prophylaxis is recommended only for HBsAg-negative/anti-HBc-positive individuals with a high risk of HBVr, while close monitoring is advised for those at moderate or low risk. However, if reliable monitoring cannot be guaranteed, NA prophylaxis should be initiated. It is important to note that immunomodulatory therapies are often managed by non-hepatology specialties, where awareness of HBVr risks may be limited. This increases the likelihood of missed monitoring intervals or incorrect assessments of HBVr parameters. Implementing NA prophylaxis not only ensures expert consultation with HBV specialists but may also enhance adherence to both prophylaxis and proper monitoring protocols.

Special topic: HCC therapy

Current locoregional treatment modalities for HCC appear to pose a particular risk of HBVr. A systematic review showed that untreated HBsAg-positive patients with HCC are at high or intermediate risk of HBVr depending on the type of HCC therapy employed.[598] Retrospective analyses from Asian cohorts suggest that TACE (especially in combination with radiotherapy or repeated cycles) poses a significant (>10%) risk of HBVr in HBsAg-negative/anti HBc-positive individuals.[599,600] In these retrospective analyses, patients with HCC who received antiviral therapy with NAs showed fewer reactivations, fewer decompensation events and, in some cases, improved survival.[598,599,601–603]

HBsAg-positive patients with HCC should always receive long-term antiviral therapy. HBsAg-negative/anti-HBc-positive patients with HCC should receive NA prophylaxis based on the type of HCC treatment, particularly if TACE, radiotherapy, or combination therapies are used Table 14.

Table 14. Risk of HBV reactivation in individuals undergoing immunosuppressive therapies.

Risk of reactivation	HBsAg-positive or HBsAg-negative/anti-HBc-positive but HBV DNA-positive	HBsAg-negative/anti-HBc-positive (HBV DNA-negative)*
High >10%	• Immunosuppression in the context of stem cell transplantation[604] • High-dose combination chemotherapy (*e.g.* R–CHOP)[605] • B cell-depleting therapies[606] • CAR-T cell immunotherapy targeting B cells (BCMA, CD19)[577] • HCC therapies (TACE, radiotherapy, resection, ablation, systemic therapies)[598] • Anthracyclines[607] • Anti-TNF therapies[586] • Corticosteroids (>4 weeks, >20 mg/day)[608] • Cyclophosphamide[609] • JAK inhibitors[610] • IL-6 receptor antagonists[594] • Anti-IL-17[610–612] • Tyrosine kinase inhibitors[593,613]	• Immunosuppression in the context of stem cell transplantation[614] • High-dose combination chemotherapy (*e.g.* R–CHOP)[605] • B cell-depleting therapies[595,596] • HCC therapies (TACE)[599,600] • Anthracyclines[588] • T cell-depleting therapy belatacept – 17% in the setting of transplantation[615]
Moderate or intermediate (1-10%)	• Anti-IL-12/23 (*e.g.* ustekinumab)[586] • T cell activation blocking therapies (ex. abatacept, belatacept)[616] • mTOR inhibitors[617]	• T cell-depleting therapies (*e.g.* abatacept[577]) • CAR-T cell immunotherapy • Corticosteroids (>40 mg)[585] • Anti-TNF therapies[586] • Anti-IL-12/23[586,610] • Anti-IL-17[610] • JAK inhibitors[590,610] • Tyrosine kinase inhibitors (*e.g.* ibrutinib) • Cyclophosphamide[524]
Low (<1%)	• Azathioprine[588] • Methotrexate[588] • Mycophenolate mofetil[588] • Corticosteroids (low-dose <10 mg/day)[608] • Immune checkpoint inhibitors[588]	• Azathioprine[588] • Methotrexate[588] • Mycophenolate mofetil[588] • mTOR inhibitors[617] • Corticosteroids (<40 mg/day) for ≤1 week)[585]

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation.
*The classification of moderate/high risk in HBsAg-negative/anti-HBc-positive patients in some cases is based on low-certainty evidence, with safety and prophylaxis decisions balanced against risk assessment.

Prophylactic NA treatment

Prophylactic antiviral therapy, defined as NA therapy for individuals without other indications for treatment, is crucial for preventing HBVr in immunosuppressed patients. The efficacy of prophylactic therapy is well documented. Lamivudine was successfully used in the early studies,[25,580] but is no longer considered the optimal therapy in light of its lower barrier to resistance when compared to tenofovir and ETV. Therefore, ETV or tenofovir (TDF or TAF) should be preferred for HBVr prophylaxis. Prospective studies and a systematic review support this and conclude that ETV or tenofovir are the most effective options for preventing HBVr.[618,619]

There are even documented cases with resolved HBV infection who, following allogenic haematopoietic stem cell transplantation and immunosuppression, developed HBsAg seroreversion due to the late emergence of lamivudine-resistant HBV during long-term lamivudine prophylaxis.[620] Consequently, ETV or tenofovir (TDF or TAF) should also be used for prophylactic and pre-emptive therapy in this setting. If prophylactic therapy is not indicated, monitoring every 3 months is recommended, with HBV DNA testing preferred. For HBsAg-negative/anti-HBc-positive individuals, HBsAg testing can be an alternative. ALT monitoring alone is inadequate, as ALT increases can lag behind HBV DNA increases by 4 to 12 weeks. A randomised study showed that an 8-week HBV DNA monitoring interval was sufficient to detect HBV reactivation in HBsAg-negative/anti-HBc-positive individuals treated with rituximab, with pre-emptive TDF therapy preventing HBsAg seroreversion.[621] Although not specifically evaluated, a 3-month monitoring interval is recommended for practical reasons.

The optimal duration of prophylactic antiviral therapy remains uncertain and likely depends on factors such as the type and duration of immunosuppressive therapy and the underlying disease (*e.g.* haematological malignancy). Current guidelines recommend continuing antiviral treatment for at least 6–12 months after immunosuppressive therapy ends.[579] A prospective randomised trial from Taiwan found no difference in the effectiveness of 24-week *vs.* 48-week post-chemotherapy TDF prophylaxis for preventing HBVr in patients with cancer.[622] However, late HBVr has been reported, particularly with B-cell-depleting therapies like rituximab, where reactivation can occur more than a year after chemotherapy.[623] A prospective study in 73 HBsAg-positive individuals with newly diagnosed diffuse large B-cell lymphoma treated with rituximab plus R–CHOP chemotherapy evaluated the efficacy of prophylactic TDF. No HBVr or HBV-related hepatitis occurred during TDF therapy (up to 48 weeks after completing chemotherapy). However, following TDF discontinuation, 17 patients (23.3%) experienced HBVr, and 6 (8.2%) developed HBV-related hepatitis a median of 88 days later (range: 37-183 days).[624]

Although the evidence is limited, extending prophylactic antiviral therapy to at least 18 months after B cell-depleting chemotherapy or in high-risk scenarios is recommended to enhance safety. Further monitoring after stopping prophylactic NA therapy is recommended.

Management of HBV infection in the setting of transplantation

How should patients with HBV infection be managed after liver transplantation to prevent HBV recurrence?

Recommendations

- Patients with HBV infection who undergo liver transplantation should receive prophylaxis to prevent HBV recurrence. The standard recommended prophylactic therapy is the combination of a NA (ETV, TDF or TAF) plus hepatitis B immunoglobulin. Hepatitis B immunoglobulin should commence during the anhepatic phase of liver transplantation, and the dosage of hepatitis B immunoglobulin after liver transplantation should be adjusted according to anti-HBs concentrations **(LoE 1, strong recommendation, strong consensus).**
- Hepatitis B immunoglobulin can be discontinued after liver transplantation, provided there is good adherence to high genetic barrier NA therapy and patients are at low risk of HBV recurrence **(LoE 2, weak recommendation, strong consensus).**
- Hepatitis B immunoglobulin-free prophylaxis can be considered after liver transplantation, provided there is good adherence to NAs and patients are at low risk of HBV recurrence **(LoE 2, weak recommendation, strong consensus).**
- In case of HBsAg seroreversion after liver transplantation, hepatitis B immunoglobulin therapy should be discontinued while antiviral therapy with NAs should be continued **(LoE 4, strong recommendation, strong consensus).**

Risk of recurrence

Patients with chronic HBV infection who undergo liver transplantation are at risk of developing *de novo* infection in the transplanted liver, if the liver graft is anti-HBc-negative and no prophylactic measures are taken.[625] However, the term HBV recurrence is used because in the case of liver transplantation from an anti-HBc-positive donor, this can also be due to HBVr. HBV recurrence is defined by the detection of HBsAg and/or HBV DNA and can be classified into various scenarios. These scenarios are typically characterised by either the persistence or recurrence of HBsAg in the serum. In most cases, recurrence is accompanied by significant HBV replication, as evidenced by detectable HBV DNA. Notably, persistent HBV DNA recurrence in the absence of HBsAg is an exceptionally rare event. When it does occur, it is often linked to the emergence of escape mutations within the 'a' determinant of the *HBs gene*.[626] Hepatitis due to HBV recurrence is usually severe if

left untreated. It leads to loss of the organ in the majority of patients and is associated with a high mortality rate.[625] A particularly rapidly progressive form can occur termed fibrosing cholestatic hepatitis B.[627]

HBIG plus NA combination prophylaxis

Combined HBV prophylaxis using HBIG plus NA therapy significantly reduces the incidence of HBV recurrence, provided treatment adherence is adequate.[626,628–630] This approach has significantly improved survival rates, with patients undergoing liver transplantation for chronic HBV infection now achieving 10-year survival rates of up to 80%.[630]

HBIG prophylaxis is initiated during the anhepatic phase of liver transplantation and continues after HBsAg negativity is achieved, aiming for a target anti-HBs concentration of ≥50–100 IU/L.[626] Protocols for HBIG administration may vary between specialised centres and are not comprehensively outlined in this guideline. For maintenance, HBIG can be administered intravenously, intramuscularly, or subcutaneously.[626,631]

The choice of NA therapy should be tailored to individual factors, including prior antiviral treatment, resistance patterns, and comorbidities (see section "Treatment"). Numerous data now show that the use of NAs with high potency (ETV, TDF or TAF) can reduce the risk of HBV recurrence to as low as 0%. Previous studies, albeit with limited case numbers, suggest that ETV and tenofovir are equally effective.[629,632–635]

Unlike TDF, TAF does not require dose adjustment based on renal function (although it is only recommended if eGFR is ≥15 ml/min/1.73 m^2 or in patients on haemodialysis) and has no significant impact on bone metabolism. Post-transplant patients have an increased risk of developing renal insufficiency and osteopenia or osteoporosis due to the simultaneous administration of calcineurin inhibitors and steroids. TDF should not be used to prevent or treat HBV recurrence without assessing individual risk factors. Instead, ETV or TAF should be considered as the primary treatment, particularly when relevant risk factors are present. Lamivudine, as well as adefovir and telbivudine, can no longer be recommended, either as monoprophylaxis or in combination with HBIG, because of significantly higher recurrence rates.

Switch from HBIG plus NA combination prophylaxis to NA monotherapy

Indefinite combination prophylaxis with HBIG and an NA is no longer considered necessary for all patients.[626] Prospective studies have shown that after achieving a maintained response with effective combination prophylaxis (defined as HBsAg-negative, anti-HBs-positive, and HBV DNA-negative), continued monotherapy with a potent NA such as ETV, TDF, or TAF is as effective as lifelong combination therapy.[626,636–641] However, HBIG therapy should only be discontinued when monotherapy includes a potent NA (ETV, TDF or TAF), adherence is ensured and there are no additional risk factors for HBV recurrence. There are various studies on the optimal timing for stopping HBIG. In many studies, HBIG was discontinued 12 months after transplantation. However, there are also data showing the successful and safe discontinuation of HBIG as early as 1 week or 3 months after liver transplantation. Additionally, some retrospective studies have demonstrated that NA prophylaxis alone, starting at the time of liver transplantation was safe and effective.[638,642–644] When HBIG is discontinued, regular monitoring of HBsAg and HBV DNA is essential. In general, it is recommended to monitor every 4-8 weeks initially, every 3 months during the first year, and every 6 months in the long term to ensure early detection of HBV recurrence.

Several factors associated with a higher risk of HBV recurrence may discourage discontinuing HBIG therapy while continuing only NA therapy, including high HBV DNA levels (>100,000 IU/ml) at the time of liver transplantation and pre-transplant HCC (details provided below). Additionally, HDV and HIV coinfection requires special management. As such, the decision to discontinue HBIG should be individualised based on these factors. The recent European Liver and Intestine Transplant Association (ELITA) position statement recommends a duration of 1 month for combined HBIG and NA prophylaxis in patients at low risk of HBV recurrence and at least 1 year in patients with detectable HBV DNA at the time of liver transplantation, provided that HBV DNA is undetectable during this period and anti-HBs titres of >500 IU/L are maintained until month 3, >100 IU/L until month 6 and >50 IU/L thereafter.[626] Special considerations for specific populations, including those with HDV or HIV coinfection or pre-transplant HCC are discussed below.

