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Chronic hepatitis B in 2025: diagnosis, treatment and future directions ☆

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ABSTRACT

Chronic hepatitis B (CHB) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC), with many patients remaining undiagnosed or undertreated despite effective vaccination and antiviral therapy.

The 2025 European Association for the Study of the Liver (EASL) guidelines mark a shift towards biomarker-led, finite and personalised therapy, aiming for functional cure as sustained HBsAg loss. This review outlines updated recommendations on diagnosis, staging, treatment initiation and cessation, along with surveillance. Accurate interpretation of hepatitis B serological and virological markers remains central, with novel biomarkers, including quantitative HBsAg, HBcrAg and HBV RNA, enhancing disease stratification, guiding therapy and informing safe discontinuation of nucleos(t)ide analogues (NAs). The guidelines also emphasise the role of metabolic comorbidities, such as metabolic dysfunction-associated steatotic liver disease (MASLD), in accelerating fibrosis and increasing HCC risk.

We summarise first-line NA and pegylated interferon options, monitoring requirements and surveillance strategies, highlighting common pitfalls such as under-recognition of at-risk patients with low viral load. Special considerations for pregnancy, immunosuppression and co-infections are addressed. Emerging therapies including RNA interference, core protein modulators and immunotherapeutics offer hope for finite, curative regimens. This article provides a practical, evidence-based guide for clinicians, trainees and allied health professionals to apply evolving recommendations in everyday practice.

Introduction

Chronic hepatitis B virus (HBV) infection remains a major global health challenge, affecting more than 250 million people and resulting in nearly 900,000 deaths annually due to cirrhosis and hepatocellular carcinoma (HCC).[1] While direct-acting antivirals (DAAs) have revolutionised hepatitis C treatment, similar curative regimens for chronic hepatitis B (CHB) remain under development.[2] Despite a highly effective vaccine, HBV continues to spread, particularly through perinatal transmission in high-prevalence regions. In many settings, inadequate screening and barriers to care further compound the issue, leading to missed opportunities for diagnosis and early intervention. In the UK, it is estimated that up to 260,000 people may be chronically infected with HBV, predominantly among migrant communities, yet only a fraction of these individuals are engaged in care.[3]

The 2025 European Association for the Study of the Liver (EASL) guidelines mark a shift towards finite therapy, biomarker-driven stratification and individualised treatment decisions, with functional cure, defined as sustained HBsAg loss, emerging as the ultimate treatment goal.[4] These advances signal a new era in which earlier diagnosis, enhanced monitoring and more precise treatment allocation can be achieved.

Epidemiology and natural history

HBV is a hepatotropic DNA virus that persists in the nucleus of hepatocytes as covalently closed circular DNA (cccDNA), acting as a template for viral replication and protein production. This stable form underlies the chronicity of infection and makes eradication challenging. The natural history of CHB comprises dynamic and overlapping clinical phases shaped by host immune response, viral replication and age at infection (Fig. 1).[5] Perinatal transmission, particularly in Asia and Africa, typically results in an 'immune-tolerant' (HBeAg-positive chronic HBV infection) phase with high HBV DNA and normal ALT levels, often persisting for decades.[6] With time, immune recognition may intensify, leading to the immune-active or HBeAg-positive chronic hepatitis B phase (formerly called immune clearance), characterised by elevated ALT and fluctuating HBV DNA levels, with associated hepatocyte injury. Patients may then enter an inactive carrier state (HBeAg-negative chronic infection) with low HBV DNA and normal ALT. However, viral

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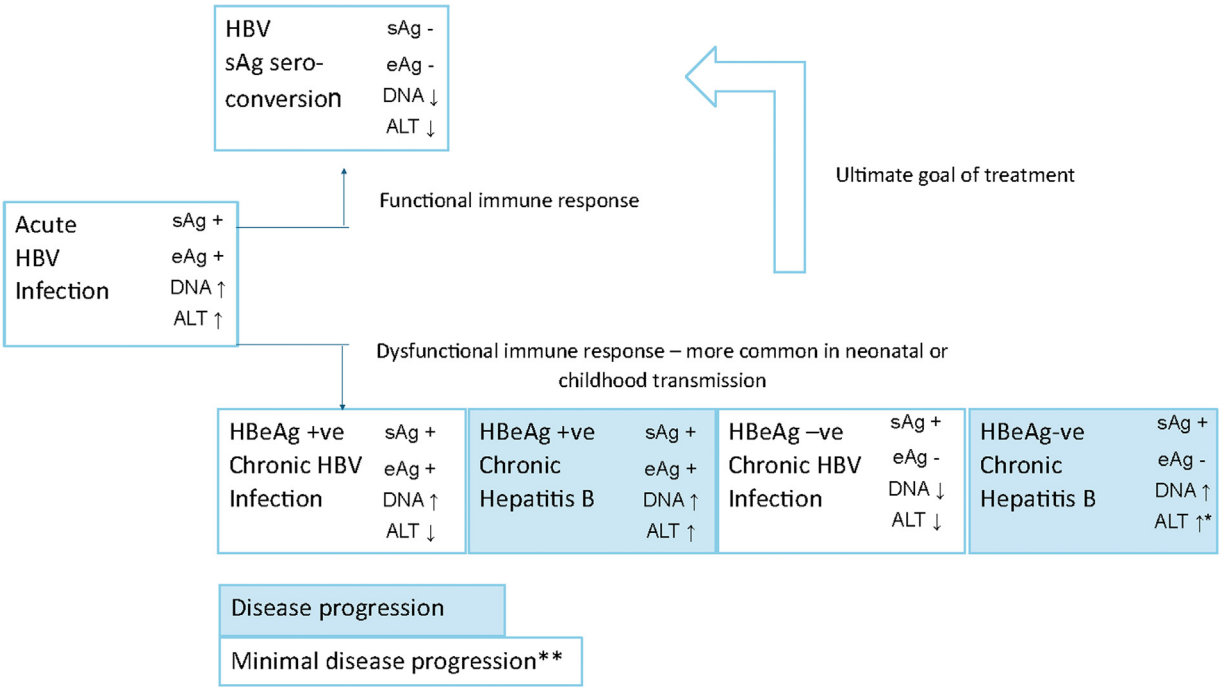

