

Review

'What is new in hepatitis B'

Upkar S Gill ,¹ Victoria J Appleby ,² Sabela Lens³

¹Centre for Immunobiology & Infection, Blizard Institute, Barts and the London Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK

²Leeds Liver Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK

³Liver Unit, University of Barcelona, Hospital Clínic Barcelona, FCRB-IDIBAPS, CIBERehd, Barcelona, Spain

Correspondence to

Dr Upkar S Gill; u.gill@qmul.ac.uk

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ABSTRACT

Chronic hepatitis B (CHB) remains a major cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide, affecting over 250 million people. In the UK, the burden is concentrated in migrant populations, yet diagnosis and treatment rates remain low. The 2025 European Association for the Study of the Liver guidelines mark a paradigm shift towards biomarker-led, personalised care, incorporating metabolic risk factors and focusing on functional cure, defined as sustained hepatitis B surface antigen (HBsAg) loss and undetectable hepatitis B virus (HBV) DNA. This review summarises key updates in diagnosis, staging, treatment initiation and cessation. The revised framework emphasises early treatment to prevent fibrosis progression and HCC, particularly in patients with metabolic dysfunction-associated steatotic liver disease, where disease progression can occur despite low viral load or normal alanine aminotransferase. Novel biomarkers, including quantitative HBsAg, hepatitis B core-related antigen and HBV RNA, are increasingly used to refine risk stratification, guide safe treatment discontinuation and identify patients for emerging therapies. Special populations, including pregnant individuals, those undergoing immunosuppression and patients with hepatitis D virus co-infection, require tailored management. Advances in minimally invasive liver fine needle aspiration allow detailed intrahepatic immune and virological profiling, supporting the development of new immunomodulatory and antiviral agents. By combining earlier diagnosis, integrated metabolic assessment, biomarker-led monitoring and novel therapies, the 2025 guidelines provide a blueprint for precision medicine in CHB, with the potential to improve outcomes and reduce the global burden of HBV-related liver disease.

INTRODUCTION

Chronic hepatitis B (CHB) management is undergoing a major transformation, with increasing focus on achieving a functional cure, a concept inspired by the curative success of hepatitis C therapies.¹ The updated 2025 European Association

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Chronic hepatitis B (CHB) is a dynamic disease in which metabolic co-morbidities accelerate fibrosis progression and increase hepatocellular carcinoma (HCC) risk.
- ⇒ Early antiviral treatment can prevent irreversible liver damage, even in patients with normal ALT or low viraemia.
- ⇒ Lifelong HCC surveillance is required in at-risk patients, regardless of viral suppression or HBsAg loss.

WHAT THIS STUDY ADDS

- ⇒ A contemporary summary of the 2025 EASL guidelines, which emphasise non-invasive tools, biomarker-led decision-making and multidisciplinary care models.
- ⇒ Highlights the potential of minimally invasive liver fine needle aspiration (FNA) to enable real-time intrahepatic immune and viral profiling, advancing therapeutic development.
- ⇒ Shows how novel biomarkers (qHBsAg, HBcrAg, HBV RNA) can refine staging, guide therapy cessation and predict outcomes.
- ⇒ Reviews emerging combination antiviral and immunomodulatory strategies that may increase the likelihood of achieving a functional cure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Supports earlier treatment initiation and broader use of biomarkers in clinical practice to improve outcomes.
- ⇒ Reinforces the need for multidisciplinary collaboration between hepatology, endocrinology, infectious diseases, and primary care.
- ⇒ Underlines the importance of maintaining HCC surveillance in all at-risk patients, even after HBsAg loss.
- ⇒ Encourages adoption of precision medicine approaches and equitable implementation of guideline-based care in both high- and low-resource settings, including patients with MASLD.



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for the Study of the Liver (EASL) Clinical Practice Guidelines (CPG) reflect a shift towards personalised, risk-based care that incorporates advances in biomarkers, broader treatment indications and novel therapeutic goals. These updates are particularly relevant for frontline clinicians managing patients with comorbidities such as metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease or immunosuppressive conditions. The guidelines also introduce updated recommendations for hepatocellular carcinoma (HCC) surveillance and hepatitis B virus (HBV) reactivation prophylaxis. While nucleos(t)ide analogues (NA's) remain the mainstay of treatment, pegylated interferon-alpha (PEG-IFN α) retains a role in selected cases, and numerous clinical trials are evaluating novel antiviral and immune-based agents.^{1,2}

Building on the 2017 CPG framework,³ the 2025 guidelines introduce refinements in emerging virological and immunological biomarkers (eg, hepatitis B core-related antigen (HBcrAg), HBV RNA), and earlier treatment eligibility,⁴ especially for patients with metabolic risk factors. These developments reflect an expanding understanding of host–virus interactions and pave the way for finite-duration, curative therapies.

This review summarises the latest updates in CHB diagnosis, treatment and monitoring and highlights future directions in biomarker development and therapeutic innovation.