HBIG-free prophylaxis

The option of a complete HBIG-free prophylaxis may even be considered in patients at low risk of recurrence (HBV DNA undetectable at liver transplantation and absence of HIV or HDV coinfection). Since the level of viraemia at the time of liver transplantation is an important predictor of the risk of recurrence, the goal for every patient on the waiting list should be to achieve viral suppression before transplantation. A key concern with HBIG-free prophylaxis is the potential for higher rates of HBsAg positivity after liver transplantation. However, it remains unclear whether an isolated HBsAg represents incomplete clearance of HBV or true recurrence. Importantly, the clinical consequences of HBsAg positivity, often transient, in the context of complete viral suppression appear to be minimal. Several studies have evaluated HBIG-free prophylaxis. In one study involving 256 patients on ETV monotherapy, durable HBsAg seroclearance was achieved in 92% of patients, with undetectable HBV DNA in 100% at 8 years and excellent long-term survival of 85% at 9 years.[645] Another study analysed 362 patients on various regimens: 49% on lamivudine, 39% on ETV, and 12% on combination NA therapy. After a median follow-up of 53 months, HBsAg negativity and undetectable HBV DNA rates at 8 years were 88% and 98%, respectively, with overall good survival.[638] However, higher recurrence rates were observed in patients taking lamivudine, underscoring the importance of using NAs with a high barrier to resistance, such as ETV, TDF, or TAF.

Special populations: HDV, HIV, HCC

HDV coinfection

Given the aggressive course of HDV infection during immunosuppression after transplantation and the current lack of curative and short-term treatment options, as well as the absence of

robust data on bulevirtide in this setting, preventing hepatitis delta recurrence is crucial.[64] HBsAg is essential for the HDV life cycle, and since hepatitis delta antigen may persist long-term after liver transplantation,[646] monoprophylaxis with NA alone is not considered sufficient for HDV coinfection.[64,626] However, there is conflicting evidence regarding the need for lifelong combination prophylaxis. Emerging data suggest that HBIG may be discontinued after 1 to 2 years. The cumulative rate of HDV reinfection in six studies in which HBIG was discontinued was 3% (3/99), while one of these patients received an HBsAg-positive liver transplant (which is not recommended).[647]

For now, while awaiting more data, both the EASL CPGs for hepatitis D and the ELITA position statement recommend treatment with HBIG and an NA (indefinitely as the gold standard or for at least the first 24 months after liver transplantation).[64,626,648]

HIV coinfection

In PLWH, liver transplantation is associated with similar graft and patient survival outcomes as in HIV-negative recipients.[649,650] It is important to ensure that antiretroviral therapy includes tenofovir (either TDF or TAF). The vast majority of patients should have undetectable HIV RNA and undetectable HBV DNA at the time of liver transplantation, so that the management of HBV antiviral prophylaxis can in principle follow the local protocol for HBV monoinfection. However, the decision to omit or discontinue HBIG remains uncertain and cannot be made with certainty until robust data are available.

HCC

Patients with chronic HBV infection and HCC have a higher risk of HBV recurrence (2–35%) after liver transplantation than patients without HCC (1.9–9.7%). The risk is particularly increased in advanced HCC.[626,651] Of note, HBV recurrence after liver transplantation is strongly associated with HCC recurrence, which can occur either in the graft, in extrahepatic sites, or both, often simultaneously.[641,652] HCC recurrence after liver transplantation has been reported in 10% to 15% of HBsAg-positive patients. Data from China demonstrate that HCC recurrence is significantly associated with reduced survival, emphasising the need for effective strategies to prevent HBV recurrence.[653] However, the association between HBV and HCC recurrence should not be interpreted as direct causality. HBV recurrence may represent an epiphenomenon of HCC recurrence due to clonal expansion of residual HCC tumour cells with HBV genomes or reactivation of HBV by non-tumour cells producing HBV RNA/HBsAg, which may then lead to *de novo* HCC.[654] The reappearance of HBV DNA or HBsAg in this subpopulation can therefore serve as a surrogate marker for HCC recurrence. Conversely, this may mean that HBV in tumour cells is not always fully accessible to prophylactic therapy. The ELITA position statement proposes that patients with HCC should no longer be classified *per se* as being at high risk of HBV recurrence. Patients with HCC should be stratified based on their virological risk profile for better risk assessment and management.[626] However, in a recent multicentre study from Italy, HBV recurrence was associated with HCC recurrence, independently of HCC-related factors, suggesting that further studies are required to clarify the relationship between HBV and HCC recurrence in this setting.[655] Given these uncertainties, no clear recommendation can currently be made regarding the discontinuation of HBIG in patients with HCC.

Management of HBV recurrence after liver transplantation

Due to the high risk of graft loss and significant mortality, treatment is indicated for all patients with HBV recurrence regardless of the histologic fibrosis stage and inflammatory activity, viral load and transaminase levels.

In patients receiving combined prophylaxis with HBIG and an NA, if HBsAg re-emerges in the absence of detectable HBV DNA, HBIG should be discontinued. In such cases, the previously administered NA therapy should be continued with regular HBV DNA monitoring every 3 months. If HBV DNA increases under NA monoprophylaxis or combination prophylaxis, either non-adherence to therapy or the development of resistance can be assumed. A resistance test can be carried out if drug adherence is ensured (see section “Treatment”).

How should HBsAg-negative patients who receive an organ from an anti-HBc-positive donor be managed to prevent HBV reactivation and de novo infection?

Recommendations

Transplantation of a liver from an HBsAg-negative/anti-HBc-positive donor:

- If the recipient is HBsAg-negative/anti-HBc-negative/anti-HBs-negative, long-term NA prophylaxis should be administered. Combined prophylaxis with hepatitis B immunoglobulin + an NA is not recommended **(LoE 2, strong recommendation, strong consensus).**
- If the recipient is HBsAg-negative/anti-HBc-negative but anti-HBs-positive, the risk of HBV reactivation is lower than in anti-HBs-negative recipients. Nevertheless, prophylaxis with an NA is also recommended **(LoE 2, strong recommendation, strong consensus).**

Table 15. Management of HBsAg-negative transplant recipients of HBsAg-negative/anti-HBc-positive organs.

	Recipient status		
Organ	**Anti-HBs**	**Anti-HBc**	**Recommendation**
Liver	Negative	Negative	Long-term NA prophylaxis; combined HBIG/NA prophylaxis is not recommended
	Positive	Negative	Risk of HBV reactivation is lower, but NA prophylaxis is recommended
	Negative	Positive	
	Positive	Positive	Risk of HBV reactivation is very low. NA prophylaxis is not required but close HBV DNA and HBsAg monitoring is essential. Initiate NA therapy if HBV monitoring is not feasible. An alternative is NA prophylaxis for 6-12 months
Other organs	Positive/Negative	Positive/Negative	HBIG/NA prophylaxis not generally recommended due to low HBV risk. Perform regular HBV DNA and HBsAg monitoring. Start NA therapy if HBV DNA or HBsAg becomes positive

HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue.

- If the recipient is HBsAg-negative, anti-HBc-positive and anti-HBs-positive the risk of HBV reactivation is particularly low. NA prophylaxis is not required but close monitoring of HBV DNA and HBsAg should be carried out. If there are concerns about feasibility of HBV monitoring, prophylactic NA therapy should be initiated. If HBV DNA and/or HBsAg positivity occur, NA therapy with an NA should be started immediately **(LoE 3, strong recommendation, strong consensus).**
- If HBV DNA and/or HBsAg positivity occur, antiviral therapy with an NA should be started immediately **(LoE 2, strong recommendation, strong consensus).**

Transplantation of other organs (*e.g.* kidney, heart, lung, pancreas, or stem cell transplantation) from an HBsAg-negative/anti-HBc-positive donor:

- Prophylaxis with hepatitis B immunoglobulin and/or an NA is not generally recommended regardless of the anti-HBs status of the transplant recipient due to the overall low risk of HBV infection. HBV DNA and HBsAg monitoring should be carried out. If HBV DNA and/or HBsAg becomes detectable, antiviral therapy with an NA should be started immediately **(LoE 2, strong recommendation, strong consensus).**

Transplantation of liver grafts from HBsAg-negative/anti-HBc-positive donors

The use of organs from HBsAg-negative/anti-HBc-positive donors in transplantation represents a valuable opportunity to expand the donor pool, especially given the high prevalence of serological evidence of HBV exposure worldwide. However, this approach carries a risk of HBVr, as anti-HBc-positive liver grafts may contain cccDNA, potentially leading to *de novo* HBV infection in the recipient. In HBsAg-negative recipients of such transplants, the risk of HBVr without antiviral prophylaxis can range from 10% to >80%, depending on the recipient's HBV immune status (see below).[626,656,657]

This risk can be significantly reduced by prophylactic antiviral NA therapy. Combination prophylaxis with an NA plus HBIG has no obvious advantages over NA prophylaxis alone,[657] and is not recommended in current guidelines.[354,626,648] In fact, the rationale for the use of HBIG is unclear, since HBsAg-negative recipients have no circulating HBsAg that could be neutralised by HBIG.

Most evidence is available for prophylaxis with lamivudine, which has a well-documented efficacy and safety profile in this setting.[658,659] There is emerging data on the additional benefits of using high-potency NAs, such as ETV, TDF, or TAF for HBVr prophylaxis in liver transplantation involving anti-HBc-positive/HBsAg-negative liver grafts.[658,660–662] Due to their lower risk of resistance with long-term use, these NAs are the preferred options in this context. However, the selection of the specific NA should be based on cost and availability.[626,659]

The optimal duration of NA prophylaxis has not yet been defined. The risk of HBVr is likely highest during the early post-transplant period when immunosuppression is most intense and decreases over time as immunosuppression is tapered. Given the high safety and tolerability of long-term NA therapy, long-term prophylaxis with high-potency agents such as ETV or tenofovir (TDF, TAF) is generally recommended in this setting to minimise the risk of HBVr, especially in anti-HBs-negative individuals.

Recipients with markers of prior HBV contact (anti-HBs, anti-HBc) have a lower risk of HBVr after receiving an anti-HBc-positive liver graft compared to HBV-naive recipients.[657] The risk correlates inversely with anti-HBs levels, with higher concentrations providing greater protection. Consequently, all patients lacking sufficient HBV immunity should be vaccinated or re-vaccinated before transplantation (see section "Prevention of HBV infection"). However, monoprophylaxis with HBV vaccination alone is not an effective prophylactic strategy.[626] Although the risk of HBVr is lower in anti-HBs-positive recipients of anti-HBc-positive liver grafts, NA prophylaxis is recommended (Table 15),[656,658] but the optimal duration of prophylaxis is unclear. NA treatment may be discontinued when stable anti-HBs titres >100 IU/ml are achieved after vaccination, under close monitoring (every 3 months during the first year, then every 3–6 months).[663–667]

The risk of HBVr is particularly low in recipients who are both anti-HBs- and anti-HBc-positive, with a reported incidence of <1.5%.[657] The benefit of prophylaxis has not been proven in this setting,[658] and thus the omission of NA prophylaxis is justifiable (Table 15). However, HBV DNA monitoring is mandatory, and if there is any concern about the feasibility of HBV monitoring, NA prophylaxis should be employed.

Transplantation of other organs (*e.g.* kidney, heart, lung, pancreas, or stem cell transplantation) from an HBsAg-negative/anti-HBc-positive donor

Non-liver organs, such as heart, lung, or kidney, do not contain cccDNA, which is key for HBVr. Therefore, transplantation of these organs is not typically associated with HBVr. The risk of HBV transmission, however, exists if HBV DNA is present in the blood of the donor. The risk of HBV transmission from an HBsAg-negative/anti-HBc-positive donor is generally very low. A systematic review of 1,385 kidney transplant recipients who received organs from HBsAg-negative/anti-HBc-positive donors found that 0.3% of recipients developed HBsAg positivity, and 2.3% tested positive for anti-HBc during the post-transplant period. Importantly, the donor's anti-HBc status did not influence recipient survival.[668,669]

Successful HBV vaccination of the recipient appears to further reduce the risk of HBV transmission through the donor organ and is therefore recommended for all patients. The presence of anti-HBc and/or anti-HBs in recipients is associated with protection against HBV transmission and HBsAg seroconversion.[658,670]

Given the low risk of HBV transmission in this clinical setting, prophylaxis is generally not recommended (Table 15). However, the AASLD and British guidelines suggest that antiviral therapy may be considered to further minimise this already low risk. If administered, treatment is recommended for a duration of 6-12 months.[344,648]

Recipients of HBsAg-negative/anti-HBc-positive organs should be tested regularly for HBsAg and HBV DNA to rule out HBV transmission and *de novo* infection (every 3 months in the first year after transplantation, and every 6 months thereafter). If

HBsAg and/or HBV DNA are positive, antiviral therapy is indicated.