Fig. 1. Stages of chronic hepatitis B infection with relevant blood parameters; *ALT levels can be variable in this phase; ** Biologically consequential events (eg HBV DNA integration, clonal hepatocyte expansion, immune dysfunction) can occur during these phases. sAg, surface antigen; eAg, hepatitis B e-antigen.

Table 1
Interpretation of serological tests in hepatitis B.

	Acute	HBeAg-positive chronic infection	HBeAg-positive chronic hepatitis	HBeAg-negative chronic infection	HBeAg-negative chronic hepatitis	Past exposure (immunity)	Vaccinated
HBsAg	+	+	+	+	+	–	–
HBeAg	+	+	+	–	–	–	–
Anti-HBe	–	–	–	+	+	+/–	–
Anti-HBc (IgM)	+	–	–	–	–	–	–
Anti-HBc (IgG)	–	+	+	+	+	+	–
Anti-HBs	–	–	–	–	–	+	+
HBV DNA	Low	High	High	Low	Variable	Undetected	Undetected
ALT	Elevated	Normal	Elevated	Normal	Elevated	Normal	Normal

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-antigen; Anti-HBe, hepatitis B e-antibody; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; HBV DNA, hepatitis B DNA; ALT, alanine aminotransferase.
This table is a simplified/general interpretation of laboratory tests and is only meant as a guide. Exceptions to the above are expected.

mutations in the pre-core or basal core promoter regions may give rise to HBeAg-negative chronic hepatitis with fluctuating viraemia and hepatic inflammation. The transitions between these phases are unpredictable and may be silent, with significant fibrosis or even cirrhosis developing in the absence of symptoms or abnormal liver enzymes.[7]

Diagnosis and initial assessment

CHB diagnosis is established by the persistence of hepatitis B surface antigen (HBsAg) for more than 6 months. Individuals with abnormal liver enzymes, evidence of liver disease, an increased risk of exposure to HBV or those undergoing immunosuppression should be screened for HBV infection. Following diagnosis, a comprehensive initial work-up is critical to assess disease activity (see Table 1), fibrosis stage and risk of complications. This includes:

- serological markers: HBsAg, HBeAg, anti-HBe, anti-HBc
- virological markers: HBV DNA
- biochemical assessment: ALT, AST, bilirubin, INR, albumin, platelet count
- fibrosis staging: transient elastography (FibroScan) or surrogate scores such as FIB-4
- imaging: baseline liver ultrasound to assess for nodularity, steatosis or focal lesions
- co-infection screening: HIV, HCV and hepatitis D virus (HDV) in HBsAg-positive individuals.

Clinicians should also assess for extrahepatic manifestations (eg cryoglobulinaemia, polyarteritis nodosa, glomerulonephropathy) and family history of liver disease or HCC. A common pitfall is referring individuals with isolated anti-HBc positivity and negative HBsAg for hepatology assessment. These individuals typically reflect past exposure and require management only if immunosuppression is planned.[8]

Disease phases and risk stratification

The updated EASL classification defines four phases (Fig. 1):

- HBeAg-positive chronic infection (high HBV DNA, normal ALT)
- HBeAg-positive chronic hepatitis (high HBV DNA, elevated ALT)
- HBeAg-negative chronic infection (low HBV DNA, normal ALT)
- HBeAg-negative chronic hepatitis (variable HBV DNA, elevated ALT).