Prevalence and disease burden and phase

CHB continues to pose a major global health burden, with HBV-related deaths projected to rise to approximately 1.15 million annually by 2030, up from 850 000 in 2015.¹ This is largely driven by increasing cases of HCC and decompensated cirrhosis, expected to grow by 25% if diagnostic and treatment practices remain unchanged.¹ While the greatest burden remains in high-prevalence regions, CHB is increasingly recognised in Western countries due to migration, adding pressure to healthcare systems.⁵ As a result, current guidelines recommend expanding HBV screening beyond high-risk groups, such as the UK's national opt-out screening initiative for hepatitis B, C and HIV in emergency departments,⁶ while Germany offers one-time HBV and HCV testing for all individuals aged 35 and older as part of routine health check-ups.⁷ These models reflect a broader shift towards population-level screening aimed at closing diagnostic gaps and meeting WHO elimination targets.

In parallel with efforts to improve individual diagnosis, global strategies continue to align with WHO's 2023–2030 HBV elimination targets, which aim to achieve 90% diagnosis and 80% treatment coverage.⁸ However, major gaps remain in preventive efforts, most notably the global uptake of the birth-dose HBV vaccination remains suboptimal, with coverage still below 50% in many high-burden regions. In response,

European and UK centres have expanded antenatal screening, early antiviral prophylaxis and linkage-to-care programmes, particularly for migrant populations where the burden of CHB is disproportionately high.⁶

Unlike HIV, where treatment is initiated at diagnosis, CHB management relies on markers of disease activity to determine treatment need. The 2017 EASL guidelines introduced a new nomenclature for disease phases, distinguishing between 'chronic infection' and 'chronic hepatitis', but created ambiguity for patients in the so-called 'grey zone'. The 2025 update recommends avoiding the term 'grey zone' and proposes a simplified treatment algorithm independent of hepatitis B e antigen (HBeAg) status, focusing on HBV DNA (>2000 IU/mL) and fibrosis stage.¹ This aims to streamline treatment decisions and improve access to antiviral therapy. Therapeutic goals have also shifted. Whereas HBV DNA suppression was once central, the 2025 guidelines now prioritise 'functional cure', defined as sustained hepatitis B surface antigen (HBsAg) loss and undetectable HBV DNA after a finite course of therapy, due to its association with reduced HCC risk and liver-related mortality.⁹

Screening and diagnosis

Effective screening and early diagnosis are critical for reducing disease transmission, initiating timely treatment and preventing progression to cirrhosis or HCC. The updated EASL 2025 CPG emphasises the need for proactive population-level screening strategies, particularly in high-risk groups and regions of intermediate to high HBV endemicity.¹ Furthermore, it is also critical to exclude the presence of hepatitis delta (HDV) infection on screening, as HDV leads to increased disease progression. Guidance on whom to screen has been recently summarised by,¹⁰ highlighting both traditional risk-based and universal screening approaches.

Initial serological screening involves testing for HBsAg and hepatitis B core antibody (anti-HBc). Persistence of HBsAg for over 6 months defines chronic HBV infection. If HBsAg is positive, further evaluation should include:

- ▶ HBeAg: To determine disease phase and replication status.
- ▶ HBV DNA: To assess viral load and treatment need.
- ▶ Alanine aminotransferase (ALT): To evaluate hepatic inflammation.
- ▶ Quantitative HBsAg (qHBsAg): For optimising disease stage allocation, treatment monitoring and prognostication.
- ▶ Anti-HDV antibodies: To diagnose coinfection due to the risk of progression of liver disease.

Non-invasive liver assessment is now preferred over liver biopsy for staging fibrosis, with tools such as transient elastography (FibroScan) and blood-based indices like fibrosis-4 (FIB-4) or aspartate aminotransferase (AST) to Platelet Ratio Index widely used to guide

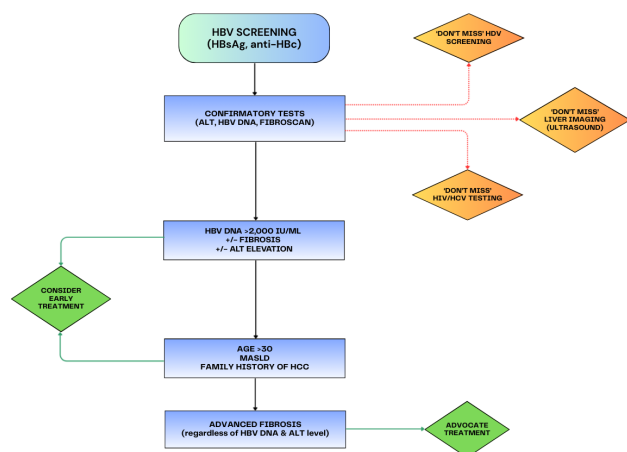


Figure 1 HBV screening and treatment algorithm. Flow chart indicating screening parameters for a new diagnosis of hepatitis B, including what not to miss. Simplified treatment algorithm based on updated EASL guidelines. ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

treatment decisions.¹ However, liver biopsy remains essential in selected cases where non-invasive results are inconclusive or when additional diagnostic information is needed.

Baseline liver ultrasound (US) is recommended to exclude focal liver lesions, evaluate signs of cirrhosis or portal hypertension and ongoing imaging surveillance is required for patients at risk of HCC. In individuals with additional MASLD, dual pathology may accelerate fibrosis and elevate HCC risk, underscoring the importance of early HBV detection and management in this group.^{11 12} Figure 1 displays a simplified algorithm for screening and diagnostic tests.