There are scarce data on the risk of HBV transmission after allogenic haematopoietic stem cell transplantation from HBsAg-negative/anti-HBc-positive donors.[671] In principle, the same procedure is recommended as for heart, lung or kidney donation. HBV parameters should always be monitored closely after haematopoietic stem cell transplantation. An occult HBV infection should be ruled out in anti-HBc-positive stem cell donors by determining HBV DNA levels prior to transplantation. The detection of anti-HBc antibodies after organ transplantation does not always mean that *de novo* HBV infection has occurred but may also be due to a transfusion of blood and blood products (*e.g.* administration of immunoglobulins) containing anti-HBc antibodies.[672]

How should patients who receive an organ from an HBsAg-positive donor be managed?

Recommendations

- All patients who receive a liver transplant from an HBsAg-positive donor should be treated with a highly potent NA (ETV, TDF, TAF) **(LoE 2, strong recommendation, strong consensus).**
- Patients with chronic hepatitis delta should not receive a liver transplant from an HBsAg-positive donor **(LoE 4, strong recommendation, strong consensus).**
- In the case of other organ transplants (*e.g.* kidney, heart, lung, pancreas, or stem cell transplantation) from an HBsAg-positive donor, prophylaxis with hepatitis B immunoglobulin plus a potent NA are indicated. In the case of a stem cell transplant or a living donation of a solid organ from an HBsAg-positive donor, the donor should also be treated with a highly effective NA as early as possible before transplantation **(LoE 4, strong recommendation, strong consensus).**

Liver transplantation can be performed under exceptional conditions with an HBsAg-positive donor organ,[673] which can expand the donor pool, in particular for HBsAg-positive recipients.[674] Careful selection, thorough risk-benefit assessment, and informed consent regarding the potential increased risk of HCC are essential.[626] Patients with HDV infection should not receive HBsAg-positive liver grafts,[626] as HDV reinfection is highly likely under such conditions, leading to poor outcomes. This is because HDV relies on the presence of HBsAg-positive liver tissue to replicate and persist, making reinfection unavoidable in these scenarios.

All patients who receive an HBsAg-positive liver graft should receive lifelong therapy with ETV, TDF or TAF. HBIG prophylaxis is not necessary in this context, as the transplanted liver is already infected with HBV and reinfection cannot be prevented.

Organ transplantation from HBsAg-positive donors may allow for the use of organs (other than the liver) that would otherwise be excluded and may benefit HBsAg-positive or carefully selected HBsAg-negative recipients. However, HBsAg-negative recipients are at risk of *de novo* HBV infection, which can be prevented by active and passive immunisation plus NA prophylaxis.

When transplanting organs other than the liver from HBsAg-positive donors and if the recipient does not have a sufficient anti-HBs concentration (ideally >100 IU/ml) at the time of transplantation, HBIG should be used in addition to NA therapy. The optimal duration of HBIG therapy has not been defined. Based on small case series, treatment for 3 months appears to be sufficient.[658,675,676] All recipients of HBsAg-positive grafts should receive long-term prophylaxis with a potent NA. The optimal duration of prophylaxis is not defined. Termination of NA prophylaxis can be considered under close monitoring of HBsAg and HBV DNA concentrations if HBV vaccination induces a stable anti-HBs response with anti-HBs concentrations >100 IU/ml.[677,678]

However, one case of a fulminant, ultimately lethal HBV infection was described 1 year after kidney transplantation of a kidney from an HBsAg-positive donor. This case involved an HBsAg "escape" mutant. However, prophylaxis with an NA had not been carried out in this case.[679]

Data on the safety of using HBsAg-positive stem cell donors or living donors of a solid organ is also currently very limited. Without prophylaxis, the risk of HBV transmission is high (48-56%) in the setting of stem cell donation.[677,680] The donor should be treated with a highly potent NA as early as possible before transplantation in order to suppress viral load.

Prevention of HBV infection

Which vaccines are available for the prevention of HBV infection?

Statement

- Several recombinant hepatitis B vaccines are available worldwide and are used in various immunisation programmes against HBV infection. The selection of a vaccine may depend on factors such as availability, cost, dosing schedule, efficacy and recommendations from local health authorities **(strong consensus).**

Hepatitis B vaccines, initially derived from plasma in the early 1980s, evolved into second-generation vaccines produced with genetically engineered mammalian or yeast cells containing the HBV surface gene (Table 16). Since its introduction, the hepatitis B vaccine has significantly reduced HBV transmission and the associated burden of liver disease. In regions where vaccination programmes have been effectively implemented, there has been a marked decrease in the incidence of HBV infections, prevalence of chronic HBV infections and the subsequent development of liver-related complications such as cirrhosis and HCC.[681,682] In addition, hepatitis B birth dose vaccination plays a critical role in preventing perinatal transmission of HBV from infected mothers to their newborns, further contributing to the reduction of HBV prevalence rates and associated morbidity and mortality.[683] Furthermore, vaccination is an essential part of protecting other vulnerable populations, including immunocompromised individuals, patients with chronic diseases and those at increased occupational or non-occupational risk of exposure.

Table 16. Examples of different hepatitis B vaccines.

Vaccine	Specific details
Hepatitis B vaccines containing a recombinant form of the small hepatitis B surface protein (S) and aluminium hydroxide as an adjuvant (*e.g.* Engerix-B, Heberbiovac HB, Recombivax HB)	Different vaccines for infants (use from birth onwards) and adults. Higher doses for patients on/before haemodialysis
Hepatitis B vaccines containing a recombinant form of the small hepatitis B surface protein (S) with amorphous aluminium hydroxyphosphate sulfate as an adjuvant (*e.g.* HBVaxPro)	Use from birth onwards possible. Higher doses for patients on/before haemodialysis
Hepatitis B vaccines containing a recombinant form of the small hepatitis B surface protein (S) and AS04C plus aluminium phosphate as an adjuvant (Fendrix)	Use in individuals >15 years and who suffer from renal insufficiency (including pre-dialysis and dialysis patients)
Combination vaccines (*e.g.* with Hepatitis A (*e.g.* Twinrix) or with diphtheria, tetanus, pertussis (acellular), poliomyelitis (inactivated), haemophilus type-b (*e.g.* Hexyon, Hexacima, Vaxelis))	Some combination vaccines can be used from 6 weeks of age onwards. Twinrix can be used from an age of 2 years onwards
Hepatitis B vaccines containing a recombinant form of three hepatitis B surface proteins (S, Pre-S1, and Pre-S2) and aluminium hydroxide as an adjuvant (PreHevbri)	Third-generation vaccine. Use from 18 years of age onwards
Hepatitis B vaccines containing a recombinant form of the small hepatitis B surface protein (S) and CpG 1018 (activates toll-like receptor 9) as an adjuvant (Heplisav-B)	Third-generation vaccine. Use from 18 years of age onwards

Conventional recombinant S-antigen vaccines (second generation) exhibit robust immunogenicity in young, healthy individuals. The recommended HBV vaccination series with second-generation vaccines consists of three doses, which are important for the development of robust and long-term immunity. Missing doses or not adhering to the recommended schedule can lead to suboptimal immune memory and reduced vaccine efficacy, compromising long-term protection against HBV. Vaccine efficacy decreases in older adults and individuals with comorbidities (see below), with <75% achieving seroprotective antibody levels (anti-HBs ≥10 IU/L) after the three-dose schedule (Table 17). Factors such as obesity, smoking, male sex, immunosuppressive conditions and chronic diseases, such as chronic liver disease and cirrhosis, chronic kidney disease and diabetes mellitus, are associated with lower response rates.[684–689] The safety of recombinant hepatitis B vaccines has been extensively demonstrated.[686] Like other vaccines, hepatitis B vaccination may cause reactions at the injection site, typically resolving within 1 to 3 days, with occasional involvement of lymph nodes. General symptoms such as low-grade fever, mild shivering, headaches, muscle aches, or fatigue are rare and transient. While isolated cases of anaphylactic reactions and allergic responses have been reported, the causal relationship between hepatitis B vaccination and neurological disorders or organ-related diseases remains unclear and likely coincidental, with no conclusive evidence supporting a causal link. Despite discussions, scientific studies have failed to establish a connection between hepatitis B vaccination and conditions such as multiple sclerosis.[690] Anecdotal instances, like the European Court of Justice's ruling on multiple sclerosis, do not alter this scientific consensus, which underscores the lack of evidence supporting

Table 17. Results of the pivotal studies comparing third-generation hepatitis B vaccines to second-generation hepatitis B vaccines.

Study	Results	Comment
CONSTANT[694] 1A-HBV (Engerix-B 20 μg) *vs.* 3A-HBV (PreHevbrio 10 μg)	n = 712 1A-HBV (0, 1, 6 month): SPR 94.8% n = 711 3A-HBV Lot A (0, 1, 6 month): n = 709 3A-HBV Lot B (0, 1, 6 month): n = 706 3A-HBV Lot C (0, 1, 6 month): SPR 99.3%	18-45 years SPR: anti-HBs ≥10 U/L at day 196 Non-inferiority
PROTECT[695] 1A-HBV (Engerix-B 20 μg) *vs.* 3A-HBV (PreHevbrio 10 μg)	n = 811 1A-HBV (0, 1, 6 month): SPR 76.5%, 73.1 (≥45 years) n = 796 3A-HBV (0, 1, 6 month): SPR 91.4%, 89.4% (≥45 years)	≥80% with age ≥45 years SPR: anti-HBs ≥10 U/L at day 196 Superiority in the age group ≥45 years
Heplisav study 1[702] Heplisav (0.5 ml) *vs.* Engerix-B (20 μg)	n = 1,809 Heplisav (0, 1 month): SPR: 95.1% n = 606 Engerix-B (0, 1, 6 month): SPR 81.1%	18-55 years SPR: anti-HBs ≥10 U/L 8 weeks after the 2nd dose of Heplisav compared to 4 weeks after the 3rd dose of Engerix-B. Superiority
Heplisav study 2[703] Heplisav (0.5 ml) *vs.* Engerix-B (20 μg)	n = 1,969 Heplisav (0, 1 month): SPR: 90% n = 483 Engerix-B (0, 1, 6 month): SPR 70.5%	40-70 years SPR: anti-HBs ≥10 U/L 8 weeks after the 2nd dose of Heplisav or Engerix-B. Superiority
Heplisav study 3[704] Heplisav (0.5 ml) *vs.* Engerix-B (20 μg)	n = 5,592 Heplisav (0, 1 month): SPR: 95.4%, 90% (T2D), 94.7% (BMI ≥30), 95.9% (smoker), 91.6% (≥60 years), 94.5% (male) n = 2,782 Engerix-B (0, 1, 6 month): SPR 81.3, 65.1% (T2D), 75.4% (BMI ≥30), 78.6% (smoker), 72.6% (≥60 years), 78.8% (male)	18-70 years, 961 participants in the per-protocol population had T2D SPR: anti-HBs ≥10 U/L at week 28

HBV, hepatitis B virus; SPR, seroprotection rate; T2D, type 2 diabetes.

such associations.[691] The primary contraindications for hepatitis B vaccination include a severe allergic reaction following prior exposure to yeast or a vaccine component. Additionally, vaccination should be postponed in cases of current moderate to severe illness, with or without fever, until the individual has recovered. Pregnant women can be vaccinated against hepatitis B,[692] although – as for all vaccinations during pregnancy – the indication should be carefully considered.

Third-generation vaccines that show higher vaccine efficacy, especially in subgroups that respond sub-optimally to conventional hepatitis B vaccines, have recently been approved by the FDA and EMA.

PreHevbrio/PreHevbri, approved by the FDA (November 2021) and EMA (April 2022) for adults ≥18 years, is a three-antigen hepatitis B vaccine (3A-HBV) containing Pre-S1, Pre-S2, and S protein components of HBsAg, expressed in Chinese hamster ovary cells. Unlike conventional HBV vaccines produced in yeast, which contain only the small surface antigen, 3A-HBV aims to enhance immunogenicity. Since its introduction in Israel (1989), studies have evaluated its efficacy across HBV-naïve neonates, children, and adults and established the efficacy and safety of the vaccine.[693] Phase III trials in North America and Europe confirmed its safety and immunogenicity, leading to approval in the US, EU, and Canada.[694,695] In a follow-up study, 88.1% of 3A-HBV recipients maintained seroprotective anti-HBs levels (*i.e.* ≥10 IU/L) after 2-3 years, compared to 72.4% for Engerix-B, with median anti-HBs titres five times higher.[696] Several investigator-initiated studies have examined the efficacy of 3A-HBV in adults with various underlying health conditions. Studies in patients with HIV,[697] inflammatory bowel disease (IBD),[698] end-stage renal disease,[699] and those on haemodialysis[700] reported non-response rates of 14-32% with 3A-HBV, compared to 19-44% with 1A-HBV (Engerix-B).[678] However, its superior response was not observed in all subgroups, *e.g.* patients with IBD.[698] The safety of the 3A-HBV vaccine was documented in the pivotal trials. 3A-HBV showed higher rates of local and systemic adverse events (especially injection site pain and myalgia) compared to Engerix-B, though most were mild, short-lived, and self-limiting. Serious adverse events were rare and comparable between groups.[693]

Availability: Due to production and distribution challenges, PreHevbrio has been withdrawn from several markets, including the EU, and is no longer widely available. In Israel, it has been marketed as Sci-B-Vac and may still be accessible through international pharmacies. While its manufacturer has discontinued PreHevbrio, its prior regulatory approvals and market potential could make it a candidate for future acquisition or licensing.