Take-home message

Early diagnosis of HBV is key to preventing transmission, evaluating the stage of liver disease and viral activity to inform safe effective treatments to prevent liver disease progression. Screening should be offered to all individuals originating from countries with intermediate-high HBsAg prevalence as well as to ‘at-risk’ groups.

For initial screening—HBsAg and anti-HBc should be determined.

Treatment for HBV

Current first-line therapies for CHB include NAs and pegylated interferon- α (PEG-IFN α) (EASL, 2025).

NAs such as entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are oral polymerase inhibitors that suppress HBV DNA replication. TDF and ETV remain first-line in most European countries, while TAF is not yet licensed in some of them.¹³ NA therapy leads to undetectable HBV DNA in >90% of HBeAg-negative and ~70% of

HBeAg-positive patients at 48 weeks, with long-term use reducing the risks of cirrhosis, HCC and liver-related mortality.¹⁴ NAs do not, however, directly eliminate covalently closed circular DNA (cccDNA), limiting HBsAg decline and resulting in functional cure rates of less than 2% per year. As a result, treatment is typically indefinite for many patients, given the risk of viral rebound on discontinuation.¹

PEG-IFN α is a finite 48-week treatment with immunomodulatory effects. It enhances immune responses and acts at multiple stages of the HBV life cycle, including inhibition of cccDNA transcription and alternation in immune cell function.^{15 16} While less effective at viral suppression compared with NA, PEG-IFN α achieves higher rates of HBeAg and HBsAg seroclearance, especially in patients with low qHBsAg and favourable genotype.^{17 18} PEG-IFN α is suitable for younger, non-cirrhotic patients seeking finite therapy and potential functional cure. Limitations include side effects and variable efficacy, but predictive models (eg, ALT and qHBsAg kinetics) aid patient selection.^{1 19}

Take-home message

HBsAg loss with undetectable HBV DNA, as markers of functional cure, is the optimal endpoint of treatment for HBV; however, sustained suppression of HBV DNA remains the core virological target with the available therapies. Treatment with NAs, resulting in normalisation of ALT levels and resolution of hepatic inflammation, is associated with improved liver-related outcomes.

Viral markers: definition, measurement and clinical relevance

There are a number of viral markers which are used to facilitate diagnosis and treatment decisions in CHB, with some novel markers augmenting management decisions. The main characteristics of these are summarised in table 1.

Hepatitis B surface antigen

HBsAg is the hallmark diagnostic marker for HBV infection. Its persistence beyond 6 months defines chronic infection, making it essential for screening, diagnosis and monitoring. HBsAg is derived from both cccDNA and integrated HBV DNA, with the latter being more prominent in HBeAg-negative patients. Most circulating HBsAg originates from non-infectious subviral particles, not complete virions.²⁰

Quantitative HBsAg

qHBsAg quantifies serum HBsAg levels (IU/mL) and reflects hepatocyte transcriptional activity. It correlates moderately with intrahepatic cccDNA ($r=0.28-0.71$; stronger correlations are seen in HBeAg-positive patients (r up to 0.7), whereas in the HBeAg-negative phase, much of the circulating HBsAg originates from integrated HBV DNA rather than cccDNA, resulting in

Table 1 Summary of HBV biomarkers and clinical utility

	Source/pathophysiology	Main clinical applications	Typical assay/units	Treatment-related insights
Biomarker				
HBV DNA	Relaxed-circular DNA transcribed from cccDNA (moderate correlation, $r \approx 0.4$)	► Disease phase classification ► Criteria for treatment ► Monitor virological response	Real-time PCR (IU/mL; detection limit ≈ 10 –20)	► Undetectable at 48 weeks ► NA: >90% in HBeAg–, ~70% in HBeAg+ ► PEG-IFNα: 14%–19%²⁷
HBeAg	Secreted protein; reflects viral replication and immunotolerance	► Defines disease phase ► Guide treatment (seroconversion goal) ► Prognosis: persistence=$\uparrow$risk fibrosis/HCC	Qualitative EIA; Quantitative PEI-U/mL (research, correlates with HBV RNA ($r=0.68$), HBcrAg ($r=0.69$), HBV DNA ($r=0.35$), and qHBsAg ($r=0.20$)) ²⁶	► Seroclearance: NA: ~10%–21% by 48 weeks ► PEG-IFNα: ~32% (durable)¹⁸
qHBsAg	Source: cccDNA and integrated DNA; reflects transcriptional activity	► Defines disease phase (<1000 IU/mL high PPV for HBeAg-neg CI) ► Predictor of PEG-IFNα response ► NA discontinuation criteria ► Functional cure marker (HBsAg loss)	Quantitative immunoassay (IU/mL)	► NA: Slow decline (~0.1 log/year; <2% annual HBsAg loss) ► PEG-IFNα: ~0.7 log decline at 48 weeks
Novel biomarkers				
HBcrAg	Combination of HBeAg, HBcAg and p22cr; reflects cccDNA activity	► Surrogate for cccDNA (esp. during NA therapy) ► Predictor of relapse after NA stop ► HCC risk stratification	CLEIA (log U/mL), correlates with intrahepatic cccDNA ($r=0.66$ –0.87) and serum HBV RNA. ³²	► Low at EOT $\rightarrow$ safer NA discontinuation ► Persistent elevation=relapse risk
HBV RNA	Pre-genomic RNA from cccDNA transcription ³⁵	► Assess residual activity during NA therapy ► Predict relapse ► Guide stop decisions (research)^{26 36}	RT-qPCR or ddPCR (log copies/mL)	► Detectable RNA=ongoing cccDNA activity³⁷ ► Emerging tool in trial endpoints³⁸
cccDNA, covalently closed circular DNA; CLEIA, chemiluminescent enzyme immunoassays; EOT, end of treatment; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue; PPV, positive predictive value; qHBsAg, quantitative HBsAg.				

weaker correlations ($r \sim 0.3$). qHBsAg is now clinically relevant for:

- Disease staging: Levels <1000 IU/mL suggest inactive carrier state.
- Treatment monitoring: Declining qHBsAg during PEG-IFN α predicts sustained response and HBsAg loss.
- Stopping criteria: qHBsAg <100 IU/mL at end-of-treatment in HBeAg-negative patients supports safe discontinuation.
- Functional cure: HBsAg loss, with or without anti-HBs, and undetectable HBV DNA remains the optimal treatment endpoint.^{1 21}

Treatment response

As reflected by changes in qHBsAg, this differs significantly between therapeutic strategies:

- NA therapy is associated with a slow decline in qHBsAg (~0.1 log/year), and results in annual HBsAg loss rates of less than 2%.²²
- PEG-IFN α induces more pronounced reductions of qHBsAg (~0.7 log at 48 weeks) and leads to higher rates of HBsAg clearance, particularly in patients with low baseline qHBsAg levels.²³

According to the 2025 EASL guidelines, qHBsAg is now recommended as a valuable tool for disease classification, treatment decision-making and predicting response, especially in patients eligible for finite

therapy. Currently, however, qHBsAg testing is mainly available in specialist centres, so NA discontinuation should only be attempted where intensive monitoring is feasible. Wider rollout is important as qHBsAg is increasingly central to treatment decisions and access to new therapies, and as costs fall and regional networks develop, availability is likely to expand.

Hepatitis B e antigen

HBeAg is a secreted non-structural protein that reflects high viral replication and immunotolerance. Its presence defines the HBeAg-positive immune phases, while its loss or seroconversion to anti-HBe marks transition to HBeAg-negative phases.

Clinical relevance

HBeAg has important clinical implications

- Disease staging: HBeAg status aids in defining the disease phase of CHB and guides appropriate monitoring.
- Treatment decisions: Seroclearance with anti-HBe seroconversion, accompanied by HBV DNA suppression and ALT normalisation, is a key goal in HBeAg-positive patients.
- Prognosis: Persistent HBeAg, especially beyond age 30 with elevated ALT, indicates higher risk of fibrosis, cirrhosis and HCC.²⁴

In Asian and Mediterranean populations, precore/core promoter mutations may cause HBeAg-negative disease despite high replication, often linked to more aggressive liver injury.²⁵

Measurement

- Qualitative HBeAg is detected via enzyme immunoassay (EIA).
- qHBeAg (PEI-U/mL), though not yet used clinically, correlates with HBV RNA ($r=0.68$), HBcrAg ($r=0.69$), HBV DNA ($r=0.35$) and qHBsAg ($r=0.20$).²⁶

Treatment response

Treatment response rates vary depending on the therapeutic strategy

- NA therapy: HBeAg seroclearance is achieved in ~10%–21% by week 48.
- PEG-IFN α : Higher efficacy, with seroclearance rates at ~32%, with more durable responses, particularly in well-selected patients.¹⁸

HBV DNA

Serum HBV DNA is a core virological marker that reflects active replication and is essential for diagnosing, staging and monitoring CHB. Most circulating HBV DNA is in the form of relaxed circular DNA, transcribed from intrahepatic cccDNA.²¹

Quantification is performed via sensitive real-time PCR assays, with detection limits as low as 10–20 IU/mL. HBV DNA informs clinical management by:

- Classifying disease phase: Levels >2000 IU/mL help identify active CHB.
- Guiding treatment: High HBV DNA with elevated ALT and/or fibrosis supports therapy initiation.
- Monitoring response: Achieving undetectable HBV DNA is the main goal of NA therapy.

The 2025 EASL guidelines emphasise that HBV DNA should be interpreted in conjunction with ALT, fibrosis stage and emerging biomarkers such as qHBsAg, HBV RNA and HBcrAg, for a more comprehensive approach¹

Treatment response

- NA therapy: Rapidly reduces HBV DNA; >90% of HBeAg-negative and ~70% of HBeAg-positive patients reach undetectable levels by 48 weeks.²²
- PEG-IFN α : Less effective virologically, with ~14%–19% achieving undetectable HBV DNA by week 48, though it offers immunomodulatory benefits.²⁷

Novel viral biomarkers

The updated guidelines incorporate emerging virological markers:

Hepatitis B core-related antigen

HBcrAg comprises denatured HBeAg, HBcAg and the precore protein p22cr translated from precore/core mRNA and secreted during active HBV transcription.