Heplisav-B, approved by the FDA (2017) and EMA (2018) for adults ≥18 years, is a recombinant HBV vaccine produced in genetically modified yeast cells. It features CpG 1018, an adjuvant that activates Toll-like receptor 9 to enhance immune response. Heplisav-B is administered as a two-dose series.[701]

The CDC Advisory Committee on Immunization Practices (ACIP) recommended Heplisav-B as a two-dose series in 2018 based on randomised-controlled trials showing 90-95.4% seroprotection, compared to 70.5-81.3% with Engerix-B (Table 17).[702–704] Its higher seroprotection rates were observed across all subpopulations, particularly in T2DM, obesity, and older adults (Table 17). A phase III study in patients on chronic haemodialysis demonstrated significantly higher seroprotection rates with Heplisav-B *vs.* Engerix-B, and non-inferiority to Fendrix, with fewer local post-injection reactions. Of the 149 participants in the modified intention-to-treat population, 76.5% had not previously responded to at least one series of hepatitis B vaccine.[705] Another study in patients on haemodialysis showed that a four-dose regimen of Heplisav-B resulted in a high seroprotection rate of 89.3% at week 20, with a majority achieving anti-HBs concentrations ≥100 IU/L and no significant safety concerns observed.[706]

A retrospective cohort study showed higher seroconversion rates with Heplisav-B than standard HBV vaccines in PLWH.[707] An international study also reported 100% seroprotection in HBV vaccine-naïve HIV-positive participants after a three-dose Heplisav-B series, with no safety concerns.[708] Other cohort studies reported seroprotection rates of 76-87% in individuals who were previously non-responsive to standard vaccines.[709–711] Retrospective cohort studies found Heplisav-B achieved 63-67.5% seroprotection in chronic liver disease, including cirrhosis, outperforming Engerix-B (33-45%), particularly in patients with cirrhosis.[712,713] Retrospective observational studies showed that the Heplisav-B vaccine was associated with superior response rates compared to conventional vaccines in patients with IBD.[714] A study evaluating pregnancy outcomes and immunogenicity in women who became pregnant after receiving Heplisav-B or Engerix-B during clinical trials found similar pregnancy outcomes between the groups, while seroprotection rates were higher in the Heplisav-B arm.[715] In clinical trials, the primary adverse effects of Heplisav-B were injection-site pain (23%-39%), fatigue (11%-17%), and headache (8%-17%). While reactogenicity was slightly higher than with Engerix-B, serious adverse events were rare and occurred at similar rates.[701]

A study observed a higher acute myocardial infarction (AMI) rate in the Heplisav-B compared to the Engerix-B group, but *post hoc* analysis across three pivotal trials linked these events primarily to pre-existing risk factors. AMI and other cardiovascular event rates were comparable to or lower than background rates, with no causal link to vaccination. A post-marketing study involving over 31,000 recipients of Heplisav-B and more than 38,000 recipients of Engerix-B indicated no increased AMI risk.[716,717] Another post-marketing study reported no significant safety concerns, with similar rates of immune-mediated diseases, herpes zoster, and no cases of anaphylaxis in Heplisav-B recipients.[718]

Who should be vaccinated against hepatitis B and who should be monitored for vaccine responses?

Recommendations

- Universal hepatitis B vaccination for all infants, children and adolescents is recommended as early as possible, preferably before the onset of puberty **(LoE 1, strong recommendation, strong consensus).**
- Newborns of HBsAg-positive mothers or mothers with unknown HBsAg status should receive the hepatitis B vaccine as early as possible after birth, ideally within 12 hours, in combination with passive immunisation using hepatitis B immunoglobulin to maximise protection against HBV transmission **(LoE 1, strong recommendation, consensus).***

- The following risk groups should be vaccinated against HBV infection **(LoE 1, strong recommendation, strong consensus)**:
  - individuals in whom a severe course of hepatitis B is to be expected due to an existing or expected immunodeficiency, immunosuppression or chronic diseases such as chronic liver or kidney disease.
  - individuals with an increased risk of non-occupational exposure, *e.g.* contact with HBsAg-positive persons (partners and family members of people living with chronic HBV infection), high-risk sexual behaviour, persons seeking evaluation for treatment of sexually transmitted infections, people who inject drugs, incarcerated persons and patients in psychiatric facilities.
  - individuals with increased occupational exposure risk, including healthcare trainees, interns, students, volunteers, laboratory and cleaning staff in healthcare facilities, paramedics, emergency responders, police officers, firefighters, soldiers, and staff in facilities with a high prevalence of chronic HBV infection.
- In addition, hepatitis B vaccination is suggested for **(LoE 4, weak recommendation, strong consensus):**
  - international travellers to regions with high or moderate prevalence of chronic HBV infection.
  - all other individuals who seek protection against HBV infection, irrespective of specific risk factors.
- Post-vaccination efficacy assessment (anti-HBs) should be carried out in individuals belonging to a specific risk group **(LoE 2, strong recommendation, strong consensus).**

Statement

- In individuals who do not belong to a specific risk group (see above), who are healthy and younger than 40 years of age, a post-vaccination efficacy assessment (anti-HBs) is not required **(strong consensus).**

Universal hepatitis B vaccination

Hepatitis B vaccination effectively prevents chronic infections and liver-related complications such as cirrhosis and HCC.[681,682] Many countries introduced universal vaccination for children up to the age of 18 years in the 1990s, and this approach has proven successful.[719] Early vaccination is critical not only to optimise the immune response, as vaccine efficacy may decline with age and in the presence of comorbidities, but also to ensure protection before individuals become sexually active, which is a major risk factor for HBV transmission.

In adults, hepatitis B vaccination is recommended for those at high risk of severe outcomes from HBV infection, including individuals with current or anticipated immunodeficiency, immunosuppression, or chronic conditions such as chronic liver or kidney disease and poorly controlled diabetes. It is also advised for those with an elevated risk of exposure, whether through occupational or non-occupational activities. However, based on epidemiological and cost-effectiveness data, the CDC ACIP has recommended expanding hepatitis B vaccination to all US adults aged 19 to 59 starting in 2022.[720] Due to the difficulties in assessing risk factors in clinical practice, which can lead to lower vaccination coverage, universal vaccination is preferred over a risk-based approach. For example, vaccination coverage for hepatitis B in adults aged 25 years and older was only 21% in the US,[721] and vaccination coverage in at-risk groups has also been shown to be low, *e.g.* 33% in US adults with chronic liver disease.[722] While vaccinating individuals up to the age of 60 years is generally a sound approach, local policies may differ based on regional coverage rates and needs. Nonetheless, EASL suggests hepatitis B vaccination to anyone who seeks protection against HBV infection, regardless of individual risk factors and age.

Birth dose vaccination to prevent MTCT

Preventing perinatal transmission of hepatitis B depends on screening all pregnant women for HBsAg and promptly administering prophylaxis with the hepatitis B vaccine and HBIG to infants born to HBsAg-positive mothers. The efficacy, safety, and cost-effectiveness of this combined active-passive post-exposure prophylaxis in newborns of HBsAg-positive mothers is well-established in most parts of the world,[683,723] though data remain limited for the WHO African region. Administering the combined birth dose vaccination, followed by the completion of the full vaccine series, provides seroprotection in 95% of healthy full-term infants.[723,724] In contrast, using the hepatitis B vaccine alone is less effective,[723] except possibly in cases where the mother has a low HBV DNA level (*i.e.*, HBeAg-negative).[725,726] Failure of immunoprophylaxis is primarily associated with maternal HBeAg positivity and high HBV DNA levels,[480] which can be addressed through antiviral treatment during pregnancy (see "What are the treatment recommendations for pregnant HBsAg-positive women?"). Nevertheless, combined active-passive immunisation is recommended for all newborns of HBsAg-positive mothers. For infants with a birth weight <2,000 grams, the vaccine response is reduced, and an additional dose (total of four vaccinations) is required to ensure adequate protection.[30,727] The birth dose vaccination should be administered within the first 24 hours after birth, ideally within 12 hours.[30,728] Data from a prospective, multicentre observational study suggest that even earlier administration, within the first hour, may provide superior protection, particularly in cases of high maternal HBV DNA, though the study lacked a control group and relied on comparisons with data from the literature.[729] Infants born to women with unknown HBsAg status should be considered in the same way as infants born to HBsAg-positive mothers, especially in endemic regions.

Post-vaccination serologic testing for anti-HBs as well as HBsAg should be conducted after completing the hepatitis B vaccine series, typically at between 9-12 months of age. Testing before 9 months is not recommended, as it may detect passive anti-HBs from HBIG administered at birth and could miss late HBV infections. Additionally, anti-HBc testing in infants is not recommended, as passively acquired maternal anti-HBc can be detected for up to 24 months after birth in infants born to HBsAg-positive mothers.[727]

HBsAg-negative infants with anti-HBs <10 IU/L should be revaccinated with a single dose of hepatitis B vaccine and undergo post-vaccination serologic testing 1–2 months later. Infants whose anti-HBs remains <10 IU/L following single dose

revaccination should receive two additional doses of hepatitis B vaccine to complete the second series, followed by post-vaccination serologic testing 1–2 months after the final dose.[727]

Worldwide, hepatitis B birth dose coverage remains low (45%, 2022 estimates), including in the WHO European region (42%), and far below the 90% coverage set for global HBV elimination. Strategies for improving timely hepatitis B birth dose administration are needed. Health policy makers and researchers with national immunisation programmes should address this gap.

Post-vaccination efficacy assessment

An anti-HBs titre >10 IU/ml, considered a general correlate of vaccination efficacy,[730] is achieved in ≥95% of vaccinated children and adolescents and in ≥90% of healthy adults under 40 years of age.[719,731] This high efficacy suggests that routine monitoring of anti-HBs titres in these groups is unnecessary, except for individuals belonging to specific risk groups (see below).

Post-vaccination efficacy testing (anti-HBs) may be considered in individuals aged ≥40 years, as the vaccine response is lower with the second-generation vaccines, but may not be required in those vaccinated with third-generation vaccines, which achieve response rates of over 90% in those aged ≥40 years (Table 17).

Quantitative anti-HBs testing is recommended 1-2 months after completion of the primary hepatitis B vaccine series for individuals whose further management depends on knowledge of their vaccine response, especially those at higher risk for severe hepatitis B such as individuals with immunodeficiency, immunosuppression and pre-existing medical conditions. Testing is also important for those at increased occupational or non-occupational risk of HBV infection and for groups expected to have a lower response rate to the vaccine (see above).

To ensure reliable protection in risk groups with a high risk of severe outcomes, such as immunocompromised persons, EASL recommends a more conservative approach and suggests an anti-HBs titre of ≥100 IU/L as an indicator of an optimal vaccine response, if measured 1-2 months after the last vaccine dose (see below).

How should vaccination be performed in immunocompromised individuals?