HBcrAg reflects intrahepatic cccDNA activity, even when HBV DNA is undetectable.^{1 28}

According to the 2025 EASL guidelines, HBcrAg is emerging as a valuable non-invasive biomarker that:

- Serves as a surrogate for intrahepatic cccDNA activity, particularly during NA therapy.
- Shows clinical utility in predicting virological relapse and treatment response following NA discontinuation.
- Helps stratify HCC risk and likelihood of HBsAg loss in both treated and inactive patients.^{1 29}
- In HBeAg-negative individuals, where integrated HBV DNA is the dominant source of antigen production, HBcrAg continues to reflect transcriptional activity driven by cccDNA, enabling better discrimination between truly inactive carriers and those with residual activity.³⁰

Measurement

HBcrAg is quantified in log U/mL via chemiluminescent EIA. It correlates strongly with intrahepatic cccDNA ($r=0.66$ – 0.87) and serum HBV RNA.^{31 32} It is:

- Detectable across both HBeAg-positive and HBeAg-negative CHB patients.
- Typically elevated during immune-active phases and suppressed in inactive carriers or under effective antiviral control.
- Persistently elevated post-treatment, which may indicate the presence of a residual intrahepatic reservoir and underscores the need for close post-treatment monitoring.³³
- Not yet routinely standard in routine care, HBcrAg is increasingly incorporated into treatment cessation strategies³⁴ and evaluation of novel therapeutic responses.

HBV RNA

Serum HBV RNA, predominantly in the form of pregenomic RNA, reflects active transcription from intrahepatic cccDNA. Unlike HBV DNA, which is generated through reverse transcription, HBV RNA serves a direct marker of ongoing viral transcription and viral replication even when HBV DNA is suppressed by NAs.^{1 35}

Clinical Use

HBV RNA bridges the interpretive gap between cccDNA and its transcriptional output presence and replication output. The 2025 EASL guidelines highlight its value for:

- Monitoring residual viral activity during NA therapy.
- Predicting virological relapse after NA discontinuation.
- Informing treatment cessation decisions, especially alongside qHBsAg and HBcrAg.^{26 36}
- Clinical trials—where detectable HBV RNA may reveal incomplete suppression of cccDNA, even in patients who have achieved DNA clearance, making it a valuable marker in assessing responses to novel antiviral strategies.³⁷

Measurement

HBV RNA is typically quantified by RT-qPCR or digital droplet PCR and reported in log copies per millilitre. While standardisation is still pending, clinical implementation is expanding as assays become more widely available.³⁸

Treatment goals

HBsAg loss, the marker of functional cure, is recognised as the optimal endpoint and a benchmark for evaluating curative therapies of finite duration.^{1 39} However, sustained suppression of HBV DNA remains the core virological target with the available therapies, with normalisation of ALT levels indicating resolution of hepatic inflammation, both of which are already associated with improved liver-related outcomes.

Additional goals include:

- ▶ HBeAg seroclearance in HBeAg-positive individuals.
- ▶ Fibrosis regression (measured by elastography or histology).
- ▶ Reduction of extrahepatic manifestations (eg, vasculitis, nephropathy).
- ▶ Improved quality of life and reduced stigma.
- ▶ Prevention of HBV transmission and reactivation.

The updated EASL guidelines promote an individualised, biomarker-driven approach (figure 1). Treatment is clearly recommended for those with HBV DNA >2000 IU/mL and elevated ALT, significant fibrosis or cirrhosis, family history of HCC or extrahepatic disease. Patients who are HBeAg positive and aged >30 with persistent viraemia and/or with metabolic risk factors such as MASLD or diabetes may also be considered for treatment, even in the absence of raised ALT or advanced fibrosis^{1 10} due to their increased risk of disease progression. Figure 1 represents a simplified algorithm indicating the indications for treatment. Furthermore, special populations

like pregnant women, transplant recipients and those coinfecting with HIV or HDV require adapted management strategies.

Therapy discontinuation

A key update in the 2025 EASL CPG is the introduction of a more clearly defined framework for NA discontinuation, in selected non-cirrhotic HBeAg-negative patients with prolonged viral suppression and low qHBsAg with close post discontinuation monitoring. The endpoint of this strategy aligns with the evolving definitions of partial cure (HBsAg positive but HBV DNA undetectable off-treatment) and functional cure (HBsAg loss with undetectable HBV DNA) now used in trials.^{40 41}

This reflects a shift towards finite therapy options in carefully selected individuals with stable viral suppression. The criteria for considering NA cessation now include:

- ▶ Sustained undetectable HBV DNA for at least 3 years on therapy;
- ▶ Low qHBsAg levels, typically <100 IU/mL (for Asians) and <1000 IU/mL (for Caucasians) at the time of discontinuation.
- ▶ Absence of cirrhosis, to minimise risk of hepatic decompensation in the event of viral relapse.
- ▶ Capacity for close post-treatment monitoring, ideally with access to regular laboratory testing and specialist follow-up.¹

Recommended monitoring following NA treatment cessation includes:

- ▶ HBV DNA and liver enzymes every 3–6 months.
- ▶ Elastography or FIB-4 to evaluate fibrosis progression.
- ▶ qHBsAg and HBcrAg to reflect intrahepatic viral activity.
- ▶ Patient-reported outcomes for holistic care.