Recommendation

- For immunosuppressed or immunodeficient individuals, including patients with cirrhosis or those on haemodialysis, an increased dose of standard (or second-generation) vaccines (double dose or dose tailored for patients on dialysis) or third-generation vaccines should be administered **(LoE 1, strong recommendation, strong consensus).**

Vaccination in patients on haemodialysis and those who are immunosuppressed or immunodeficient

Patients on haemodialysis have been repeatedly shown to respond better to a higher dose of vaccine, as have immunosuppressed or immunodeficient individuals[732–734] and individuals with chronic alcohol abuse.[735]

Third-generation vaccines have been studied in patients on haemodialysis[706,736,737] and in immunocompromised or immunodeficient individuals, as well as in patients with chronic liver disease[713] (see above), and have shown a stronger response in many studies compared to second-generation vaccines (*e.g.* Engerix-B). In patients on haemodialysis, Heplisav-B was used as a three- or four-instead of two-injection schedule in some studies.[706,736,737]

The hepatitis B vaccination strategy for PLWH depends on their immune status. Immunocompetent HIV-positive people can be vaccinated according to the same schedule as healthy individuals (also recommended by other guidelines[738]), but vaccination success should be monitored. HIV-positive individuals with low CD4 counts, like other immunocompromised patients, may require higher doses of vaccine. Based on the available studies, there is a debate about whether standard or double doses of vaccines should be recommended for all PLWH.[738] Long-term immune responses to hepatitis B vaccination in adults with HIV infection were investigated in an open-label, multicentre phase III study comparing standard, double-dose and low-dose regimens. It was shown that a four-dose double-dose regimen achieved significantly higher response rates compared to the standard three-dose regimen..[739,740] In a multivariable analysis, the variables associated with the initial response after primary immunisation (in addition to regimen group) were female sex, being younger, no active smoking, a higher baseline CD4 count, and an undetectable plasma HIV RNA.[740] Other retrospective studies also showed better responses associated with younger age and higher CD4 counts.[741] A meta-analysis concluded that an increased-dose vaccination regimen improves the anti-HBs response rate in previously unvaccinated HIV-positive individuals compared to standard vaccination.[742] However, a randomised-controlled trial in HIV-infected adults who failed to respond to prior hepatitis B vaccination found that a double-dose revaccination regimen did not significantly improve response rates compared to the standard-dose regimen. Nevertheless, the double dose resulted in a more robust and durable immunologic response.[743] Although the response to vaccination is related to the CD4 count,[744] the initial HBV vaccination should not be deferred in patients with low CD4 counts who are at risk of HBV infection.[738] If available, third-generation vaccines should be used in adult HIV-infected individuals, especially if the primary vaccination has shown suboptimal responses (see above). Retrospective cohort studies in PLWH showed higher response rates with Heplisav-B compared (either directly or with historical controls) to other previously used recombinant hepatitis B vaccines.[707–711] In addition, a recent modelling study has shown that the use of the Heplisav-B vaccine in PLWH results in lower costs and higher benefits compared to Engerix-B.[745]

In individuals with immunosuppressive conditions, the response to the vaccine may vary depending on the degree of immunosuppression, leading to inconsistent results in studies comparing the double dose with the standard dose. While one study showed a numerical but non-statistically significant difference in serologic response between the double and standard dose in patients with autoimmune diseases (including IBD) taking immunosuppressive medication,[746] another study suggested a stronger serologic response to the double dose in patients with IBD.[747] In addition, response rates to the vaccine

are low even with the double dose.[748] Heplisav-B appears to achieve a higher response rate in patients with IBD.[714]

Patients with cirrhosis, a condition associated with immune dysfunction,[749] may benefit from a double dose of the hepatitis B vaccine, according to a systematic review of 11 studies involving 961 patients, which showed a response rate of 38% for the standard dose and 53% for the high-dose vaccine regimens.[685] However, even after a second vaccine series with the double dose, response rates are suboptimal.[750,751] The third-generation vaccines may elicit better responses in patients with chronic liver disease and cirrhosis (see above).[713]

How should an inadequate response to the first vaccination schedule be managed?

Statement

- The seroprotection rate is defined as anti-HBs ≥10 IU/L. However, for risk groups with higher risk of severe outcomes, such as immunocompromised individuals, the vaccination schedule is considered optimal if the anti-HBs level is ≥100 IU/L 1-2 months after the last vaccination. This indicates long-term, possibly lifelong protection against hepatitis B **(strong consensus).**

Recommendations

- Individuals with anti-HBs titres ≥100 IU/L 1-2 months after completion of the vaccination series do not require further monitoring and booster vaccination. Exceptions include immunocompromised individuals, who should undergo a follow-up test for anti-HBs (and receive a booster vaccination if anti-HBs <100 IU/L). Anti-HBs test intervals range from annually to every 10 years, depending on the risk **(LoE 2, strong recommendation, strong consensus).**
- For risk groups with anti-HBs titres between 10 and 100 IU/L 1-2 months after completion of the vaccination series an additional booster dose is suggested, followed by reassessment of anti-HBs titres after 1-2 months **(LoE 3, weak recommendation, strong consensus).**
- Individuals with anti-HBs titres of <10 IU/L 1-2 months after completion of the vaccination series should be revaccinated with a complete vaccination course (possibly with an optimised vaccination schedule) and anti-HBs titre should be determined again after 1-2 months. The exclusion of an ongoing HBV infection (HBsAg, anti-HBc) should be considered before revaccination in these individuals **(LoE 1, strong recommendation, strong consensus).**

Optimal anti-HBs threshold

Hepatitis B vaccination generates neutralising antibodies in successfully vaccinated individuals, with anti-HBs titres of ≥10 IU/L associated with protection against HBV infection.[752] This threshold is therefore used as the seroprotection rate in pivotal vaccine studies (Table 17). Despite successful vaccination, anti-HBs levels can decline to <10 IU/L within 4 to 10 years in about 10-50% of immunologically healthy vaccinated individuals. Nevertheless, it is assumed that these individuals are protected due to a robust immunological memory that persists beyond the presence of anti-HBs.[354,753–757] This enduring memory facilitates a rapid immune response upon exposure to HBV, rapidly terminating the infection and preventing severe hepatitis or chronic infection. Re-vaccination of individuals who lost anti-HBs leads to a marked increase in antibodies after 3-7 days.[758,759] Such an "anamnestic" immune response could even be detected up to 35 years after basic immunisation in over 70% of all individuals whose antibodies had declined to <10 IU/L.[760] Therefore, vaccinated infants or young children without specific risks or immunosuppression typically do not need revaccination. However, if the risk of exposure increases later (*e.g.* due to a medical profession), a serological check and booster vaccination are recommended.

Unlike the recommendations of the CDC ACIP, the EASL panel adopted a more conservative approach similar to the German guidelines,[354] and recommends a threshold of anti-HBs titres of ≥100 IU/L to define a response, in particular for those who are at higher risk for severe infections, such as immunocompromised persons. This recommendation is based on several factors to ensure optimal efficacy in this group. One study documented breakthrough infections predominantly with non-A2 strains in individuals with anti-HBs titres between 2 and 96 IU/L. These infections were transient and did not lead to severe hepatitis or chronicity.[761] However, the cases were identified in healthy blood donors and breakthrough infections in vulnerable patient populations, such as those with chronic liver disease or immunocompromised individuals, where post-vaccination efficacy evaluation is required, should be avoided whenever possible. Additionally, there is significant variability in anti-HBs test results, particularly in the lower range of 0-20 IU/L,[762] and anti-HBs titre can rapidly decline after vaccination, which further support the higher threshold.

Management in low and non responders

Groups at high risk of severe infections who fail to achieve an anti-HBs titre of ≥100 IU/L 1–2 months after vaccination should ideally receive additional doses to reach this target threshold. For immunocompetent individuals in high-risk groups with ongoing occupational or non-occupational exposure (*e.g.* healthcare workers, sex workers) and anti-HBs titres between 10 and 100 IU/L, an additional booster dose to increase antibody levels may be considered. However, from a public health perspective, the cost-effectiveness of recommending booster vaccinations for healthy, non-immunocompromised individuals with anti-HBs titres >10 IU/L (but <100 IU/L) is more debatable, particularly in the absence of evidence showing that such boosters prevent clinical disease.

Poor- or non-responders, defined as individuals with anti-HBs titres <10 IU/L, typically require a complete revaccination series. Studies show that 50-100% of non-responders achieve seroconversion after receiving up to three additional vaccine doses administered at 1–3-month intervals.[763,764] Therefore, non-responders should receive up to three additional standard vaccinations or third-generation vaccines if available, as these have demonstrated improved response rates in some retrospective cohort studies.[711] This aligns with the significantly higher response rates observed with third-generation vaccines in populations that typically exhibit suboptimal responses to earlier-generation vaccines (see above).

Intradermal vaccination has been used for non-responders, but despite being immunologically plausible, no clear evidence shows a significantly better vaccine response in immunocompromised individuals.[765]

If HBsAg and anti-HBc have not been tested prior to vaccination, these tests should be performed in individuals who do not respond to the hepatitis B vaccine, as this may also indicate an underlying chronic HBV infection.

Open questions and future directions

This section outlines the key open research questions for each of the previous topics, which should be addressed to advance the management of HBV infection.

Natural course and heterogeneity of chronic HBV infection

Chronic HBV infection is highly heterogeneous and cannot be fully captured by the four traditional phases outlined in Table 4. To address this, terms such as "grey zone" and "intermediate phase" have been introduced in studies to describe patient populations that fall outside these classical categories.

In clinical practice, it is essential to maintain a simple and practical nomenclature for chronic HBV infection. However, in clinical research, a more accurate classification of the different phases of HBV infection is crucial to capture the dynamic nature of chronic infection. To support this, the phases have been refined specifically to enhance their relevance for research purposes.

Appendix Table 2 outlines 11 distinct patient populations within chronic HBV infection, categorised based on variations in viral markers, inflammatory activity, disease stage, and risk of progression. These distinctions are vital for defining patient cohorts in preclinical, translational, and clinical research.

Future endpoint conferences of the societies may continue to refine this classification and nomenclatures to further improve their utility for clinical research and clinical trials.

Diagnostics and treatment in resource-limited settings

The lack of access to comprehensive diagnostic tools, such as HBV DNA testing, presents a significant challenge to the effective implementation of guideline recommendations for hepatitis B management. This diagnostic gap can lead to reliance on simplified approaches, which may compromise treatment prioritisation, clinical outcomes, and the broader goals of HBV elimination. The rapid development and widespread implementation of point-of-care NAT during the COVID-19 pandemic demonstrated the feasibility of deploying accessible, accurate, and scalable diagnostic technologies in diverse settings. This success underscores the potential for adopting similar strategies to address diagnostic gaps in HBV care.

HBsAg loss as a treatment goal

Achieving functional cure (HBsAg loss) remains rare with current therapies. The prospect of effective finite treatments is highly appealing, particularly given the challenges associated with the strict adherence required for prolonged NA therapy, especially for young patients. Thus, there is an unmet need for curative therapies. Several novel compounds with distinct mechanisms of action are currently in advanced clinical development.[766–768] In parallel, the development of reliable biomarkers to predict and monitor functional cure across different therapies and clinical settings is critical. Such biomarkers would facilitate better patient stratification, guide therapeutic decision-making, and improve treatment efficiency. These tools are essential for advancing curative strategies and optimising treatment outcomes across diverse patient populations.

Treatment indication for all HBV DNA-positive individuals

While antiviral therapy provides significant benefits and the debate persists regarding universal treatment for all HBV DNA-positive individuals, particularly those with low-risk profiles. The early treatment of young HBeAg-positive individuals with normal ALT levels and no fibrosis remains controversial. Potential long-term advantages, such as reducing HBV DNA integration and clonal expansion, must be carefully balanced against the challenges of strict adherence and the uncertain clinical benefits. Future studies, particularly those evaluating novel therapies targeting HBV functional cure, should include this population.

Choice of NA

Discrepancies remain regarding the preferred NA, such as ETV *vs*. tenofovir, across various clinical scenarios, including the prevention of HCC, recurrence of HCC, and treatment of decompensated liver disease. Additionally, the differing kinetics of HBV relapse following NA cessation between ETV and tenofovir require further mechanistic clarification. These differences may also hold significant relevance as NAs form the backbone of novel therapeutic strategies aimed at achieving HBV functional cure.

Discontinuation of NA therapy

Recommendations for stopping NA therapy prior to achieving HBsAg loss remain controversial, particularly due to concerns about clinical relapse. Predictive markers such as HBcrAg and HBV RNA require further validation to enhance patient stratification for safe and effective NA discontinuation. Moreover, the development of novel biomarkers, including immune markers, is urgently needed to better predict outcomes following NA cessation. Additionally, the mechanisms underlying the increased rates of HBsAg loss observed after stopping NA therapy need to be clarified to guide future treatment strategies.

HCC risk factors

The impact of steatotic liver disease on HCC risk remains uncertain and requires further mechanistic investigation. Moreover, it is unclear whether antiviral therapy effectively reduces HCC risk in the presence of modifiable factors such as obesity, type 2 diabetes mellitus, hypertension and air pollution. Additionally, further research is needed to explore the effects of aging and immunosenescence in individuals with HBV infection.

Advancing HCC surveillance

Current HCC surveillance strategies primarily rely on imaging and AFP levels, which have limitations in sensitivity, specificity, and applicability across different patient populations and

disease stages. There is a critical need for more robust biomarkers – encompassing viral, genetic, epigenetic, and immunologic factors – to improve HCC risk prediction, enhance risk stratification, and guide therapeutic decisions in diverse clinical settings. In addition to biomarker development, advanced imaging techniques such as radiomics and artificial intelligence-driven models are expected to refine HCC prediction, optimise surveillance strategies, and integrate into electronic health record systems for automated, risk-based screening protocols.[769–772]

Hepatitis delta

Several unresolved issues remain in the management of chronic HDV infection, requiring further research and long-term clinical data. The impact of bulevirtide on cirrhotic complications and HCC incidence is still unclear, as most studies have focused on viral suppression and biochemical responses rather than clinical outcomes. Additionally, the long-term efficacy and safety of bulevirtide, as well as optimal treatment duration and criteria for stopping therapy, remain undefined. The role of NAs in HDV coinfection is also debated, particularly in patients without active HBV replication, for whom the clinical benefit is uncertain.