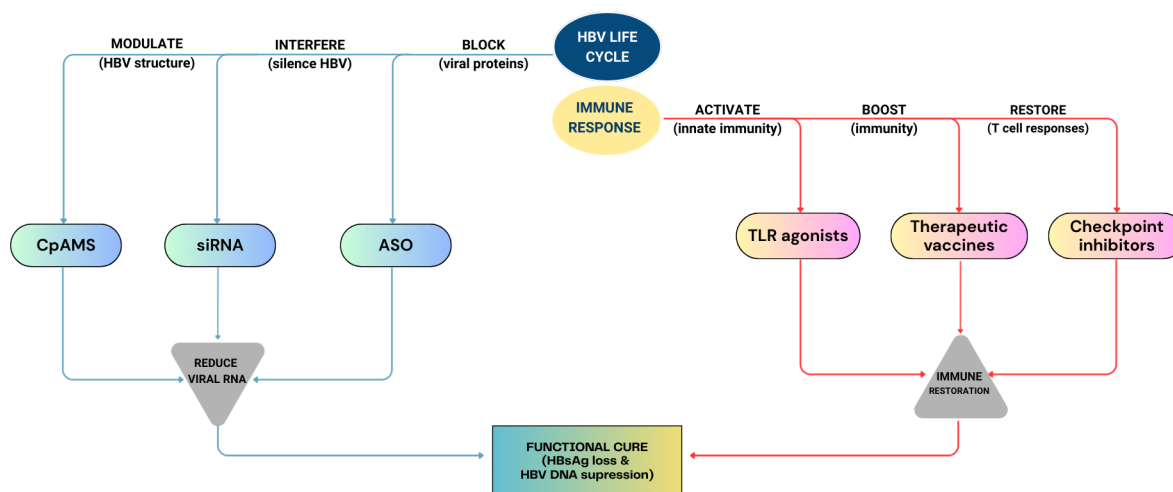


Figure 2 Schematic of novel pipeline therapies and their impact on the HBV life cycle/immune responses. Schematic indicating mechanism of action of novel agents (see table 2 for further details and examples), with their impact on the HBV life cycle or immune responses to deliver potential functional cure. ASO, antisense oligonucleotide; CpAMS, core protein allosteric modulators; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

In addition, the use of HBcrAg and HBV RNA is recommended to refine patient selection. These biomarkers offer insight into residual cccDNA transcriptional activity. Patients with low or undetectable HBcrAg and serum HBV RNA at the time of stopping therapy are more likely to maintain viral suppression and avoid virological relapse.^{30 38}

For PEG-IFN α , the guidelines maintain existing stopping rules based on week-12 virological response and qHBsAg decline. Patients who fail to demonstrate early virological or biomarker response are unlikely to achieve treatment endpoints, and discontinuation is advised to avoid unnecessary adverse effects.^{1 18}

Take-home message

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.

New therapies and strategies

The 2025 EASL CPG underscores a significant shift in the therapeutic landscape of CHB, moving beyond

long-term viral suppression towards finite-duration regimens and ultimately, functional or complete cure. A growing pipeline of novel agents is being evaluated in clinical trials, with promising potential to disrupt HBV persistence at various stages of the viral life cycle and to reinvigorate host immune responses (figure 2). While none of these agents are currently licensed for routine clinical use in HBV monoinfection, the 2025 EASL guidelines urge clinicians to remain informed about ongoing developments and consider trial enrolment for eligible patients. The paradigm is shifting towards rational combination therapies that attack HBV at multiple checkpoints, replication, antigen production and immune escape.¹ Table 2 outlines certain new compounds, indication phase of trials where they have been/being tested along with the mechanism of action.

Special populations

The 2025 EASL CPG offers detailed, pragmatic recommendations for the management of special populations living with CHB, reflecting an evolving understanding of risk factors beyond classical virological thresholds.¹

Pregnant individuals

For the prevention of mother-to-child transmission, the updated guidelines recommend initiating

Table 2 Novel compounds for the treatment of CHB

Mechanism of compound	Agents	Trial phase	Mechanism of action
Viral entry inhibitors	Hepcludex	III	► Binds to NTCP to block entry of HBV and HDV into hepatocytes. ► Currently licensed for HBV-HDV co-infection and compensated liver ► Combination therapy with Peg-IFN-α is associated with HBsAg loss; further studies are required.⁵³
	Hepalptide	II	
Short interfering RNAs (siRNAs)	VIR-2218	II	► siRNAs inhibit translation and HBV replication by selectively targeting and forming complementary base pairs with mRNAs transcribed from the HBV genome. ► Rebound effects following reduction in HBsAg levels have been observed when used as monotherapy.⁵⁴ ► In combination with NAs, JNJ-3989 and VIR-2218 have shown potent HBsAg declines in Phase two studies, especially in combination with NAs.^{55 56}
	JNJ-3989	IIb	
Antisense oligonucleotides (ASOs)	Bepirovirsen	III	► ASOs are short, single-stranded nucleic acids that target HBV mRNA and impede viral translation and the generation of viral and subviral particles. ► Weekly Bepirovirsen as monotherapy and in combination with daily NA met phase IIb trial end points of functional cure in the phase IIb B-CLEAR study (eg, HBsAg loss and HBV DNA <20 IU/mL in ~9%–10% of patients on combination therapy).^{57 58} ► AHB-137 has higher rates of HBsAg loss in the ongoing phase IIb trial (AB-10-8003).
	AHB-137		
Core Protein Allosteric Modulators (CpAMs)	RO7049389	I	► CpAMs interfere with the assembly of HBV nucleocapsids, thereby preventing pregenomic RNA encapsidation and subsequent reverse transcription. ► ALG-000184 is being explored in clinical trials with significant reductions in HBV DNA, RNA and other viral antigens.
	ABI-H3733	II	
	ALG-000184		
Toll-like receptor agonists (TLR)	selgantolimod (TLR8)		► Immune targeted drugs in HBV promote innate immune responses resulting in inhibition of HBV replication in hepatocytes. ► Phase II trials using selgantolimod demonstrated monotherapy was not sufficient in achieving the primary endpoint of HBsAg reduction of $\geq 1 \log_{10}$ IU/mL.⁵⁹
	GS-9688		
Therapeutic vaccines	GS-4774	II	► Therapeutic vaccines disrupt host immune tolerance through the delivery of HBsAg, inducing an immune response to clear HBV. ► These are being tested alone or in combination with siRNA or CpAM agents to synergistically promote HBsAg clearance.⁶⁰
	NASVAC	III	

CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; NAs, nucleos(t)ide analogues; NTCP, na+(sodium)-taurocholate co-transporting polypeptide.

antiviral therapy in the third trimester, as prophylaxis, in HBeAg negative women if the HBV DNA is $\geq 200\,000$ IU/mL. In HBeAg positive women, where HBV DNA levels cannot be tested, antiviral therapy should be offered. TDF remains the first-line agent due to its robust safety profile in pregnancy and breastfeeding. However, the use of TAF may now be considered where TDF is poorly tolerated, acknowledging emerging safety data.⁴² Routine neonatal immunoprophylaxis with HBV vaccine and HBIG within 12 hours of birth continues to be essential. Women with established treatment indications should continue antiviral therapy throughout pregnancy and postpartum.

Immunosuppressed patients

The updated guidelines provide refined risk stratification for HBV reactivation in immunocompromised hosts, including those receiving chemotherapy, biologics or undergoing organ transplantation. Prophylactic antiviral therapy with high-barrier NAs is recommended for HBsAg-positive patients regardless of HBV DNA levels, and for HBsAg-negative/anti-HBc-positive patients deemed at high risk. Stratification is based on agent class, treatment duration and baseline serology.¹ With regard to liver transplantation and the use of HBIG and NAs, data remain conflicting and reports from ongoing work in the UK and other centres suggest that ongoing HBIG may not be required post-transplant, with NA prophylaxis alone being sufficient in most cases. Multicentre studies and the ELITA consensus indicate that lifelong HBIG administration does not reduce HBV recurrence,⁴³ and a more rational and harmonised approach to HBV prophylaxis across LT programmes is required to reduce variability in practice between centres.⁴⁴

HIV and HDV coinfection

For individuals with HIV-HBV coinfection, the guidelines align with HIV treatment protocols, endorsing tenofovir-based regimens (TDF or TAF) as preferred backbones. In HBV-HDV coinfection, the introduction of bulevirtide (Hepcludex) represents a significant milestone, with several novel agents also in the clinical trial pipeline for HBV-HDV coinfection.

Metabolic dysfunction and MASLD

A landmark update in the 2025 guidelines is the formal recognition of MASLD as a relevant disease modifier in CHB. This includes patients with insulin resistance, obesity, type 2 diabetes, dyslipidaemia or cardiovascular risk factors, who may now be considered for earlier antiviral therapy. Transient elastography should be performed in all patients with metabolic comorbidities. Where fibrosis $\geq$ F2 is detected even if HBV DNA is <2000 IU/mL, treatment may be initiated to mitigate additive risks of fibrosis progression and HCC.^{12 45} The control of metabolic factors is also critical, as disease may otherwise progress even in

the presence of antiviral therapy. The guidelines thus support a shift from rigid viral load cut-offs toward a more holistic, risk-based approach.

Take-home message

The 2025 EASL guidelines emphasise a more individualised, risk-based approach to HBV management in special populations. Key updates include earlier antiviral prophylaxis in pregnancy, refined reactivation risk stratification in immunosuppressed patients, and recognition of MASLD as a relevant modifier warranting earlier treatment.

HCC surveillance and risk stratification

The 2025 EASL guidelines reaffirm the central role of HCC surveillance in the long-term management of CHB, while also incorporating new recommendations based on emerging evidence and risk prediction tools.¹

Surveillance for HCC continues to be recommended for all CHB patients who are at intermediate or high risk, regardless of treatment status. The updated guidelines emphasise:

- ▶ US every 6 months as the primary modality.
- ▶ Alpha-fetoprotein may be used as an adjunct in selected settings but is not mandatory.
- ▶ Cross-sectional imaging (eg, MRI or CT) is advised if US quality is suboptimal or for further assessment of nodules >1 cm.

These intervals and modalities are based on balancing cost-effectiveness, diagnostic accuracy and patient risk.