HBV reactivation risk classification

Determining the exact reactivation risk for new or less-studied immunosuppressive and biologic therapies remains an ongoing challenge, leading to variability in risk assessment and prophylaxis strategies. Establishing comprehensive, real-world registries is critical to addressing these gaps.

Prevention of HBV recurrence after liver transplantation

The role of long-term HBIG in addition to NAs for prophylaxis of HBV recurrence after liver transplantation in certain situations, *e.g.* HBV/HDV coinfection and in patients with HCC prior to transplantation, needs to be further defined.

Impact of co-medication and dietary factors

While this guideline provides comprehensive recommendations for the management of HBV infection, one area that remains underexplored is the role of commonly used co-medications in HBV care.

Emerging evidence from retrospective studies suggests that widely prescribed medications, such as statins,[773] SGLT2 inhibitors,[774] angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,[775] and aspirin[776,777] may offer beneficial effects in patients with HBV, including a reduced risk of HCC. However, these potential benefits have not yet been incorporated into this guideline.

Similarly, dietary factors, particularly coffee consumption, have been linked to hepatic benefits, including protective effects against liver fibrosis and HCC.[778] Despite this, the role of nutrition in HBV management has not been systematically evaluated, and its clinical relevance remains an open area for future research, particularly through randomised-controlled trials. Integrating this knowledge into future guideline updates could help optimise HBV care, ensuring that patients benefit from evidence-based treatment strategies while avoiding unnecessary restrictions due to misconceptions about liver toxicity.

Appendix 1. Delphi round agreement on the recommendations of the present clinical practice guidelines.

Recommendation/statement	Consensus
For initial screening of HBV infection, HBsAg and anti-HBc should be determined **(strong recommendation).** **The recommendation not to include anti-HBs in the initial screening did not achieve strong consensus, as some Delphi panellists advocated for incorporating anti-HBs testing into the screening process.*	94%
HBV screening should be performed in individuals **(strong recommendation)**: • with elevated liver enzymes and/or clinical signs of liver disease • with cirrhosis/fibrosis of the liver • with liver cancer (HCC or biliary tract cancer) • with extrahepatic manifestations possibly related to HBV • with end-stage kidney disease undergoing haemodialysis • with HIV infection • with HCV infection • being considered for or undergoing immunosuppressive/immunomodulatory therapy or chemotherapy • with congenital immunodeficiency • considered for stem cell/bone marrow or organ transplants and recipients of such transplants • with an increased risk of exposure to HBV ◦ individuals from regions with intermediate to high HBsAg prevalence ◦ family or household members of HBV-infected individuals ◦ sexual partners of HBV-infected individuals ◦ individuals in care/correctional facilities ◦ individuals with multiple sexual partners ◦ individuals who seek examination or treatment for sexually transmitted diseases ◦ individuals with nonmedical exposure to body fluids ◦ active and former people who inject drugs	98%
HBV screening (HBsAg [anti-HBc not required) should be performed to prevent transmission in **(strong recommendation)**: • Blood, tissue, semen, and organ donors • Healthcare workers • Pregnant women	98%

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Recommendation/statement	Consensus
Because of the importance of early diagnosis of HBV infection (prevention of transmission, availability of safe and effective treatment measures), EASL advocates population-based screening beyond risk groups to identify unknown cases, especially in countries with intermediate to high endemicity.	98%
In HBsAg-positive individuals, the serological and virological diagnostics shown in Table 5 should be considered **(strong recommendation).**	95%
Baseline liver disease assessment should be performed in all HBsAg-positive individuals **(strong recommendation).**	100%
Abdominal ultrasound should be performed at diagnosis in all HBsAg-positive individuals **(strong recommendation).**	98%
Non-invasive methods should be used to assess liver fibrosis and stage liver disease in all HBsAg-positive individuals **(strong recommendation).**	100%
Liver biopsy can be performed in case of diagnostic uncertainty, discordant non-invasive test results or the presence of liver-related comorbidities **(weak recommendation).**	100%
For individuals newly diagnosed with chronic HBV infection, monitoring (ALT and HBV DNA) should be performed every 3-6 months for the first year after diagnosis or until treatment is initiated. After this initial phase, the monitoring frequency should be adjusted to every 6-12 months, depending on the disease phase **(strong recommendation).**	95%
HBsAg levels should be determined every 12 months. If a quantitative determination of HBsAg is not possible, a qualitative HBsAg test is the minimum requirement **(strong recommendation).**	100%
HBeAg and anti-HBe should be tested in HBeAg-positive individuals every 12 months or when ALT levels or HBV DNA levels change significantly **(strong recommendation).**	98%
Non-invasive methods should be used to assess liver fibrosis progression. The frequency and intervals should be individualised based on factors such as disease phase and presence of comorbidities **(strong recommendation).**	90%
The clinical goal of treating chronic HBV infection is to reduce morbidity (cirrhosis, hepatic decompensation, liver failure, HCC) and improve survival. Since clinical endpoints such as cirrhosis, end-stage liver disease and HCC manifest over a longer period of time, surrogate markers are instrumental in defining treatment success**:** • Persistent suppression of HBV DNA (preferably undetectable HBV DNA) is the primary goal of antiviral therapy. • HBsAg loss is the ultimate goal of therapy. • Normalisation of ALT is an additional endpoint. Additional goals of antiviral therapy are: • Confirmed loss of HBeAg and seroconversion to anti-HBe antibodies (for HBeAg-positive patients) in combination with HBV DNA <2,000 IU/ml can serve as an intermediate treatment endpoint. • Improvement of liver fibrosis • Improvement of HBV-associated extrahepatic manifestations • Improvement of health-related quality of life and patient-reported outcomes • Prevention of HBV transmission • Prevention of HBV reactivation and/or hepatitis	100%
In principle, all HBsAg-positive individuals with detectable HBV DNA are candidates for antiviral therapy. The indication for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage and risk of liver disease progression and HCC.	95%
Patients with HBeAg-positive or HBeAg-negative chronic hepatitis B, HBV DNA level ≥2,000 IU/ml and elevated ALT (>ULN) and/or significant fibrosis should receive antiviral therapy **(LoE 1, strong recommendation).**	98%
Patients with cirrhosis should be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT **(LoE 3, strong recommendation).**	100%
Patients with advanced liver disease (corresponding to Metavir fibrosis score ≥F3 on liver histology or defined by a LSM ≥8 kPa) can be treated if HBV DNA is detectable, regardless of the level of viraemia and serum ALT **(LoE 5, weak recommendation).**	96%
Patients with persistently low HBV DNA (<2,000 IU/ml) and persistently elevated ALT (>ULN) can be treated. However, it should be considered that other liver diseases may also be implicated **(LoE 5, weak recommendation).**	93%
Individuals with HBeAg-positive or HBeAg-negative chronic HBV infection require a personalised assessment to determine the appropriate treatment indication (details see next two recommendations)	98%
In young individuals (<30 years) with HBeAg-positive chronic HBV infection, persistently normal ALT levels, no significant liver fibrosis, no family history of HCC and no immunosuppressive condition, current clinical evidence does not support immediate antiviral treatment. However, the potential benefits of early therapy – such as reducing HBV DNA integration and clonal expansion – should be balanced against the need for strict adherence to long-term daily treatment and the difficulty of achieving rapid and complete viral suppression in patients with high viral loads.	94%
Individuals with HBeAg-positive chronic infection and an increased HCC risk should be treated **(LoE 3, strong recommendation).**	98%
Individuals with HBeAg-positive chronic infection and HBV-related extrahepatic manifestations should be treated **(LoE 4, strong recommendation).**	100%
Individuals with HBeAg-positive chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral treatment to prevent hepatitis **(LoE 2, strong recommendation).**	100%
Selected individuals with HBeAg-positive chronic infection can be treated to prevent HBV transmission **(LoE 3, weak recommendation).**	95%
In pregnant women with HBV DNA ≥200,000 IU/ml, antiviral therapy should be administered to prevent mother-to-child transmission (specific recommendation see "What are the treatment recommendations for pregnant HBsAg-positive women?") **(LoE 1, strong recommendation).**	96%
Patients with HBeAg-negative chronic infection (persistent HBV DNA <2,000 IU/ml, persistently normal ALT, no signs of liver fibrosis) have a low risk of disease progression and transmission and usually do not require immediate antiviral treatment.	98%
Individuals with HBeAg-negative chronic infection and a high risk of HCC should be treated **(LoE 4, strong recommendation**	98%
Individuals with HBeAg-negative chronic infection and HBV-related extrahepatic manifestations should be treated **(LoE 4, strong recommendation**	98%
Individuals with HBeAg-negative chronic infection who are being considered for immunosuppressive therapy or who are immunocompromised should receive antiviral therapy to prevent HBV reactivation/hepatitis **(LoE 2, strong recommendation**	100%

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Recommendation/statement	Consensus
Selected individuals with HBeAg-negative chronic infection can be treated to prevent HBV transmission **(LoE 4, weak recommendation).** **The recommendation did not reach a strong consensus, because some panelists argued that chronic HBeAg-negative infection is typically associated with very low HBV DNA levels, resulting in a minimal risk of transmission that may not justify routine antiviral treatment. However, this recommendation remains relevant for individuals performing exposure-prone procedures to further reduce any potential transmission risk.*	90%
Two different therapeutic options are recommended for the treatment of chronic HBV infection: NAs or PEG-IFNα.	98%
When choosing between NAs and PEG-IFNα as first-line treatments, the distinct characteristics of each treatment option (Table 10) and individual patient preferences should be comprehensively considered **(LoE 1, strong recommendation).**	98%
ETV, TDF, or TAF should be used as first-line NA therapy. When selecting between ETV, TDF and TAF, comorbidities (especially renal insufficiency and reduction in bone density) and concomitant circumstances (*e.g.* women of childbearing age, pregnancy, age) as well as previous therapies should be taken into account **(LoE 1, strong recommendation).**	98%
Determination of HBV DNA and ALT levels should be carried out every 3-6 months until a virological response (see definition of treatment response) is achieved. Thereafter, the monitoring interval can be extended to 6-12 months for therapy with ETV or tenofovir (TDF or TAF) **(LoE 2, strong recommendation).**	100%
HBsAg status should be tested every 12 months. Ideally, a quantitative determination of HBsAg should be performed **(LoE 3, strong recommendation).**	98%
It is suggested to test HBeAg and anti-HBe in HBeAg-positive patients every 12 months **(LoE 2, weak recommendation).**	94%
Kidney function should be assessed before treatment initiation and monitored regularly during treatment to adjust the NA dose **(LoE 1, strong recommendation).**	98%
Treatment with TDF should be switched to another NA (ETV or TAF) if the glomerular filtration rate decreases, if tubulopathy occurs, and in case of hypophosphatemia or osteoporosis. Previous therapies and resistance should be taken into account when choosing the NA **(LoE 1, strong recommendation).**	96%
Non-invasive fibrosis assessment should be performed every 12-24 months **(LoE 3, strong recommendation).**	90%
In the event of a partial virological response or virological non-response, the patient's adherence to treatment should be assessed in the first instance **(LoE 1, strong recommendation).**	100%
A test for HBV variants associated with NA resistance can be performed if treatment adherence is confirmed **(LoE 2, weak recommendation).**	98%
In the event of a partial virological response, virological non-response or virological resistance, the following treatment adjustments are recommended **(LoE 1-2, strong recommendation)**: • Switch to tenofovir (TDF or TAF) if a nucleoside analogue was previously used **(LoE 1).** • Switch to ETV or tenofovir (TDF or TAF) if adefovir was previously used **(LoE 1).** • Switch to or add-on ETV if tenofovir (TDF or TAF) was previously used **(LoE 2).**	98%
In case of persistent low-level HBV DNA (<2,000 IU/ml) or blips during treatment with tenofovir (TDF or TAF) or ETV, treatment does not need to be immediately adjusted in the absence of advanced liver fibrosis and when resistance has been excluded. Potential explanations, such as poor adherence to treatment or reduced absorption in the intestine, should be considered **(LoE 4, weak recommendation).**	100%
In patients with cirrhosis, the goal is to achieve undetectable HBV DNA ideally after 12 months of treatment. If this is not achieved, treatment adjustment should be considered **(LoE 3, strong recommendation).**	98%
Antiviral therapy with NAs should only be discontinued after consultation with a physician experienced in the treatment of hepatitis B and if close monitoring is guaranteed. HBsAg levels, HBeAg status, comorbidities, duration of HBV DNA suppression, stage of liver fibrosis in addition to patient understanding and preference should be taken into account **(LoE 2, strong recommendation).**	100%
Antiviral therapy with NAs should be stopped after confirmed HBsAg loss with or without anti-HBs seroconversion in the absence of coexisting risk factors **(LoE 2, strong recommendation).**	93%
When considering NA discontinuation in HBsAg-positive individuals, HBsAg levels should be used to select patients **(LoE 2, strong recommendation**	96%
In HBeAg-positive patients without advanced liver disease, antiviral therapy with NAs can be stopped 12 months after confirmed HBeAg/anti-HBe seroconversion and undetectable HBV DNA if close monitoring is guaranteed after the end of therapy **(LoE 2, weak recommendation** **Given the higher risk of clinical relapse after discontinuing NA therapy in initially HBeAg-positive patients, the recommendation did not achieve strong consensus. Some panellists expressed a preference against stopping therapy before HBsAg loss.*	87%
In selected HBeAg-negative patients without advanced liver disease, NA therapy can be discontinued before HBsAg loss if HBV DNA has been undetectable for at least 3-4 years, HBsAg level is low, and close monitoring is guaranteed after the end of therapy **(LoE 1-2, weak recommendation)** **Although evidence for the effectiveness and safety of stopping NA therapy in selected patients is strong (Evidence Level 1 from the German prospective STOP-NUC trial), the recommendation did not achieve strong consensus. Concerns remain about the potential risk of flares if treatment discontinuation is implemented broadly in general clinical practice rather than in specialised expert settings*	89%
In addition to HBsAg level, HBcrAg and HBV RNA level can be used to further improve the patient stratification before discontinuing therapy **(LoE 3, weak recommendation)** **Although evidence supporting the use of HBcrAg and HBV RNA remains limited, we opted for a weak recommendation, recognising the importance of improving patient stratification for the NA discontinuation approach. However, this recommendation has not achieved strong consensus among the panellists.*	78%
Predictive factors should be used to guide the decision to initiate PEG-IFNα treatment. In addition, PEG-IFNα-associated side effects should be considered, and the patient's treatment preferences should be taken into account to support the decision-making process **(LoE 2, strong recommendation).**	100%
PEG-IFNα should be administered once a week, typically for a duration of 48 weeks. The dose of PEG-IFNα-2a should be 180 μg weekly (s.c.) **(LoE 1, strong recommendation).**	100%
Stopping rules should be considered based on the quantitative determinations of HBV DNA and HBsAg at treatment week 12 and 24 **(LoE 2, strong recommendation).**	96%