Expanded risk stratification

For the first time, the guidelines incorporate risk prediction models to better personalise surveillance. These include:

- ▶ PAGE-B and mPAGE-B: Widely validated in treated populations to estimate 5-year HCC risk.
- ▶ REACH-B: Useful in untreated, predominantly Asian populations.
- ▶ aMAP score: Recently validated across diverse ethnicities and treatment settings.^{46 47}

The use of these scores is now encouraged to determine surveillance eligibility and intensity, especially in HBeAg-negative or virologically suppressed individuals, where clinical decision-making has historically been uncertain.

Of note, however, these risk scores have limited validation in patients from under-represented ethnicities such as sub-Saharan African cohorts and should be applied cautiously in multiethnic populations until further validation is available, and standard surveillance should continue in all at-risk patients.

Treatment and risk reductions

While antiviral therapy with NAs significantly reduces the risk of HCC, it does not eliminate it, particularly in patients with baseline cirrhosis or older age. Therefore, surveillance must continue indefinitely in all cirrhotic

patients, including those with undetectable HBV DNA and/or HBsAg loss.⁴⁸

HCC surveillance remains essential for all at-risk CHB patients, even if virologically suppressed or treated. The 2025 EASL guidelines endorse personalised risk-based strategies using validated prediction tools to optimise long-term outcomes. Family history of HCC and age >50 at the time of HBsAg loss remain important risk factors, and such patients should continue HCC surveillance even after viral clearance. While HBsAg loss substantially reduces HCC risk, it does not abolish it, particularly in those with prior fibrosis/cirrhosis or other risk factors such as MASLD or alcohol use, reflecting the persistence of integrated HBV DNA. Tools such as PAGE-B (European cohorts) and REAL-B (Asian cohorts) can assist with risk stratification, but further validation in UK populations is needed.

Take-home message

HCC surveillance is essential in at-risk CHB patients, even if virologically suppressed or after HBsAg loss. Continue surveillance in all with cirrhosis, family history or HBsAg loss >50 years. Risk scores (PAGE-B, mPAGE-B, REACH-B, aMAP) can help personalise surveillance.

Summary and future outlook

The 2025 EASL hepatitis B guidelines mark a turning point in the clinical approach to CHB. By redefining treatment eligibility, integrating novel biomarkers, acknowledging the importance of metabolic comorbidities such as MASLD, and setting the stage for functional cure, these guidelines promote a more nuanced and proactive management strategy. For clinicians, this means adapting workflows, embracing non-invasive tools and preparing for an era of potentially curative therapies. As HBV care enters a precision medicine era, these guidelines offer a robust framework to improve patient outcomes across diverse healthcare settings.

A central theme is the importance of early treatment initiation to prevent progression to HCC, particularly in those with coexisting metabolic risk factors, where fibrosis (and HBV DNA integration) can advance despite normal ALT or low viraemia.⁴⁹ The broader treatment eligibility and biomarker-guided approach endorsed by the 2025 guidelines will require earlier integration of care pathways between hepatology, endocrinology, infectious diseases and primary care. This multidisciplinary model will help address the added complexity of patients with CHB and MASLD, optimise timing of intervention and minimise missed opportunities for prevention of advanced liver disease.

In the UK, where NA therapy is predominantly initiated in specialist care, the inclusion of metabolic risk assessment and non-invasive fibrosis tools (eg, transient elastography, FIB-4) may necessitate closer collaboration between secondary and primary care providers.

Guideline adoption is also likely to encourage more proactive screening and earlier diagnosis, especially in high-prevalence migrant communities.

Globally, these recommendations are particularly relevant to low-income and middle-income countries (LMICs) where HBV prevalence is high, resources are limited and liver biopsy is often unavailable. The endorsement of simplified, non-invasive tools and integration of novel biomarkers provides an opportunity to scale up diagnosis and management in resource-constrained settings.

The development of new therapies further underscores the need for deeper immune-virological insight. To evaluate mechanisms of action and optimise patient selection, both peripheral and intrahepatic immune and viral marker data will be essential. Minimally invasive liver fine needle aspiration has emerged as a feasible and informative method to obtain liver-specific data in longitudinal studies, enabling measurement of HBV cccDNA transcriptional activity and immune responses within the hepatic compartment.^{50 51}

In parallel, there is an urgent need for improved biomarkers that can stratify patients by risk, predict treatment response and identify those most likely to achieve a functional cure. Recently, rapid immune assays have demonstrated the potential to provide scalable, reproducible measures of HBV-specific immune responses, with applications both in high-resource research settings and as point-of-care tools in LMICs.⁵² The integration of such assays into clinical care could accelerate biomarker-led decision-making and support personalised treatment strategies.

In summary, the 2025 guidelines lay the groundwork for a new era in CHB management, one in which earlier diagnosis, metabolic risk assessment, biomarker-led therapy and novel treatment modalities converge. By embracing these advances, clinicians can work towards the ultimate goal of functional cure while reducing the global burden of HBV-related liver disease. Importantly, patient advocacy and education are increasingly recognised as integral to holistic HBV care, and support groups can play a key role in empowering patients and improving engagement with treatment.

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ORCID iDs

Upkar S Gill <https://orcid.org/0000-0001-6146-9708>

Victoria J Appleby <https://orcid.org/0000-0001-5965-8139>

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