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Recommendation/statement	Consensus
De novo combination therapy with PEG-IFNα and NAs cannot be generally recommended. PEG-IFNα as an add-on therapy can be considered in selected HBeAg-negative patients undergoing NA therapy with low HBsAg levels **(LoE 2, weak recommendation).** **Although the evidence for PEG-IFNα add-on therapy is limited, we decided in favour of a weak recommendation to keep this option available for selected patients in experienced centres. As expected, strong consensus was not achieved*	84% .
During and after therapy with PEG-IFNα, regular safety-related blood tests should be carried out and adverse reactions should be monitored **(LoE 1, strong recommendation).**	100%
The inclusion of patients at risk of HCC in surveillance programmes is recommended. The strength of this recommendation for HCC surveillance is based on the individual risk level **(LoE 2, strong recommendation).**	100%
Individual risk assessment can be enhanced by applying HCC risk scores **(LoE 2, weak recommendation).**	95%
HCC surveillance should involve abdominal ultrasound performed every 6 months by an experienced operator in all at-risk populations **(LoE 2, strong recommendation).**	100%
HCC surveillance should be continued in at-risk patients irrespective of effective antiviral therapy or HBsAg loss **(LoE 2, strong recommendation).**	98%
Other imaging modalities (contrast-enhanced CT, MRI) should be used if abdominal ultrasound cannot provide reliable information **(LoE 3, strong recommendation).**	100%
Tumour biomarkers (*e.g.* alpha-fetoprotein [AFP]) can be used in addition to imaging for HCC surveillance **(LoE 2 (for AFP), weak recommendation).** *****Some panellists, including patient representatives, advocated for upgrading the recommendation to use biomarkers such as AFP to a strong recommendation. This underscores a critical unmet need for more effective biomarkers to enhance HCC risk prediction.*	91%
Given the high spontaneous clearance rate of HBsAg during acute HBV infection in adults, antiviral treatment is not required in this clinical setting as long as synthetic liver function is not impaired	100%
Patients with acute hepatitis B and impaired synthetic liver function should be treated with NAs and should be managed in cooperation with a transplant centre **(LoE 2, strong recommendation).**	100%
In pregnant women on antiviral therapy, tenofovir (TDF, TAF) should be continued, ETV or adefovir should be switched to tenofovir (TDF, TAF). Treatment with PEG-IFNα should be discontinued and switched to tenofovir (TDF, TAF) **(LoE 2, strong recommendation).**	100%
Untreated pregnant women should receive antiviral therapy during pregnancy in the following cases **(LoE 1, strong recommendation):** • Chronic hepatitis, in accordance with the recommendations for non-pregnant women. • HBV DNA levels ≥200,000 IU/ml, to prevent mother-to-child transmission of HBV. • Positive HBeAg irrespective of HBV DNA level, in areas where HBV DNA testing is unavailable, to prevent mother-to-child transmission.	96%
Treatment to prevent mother-to-child transmission should ideally be started before the last trimester of pregnancy. Tenofovir (TDF, TAF) should be used during pregnancy **(LoE 2, strong recommendation).**	98%
Maternal antiviral prophylaxis with tenofovir can be continued long-term post-delivery to maintain viral suppression **(LoE 2, weak recommendation).**	95%
During maternal antiviral prophylaxis with tenofovir, the newborn can be breastfed **(LoE 4, weak recommendation).**	100%
HBsAg-positive patients with decompensated cirrhosis or acute-on-chronic liver failure should be treated with ETV or tenofovir (TDF, TAF), irrespective of HBV DNA levels. PEG-IFNα should not be used in patients with decompensated cirrhosis or ACLF **(LoE 1, strong recommendation).**	100%
HBsAg-positive patients with HCC should be treated with NAs, irrespective of HBV DNA levels **(LoE 2, strong recommendation).**	100%
TDF is suggested as the preferred NA for tertiary prophylaxis after curative treatment (*e.g.* surgery or locoablative therapy) for HCC **(LoE 2, weak recommendation).**	96%
HBsAg-positive individuals living with HIV should receive anti-HBV treatment regardless of ALT or HBV DNA levels **(LoE 2, strong recommendation).**	98%
HBV therapy should be given as part of antiretroviral HIV therapy. In HBsAg-positive individuals living with HIV, the antiretroviral therapy should contain tenofovir (TDF or TAF) **(LoE 1, strong recommendation).**	100%
Treatment monitoring and adjustments should be carried out in accordance with the recommendations for HBV-monoinfected patients, taking into account the HIV coinfection **(LoE 5, strong recommendation).**	100%
Anti-HBV-containing antiretroviral therapy should not be discontinued in HBV/HIV coinfection due to the risk of HBV rebound and biochemical relapse **(LoE 2, strong recommendation).**	100%
Patients with decompensated liver disease may be treated with bulevirtide monotherapy depending on the individual's risk benefit assessment. If decompensation occurs during therapy with bulevirtide monotherapy, therapy can be continued **(LoE 4, weak recommendation).**	95%
The indications for anti-HBV treatment are generally the same as those for chronic HBV monoinfection. However, in the context of anti-HCV therapy, there are additional factors to consider.	100%
HBsAg-positive patients with chronic HCV infection should be treated with HCV-specific direct-acting antivirals **(LoE 2, strong recommendation).**	100%
All HBsAg-positive patients with cirrhosis (even if HBV DNA is undetectable) should receive NA therapy during anti-HCV direct-acting antiviral therapy to prevent HBV reactivation **(LoE 2, strong recommendation).**	100%
Prophylactic NA treatment to prevent reactivation during anti-HCV direct-acting antiviral treatment can be given in patients not meeting the indication for treatment of chronic HBV monoinfection (*e.g.* HBV DNA <2,000 IU/ml, normal ALT and absence of advanced fibrosis/cirrhosis) **(LoE 2, weak recommendation).**	95%
Antiviral treatments approved for children and adolescents include**:** • IFNα-2b: approved by both the FDA and EMA for children aged 1 year and older. • PEG-IFNα-2a: approved for children aged 3 years and older. • Lamivudine: approved for children aged 3 years and older. • Entecavir: approved for children aged 2 years and older. • Tenofovir disoproxil fumarate: approved by the EMA for children aged 2 years and older, and by the FDA for those 12 years and older. • Tenofovir alafenamide: EMA approved for children aged 12 years and older or those weighing more than 35 kg, regardless of age.	98%

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Recommendation/statement	Consensus
HBV reactivation risk assessment and the indication for prophylaxis is based on HBV markers (HBsAg, anti-HBc and HBV DNA status), the planned immunosuppressive regimen and the underlying disease requiring immunosuppression (Table 14). Thus, HBsAg and anti-HBc antibody status should be assessed before starting immunosuppressive therapy. HBsAg-positive individuals starting immunosuppressive therapy should undergo the same clinical evaluation recommended for all HBsAg-positive individuals. HBsAg-negative and anti-HBc-positive individuals should be tested for HBV DNA before starting immunosuppressive therapy **(LoE 1, strong recommendation).**	98%
HBsAg-positive individuals at high and moderate risk of reactivation should receive prophylactic antiviral therapy with NAs **(LoE 1, strong recommendation).**	100%
HBsAg-positive individuals at low risk of reactivation do not need to be treated if HBV DNA monitoring is performed at least every 3 months. If there are concerns about feasibility of HBV DNA monitoring, prophylactic NA therapy should be initiated **(LoE 2, strong recommendation).**	98%
HBsAg-negative, anti-HBc-positive and HBV DNA-positive individuals should be managed in the same way as HBsAg-positive individuals **(LoE 2, strong recommendation).**	100%
HBsAg-negative, anti-HBc-positive, HBV DNA-negative individuals should receive prophylactic NA therapy if immunosuppressive therapy associated with a high risk of HBV reactivation is planned **(LoE 2, strong recommendation).**	98%
HBsAg-negative, anti-HBc-positive, HBV DNA-negative individuals who will receive an immunosuppressive regimen with moderate or low risk of reactivation do not need to be treated and should be monitored closely (HBsAg and/or HBV DNA every 3 months). If there are concerns about feasibility of HBV monitoring, prophylactic NA therapy should be initiated **(LoE 3, strong recommendation).**	93%
ETV or tenofovir (TAF or TDF) should be used for the prophylaxis of HBV reactivation. The duration of NA prophylaxis is not well-defined. NA therapy should be administered for at least 6-12 months after completing immunosuppressive therapy. In high-risk settings, such as with B cell-depleting therapies, it should be continued for at least 18 months after completing immunosuppressive therapy. Ideally, NA discontinuation should follow established criteria for NA withdrawal, particularly if HBV DNA was positive before starting NA therapy (**LoE 3, strong recommendation).**	96%
Patients with HBV infection who undergo liver transplantation should receive prophylaxis to prevent HBV recurrence. The standard recommended prophylactic therapy is the combination of a NA (ETV, TDF or TAF) plus hepatitis B immunoglobulin. Hepatitis B immunoglobulin should commence during the anhepatic phase of liver transplantation, and the dosage of hepatitis B immunoglobulin after liver transplantation should be adjusted according to anti-HBs concentrations **(LoE 1, strong recommendation).**	96%
Hepatitis B immunoglobulin can be discontinued after liver transplantation, provided there is good adherence to high genetic barrier NA therapy and patients are at low risk of HBV recurrence **(LoE 2, weak recommendation).**	96%
Hepatitis B immunoglobulin-free prophylaxis can be considered after liver transplantation, provided there is good adherence to NAs and patients are at low risk of HBV recurrence **(LoE 2, weak recommendation).**	100%
In case of HBsAg seroreversion after liver transplantation, hepatitis B immunoglobulin therapy should be discontinued while antiviral therapy with NAs should be continued **(LoE 4, strong recommendation**	100%
Transplantation of a liver from an HBsAg-negative/anti-HBc-positive donor:	
• If the recipient is HBsAg-negative/anti-HBc-negative/anti-HBs-negative, long-term NA prophylaxis should be administered. Combined prophylaxis with hepatitis B immunoglobulin + an NA is not recommended **(LoE 2, strong recommendation).**	98%
• If the recipient is HBsAg-negative/anti-HBc-negative but anti-HBs-positive, the risk of HBV reactivation is lower than in anti-HBs-negative recipients. Nevertheless, prophylaxis with an NA is also recommended **(LoE 2, strong recommendation).**	100%
• If the recipient is HBsAg-negative, anti-HBc-positive and anti-HBs-positive the risk of HBV reactivation is particularly low. NA prophylaxis is not required but close monitoring of HBV DNA and HBsAg should be carried out. If there are concerns about feasibility of HBV monitoring, prophylactic NA therapy should be initiated. If HBV DNA and/or HBsAg positivity occur, NA therapy with an NA should be started immediately **(LoE 3, strong recommendation).**	98%
• If HBV DNA and/or HBsAg positivity occur, antiviral therapy with an NA should be started immediately **(LoE 2, strong recommendation).**	100%
Transplantation of other organs (*e.g.* kidney, heart, lung, pancreas, or stem cell transplantation) from an HBsAg-negative/anti-HBc-positive donor:	
• Prophylaxis with hepatitis B immunoglobulin and/or an NA is not generally recommended regardless of the anti-HBs status of the transplant recipient due to the overall low risk of HBV infection. HBV DNA and HBsAg monitoring should be carried out. If HBV DNA and/or HBsAg becomes detectable, antiviral therapy with an NA should be started immediately **(LoE 2, strong recommendation).**	95%
All patients who receive a liver transplant from an HBsAg-positive donor should be treated with a highly potent NA (ETV, TDF, TAF) **(LoE 2, strong recommendation).**	100%
Patients with chronic hepatitis delta should not receive a liver transplant from an HBsAg-positive donor **(LoE 4, strong recommendation).**	100%
In the case of other organ transplants (*e.g.* kidney, heart, lung, pancreas, or stem cell transplantation) from an HBsAg-positive donor, prophylaxis with hepatitis B immunoglobulin plus a potent NA are indicated. In the case of a stem cell transplant or a living donation of a solid organ from an HBsAg-positive donor, the donor should also be treated with a highly effective NA as early as possible before transplantation **(LoE 4, strong recommendation).**	100%
Several recombinant hepatitis B vaccines are available worldwide and are used in various immunisation programmes against HBV infection. The selection of a vaccine may depend on factors such as availability, cost, dosing schedule, efficacy and recommendations from local health authorities.	100%
Universal hepatitis B vaccination for all infants, children and adolescents is recommended as early as possible, preferably before the onset of puberty **(LoE 1, strong recommendation).**	100%
Newborns of HBsAg-positive mothers or mothers with unknown HBsAg status should receive the hepatitis B vaccine as early as possible after birth, ideally within 12 hours, in combination with passive immunisation using hepatitis B immunoglobulin to maximise protection against HBV transmission **(LoE 1, strong recommendation).** **The recommendation on birth dose vaccination did not achieve strong consensus, and no specific comments were provided by the Delphi panellists regarding the combined active and passive birth dose vaccination. However, one comment emphasised the importance of administering the first dose of HBV vaccine to all newborns within the first 24 hours after birth, regardless of maternal HBsAg status, in line with WHO recommendations (www.who.int). This recommendation is particularly important in regions with a high prevalence of HBsAg and where routine HBsAg screening during pregnancy is not implemented, as it serves as a key strategy for preventing HBV transmission.*	93%

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Recommendation/statement	Consensus
The following risk groups should be vaccinated against HBV infection **(LoE 1, strong recommendation)**: • individuals in whom a severe course of hepatitis B is to be expected due to an existing or expected immunodeficiency, immunosuppression or chronic diseases such as chronic liver or kidney disease. • individuals with an increased risk of non-occupational exposure, e.g. contact with HBsAg-positive persons (partners and family members of people living with chronic HBV infection), high-risk sexual behaviour, persons seeking evaluation for treatment of sexually transmitted infections, people who inject drugs, incarcerated persons and patients in psychiatric facilities. • individuals with increased occupational exposure risk, including healthcare trainees, interns, students, volunteers, laboratory and cleaning staff in healthcare facilities, paramedics, emergency responders, police officers, firefighters, soldiers, and staff in facilities with a high prevalence of chronic HBV infection.	98%
In addition, hepatitis B vaccination is suggested for **(LoE 4, weak recommendation):** • international travellers to regions with high or moderate prevalence of chronic HBV infection. • all other individuals who seek protection against HBV infection, irrespective of specific risk factors.	100%
Post-vaccination efficacy assessment (anti-HBs) should be carried out in individuals belonging to a specific risk group **(LoE 2, strong recommendation).**	100%
In individuals who do not belong to a specific risk group (see above), who are healthy and younger than 40 years of age, a post-vaccination efficacy assessment (anti-HBs) is not required.	100%
For immunosuppressed or immunodeficient individuals, including patients with cirrhosis or those on haemodialysis, an increased dose of standard (or second-generation) vaccines (double dose or dose tailored for patients on dialysis) or third-generation vaccines should be administered **(LoE 1, strong recommendation).**	100%
The seroprotection rate is defined as anti-HBs ≥10 IU/L. However, for risk groups with higher risk of severe outcomes, such as immunocompromised individuals (9.3), the vaccination schedule is considered optimal if the anti-HBs level is ≥100 IU/L 1-2 months after the last vaccination. This indicates long-term, possibly lifelong protection against hepatitis B.	98%
Individuals with anti-HBs titres ≥100 IU/L 1-2 months after completion of the vaccination series do not require further monitoring and booster vaccination. Exceptions include immunocompromised individuals, who should undergo a follow-up test for anti-HBs (and receive a booster vaccination if anti-HBs <100 IU/L). Anti-HBs test intervals range from annually to every 10 years, depending on the risk **(LoE 2, strong recommendation).**	100%
For risk groups with anti-HBs titres between 10 and 100 IU/L 1-2 months after completion of the vaccination series an additional booster dose is suggested, followed by reassessment of anti-HBs titres after 1-2 months **(LoE 3, weak recommendation**	98%
Individuals with anti-HBs titres of <10 IU/L 1-2 months after completion of the vaccination series should be revaccinated with a complete vaccination course (possibly with an optimised vaccination schedule) and anti-HBs titre should be determined again after 1-2 months. The exclusion of an ongoing HBV infection (HBsAg, anti-HBc) should be considered before revaccination in these individuals **(LoE 1, strong recommendation).**	100%

Appendix 2. Classification of chronic HBV infection and chronic hepatitis B* based on viral markers, inflammatory activity, disease stage and risk of disease progression.

Population	ALT	HBV DNA	HBsAg	Specifics	Serum HBcrAg	Serum HBV RNA
HBeAg positive						
HBeAg-positive infection, high replicative	Normal (low normal)	Very high, usually ≥10^8	Very high, (usually ≥25,000 IU/ml)	Young age, no/mild fibrosis, no disease progression if stable	Positive ++++	Positive ++++
HBeAg-positive infection, impending phase transition	Normal (high normal)	High, usually ≥10^6	Intermediate to high (usually <25,000 IU/ml)	Age usually ≥30 years, fibrosis can be present	Positive ++++	Positive ++++
HBeAg-positive hepatitis	Elevated	High, usually ≥10^4	Intermediate to high (usually <25,000 IU/ml)	Any age, high risk for disease progression	Positive ++++	Positive ++++
HBeAg-positive cACLD	Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	cACLD according to BAVENO VI[80]	Positive + to +++	Positive Any value is possible
HBeAg negative						
HBeAg-negative cACLD	Normal or elevated	Usually high, but any HBV DNA is possible	Usually high, but any HBsAg is possible	cACLD according to BAVENO VI[80]	Positive +++ or negative	Positive Any value is possible
HBeAg-negative hepatitis	Elevated	Usually ≥2,000 IU/ml	Low to high	High risk for disease progression	Positive ++	Positive or negative Any value is possible
HBeAg-negative infection, high replicative, high-risk infection	Normal	Usually >20,000 IU/ml	Low to high	Usually older age, fibrosis	Positive ++	Positive Any value is possible
HBeAg-negative infection, high replicative, low-risk infection	Normal	Usually >2,000-20,000 IU/ml	Low to high	No disease progression if stable for ≥3 years	Positive ++	Positive or negative Any value is possible
HBeAg-negative infection, low replicative	Normal (low normal)	<2,000 IU/ml	Usually <1,000 IU/ml	No/mild fibrosis, no disease progression if stable	Negative or +	Negative or +
HBeAg-negative infection, partial cure	Normal (low normal)	Not detectable	<100 IU/ml	High chance to achieve HBsAg loss	Negative or +	Negative
HBsAg-negative (functional cure)	Normal	Not detectable	<0.05 IU/ml	Associated with best prognosis	Negative or +	Negative

*Compensated chronic liver disease, cACLD, compensated advanced chronic liver disease

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ACIP, Advisory Committee on Immunization Practices; ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AMI, acute myocardial infarction; APRI, AST-platelet ratio index; AST, aspartate aminotransferase; BMD, bone mineral density; cccDNA, covalently closed circular DNA; CPGs, clinical practice guidelines; CSPH, clinically significant portal hypertension; DAAs, direct-acting antivirals; EASL, European Association for the Study of the Liver; EGD, EGD, oesophagogastroduodenoscopy; ELITA, European Liver and Intestine Transplant Association; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, HBV reactivation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; ICIs, immune checkpoint inhibitors; Ig, immunoglobulin; LMICs, low- and middle-income countries; LOD, limit of detection; LOQ, limit of quantification; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; MTCT, mother-to-child transmission; NAs, nucleos(t)ide analogues; NAT, nucleic acid testing; PEG-IFNα, pegylated interferon-alfa; PLWH, people living with HIV; PROs, patient-reported outcomes; RDTs, rapid diagnostic tests; SLD, steatotic liver disease; SWE, shear wave elastography; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; WHO, World Health Organization.

Conflict of interest

Pietro Lampertico has served on the Advisory Board/Speaker Bureau for Roche Pharma/Diagnostics, Gilead Sciences, GSK, AbbVie, Janssen, Myr, Eiger, Antios, Aligos, Vir, Grifols, Altona, and Roboscreen. Testoni Barbara has received research funding from Aligos, Assembly Biosciences, Bluejay Therapeutics and Beam Therapeutics; has received fees for expert testimony from the International Hepatology Education Program; and has a patent pending with Beam Therapeutics. Francesco Paolo Russo has held lectures for Gilead Sciences, AbbVie, Biotest, Grifols, and Johnson and Johnson, received support for attending meetings from Gilead Sciences and Biotest, received funding from Gilead Sciences, served as an advisory board member for GSK, Gilead Sciences and AbbVie. Lisa Sandmann has received lecture honoraria and personal fees from Falk Pharma e.V., Gilead Sciences and Roche, and travel support from AbbVie and Gilead Sciences. Jerzy Jaroszewicz has held lectures and obtained advisory grants from AbbVie, Roche, Gilead Sciences, Grifols, GSK, MSD, Novo Nordisk, and Novartis. Grace L Wong has served as an advisory committee member for AstraZeneca, Gilead Sciences, GSK, Janssen and Virion Biotherapeutics; as a speaker for Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Ferring, Gilead Sciences, GSK, Janssen, and Roche. She has also received research grants from Gilead Sciences. Sabela Lens has served on the Speaker Bureau/Advisory Board for Gilead Sciences, AbbVie, GSK and Roche; and received research grants from Gilead Sciences. Markus Cornberg has held lectures for AbbVie, Gilead Sciences, MSD and Falk Foundation and served as an advisory board member for AbbVie, AiCuris, AstraZeneca, Gilead Sciences, GSK, Roche. Patrick Kennedy has served as an

advisor/speaker for Gilead Sciences, GSK, Janssen, Abbott, Aligos, Assembly Bioscience and Bluejay Therapeutics. He has also received research grants from Gilead Sciences and Vir Biotechnology. Maud Lemoine has received consultant fees from Abbott, Cepheid, Gilead Sciences, ViiV healthcare and GSK. Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgements

The authors would like to thank the members of the Delphi Panel of this Clinical Practice Guideline for their valuable contribution: Kosh Agarwal, Soo Aleman, Marina Berenguer, Thomas Berg, Marc Bourlière, Peer Brehm Christensen, Maurizia Brunetto, Maria Buti, Hélder Cardoso, Tetiana Chaban, Nicola Coppola, Elisabetta Degasperi, Sylvia Drazilova, Geoff Dusheiko, Ahmed Elsharkawy, Eoin Feeney, Robert Flisiak, Xavier Forns, Liana Gheorghe, Stephanie Hametner-Schreil, Eibhlín Higgins, Mathias Jachs, Harry Janssen, Zeki Karasu, Pavol Kristian, Limas Kupcinskas, Ivana Lazarevic, Spilios Manolakopoulos, Mojca Maticic, Philippa Matthews, Francesco Negro, George Papatheodoridis, Jean-Michel Pawlotsky, Malgorzata Pawlowska, Isabel Pedroto, Jörg Petersen, Ulrike Protzer, Manuel Rodriguez, Amir Shlomai, Milan Sonneveld, Jan Sperl, Christiane Stern, Ieva Tolmane, Thomas Vanwolleghem, Adriana Vince, Su Wang, Nina Margrethe Weis, Suna Yapali, Igor A. Zaytsev, Fabien Zoulim, Ingo van Thiel. The authors would also like to thank David Mutimer, Heiner Wedemeyer, Alessandra Mangia, Rachel Jeng and the EASL Governing Board for their valuable contribution to the review process.

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Received 20 March 2025; accepted 20 March 2025; Available online xxx