ALT and HBV DNA remain cornerstones of disease staging, but their limitations are well recognised. ALT may be normal despite ongoing his-

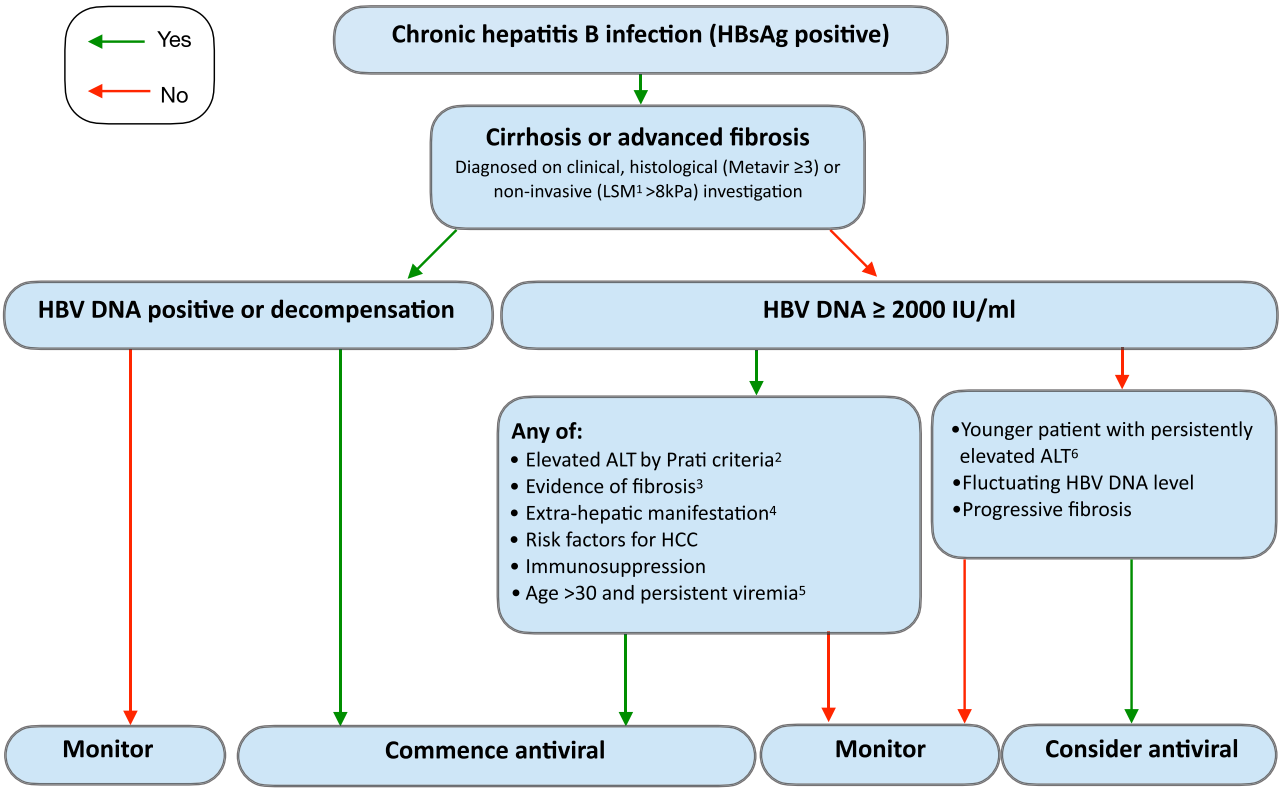

Fig. 2. Treatment indications for CHB: 1. Liver stiffness measurement on transient elastography. 2. Sex-specific Prati criteria (19 IU/L for women, 30 IU/L for men). 3. Metavir ≥F2 or LSM >7 kPa. 4. e.g. HBV-associated vasculitis, glomerulonephritis. 5. Especially if metabolic dysfunction or family history of HCC is present. 6. Following exclusion of other liver disease.

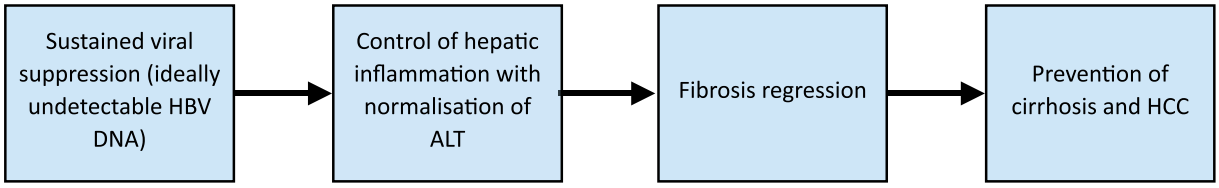

Fig. 3. Goals of anti viral therapy.

tological activity, particularly if laboratory upper limits are not adjusted according to sex-specific Prati criteria (19 IU/L for women, 30 IU/L for men). HBV DNA levels may also underestimate activity in HBeAg-negative disease. Consequently, newer biomarkers such as quantitative (q)HBsAg and hepatitis B core-related antigen (HBcrAg) (at present only utilised as a research tool) are increasingly incorporated to improve diagnostic accuracy and guide treatment decisions.[9] These markers provide additional insight into intrahepatic viral activity and immune control.[10,11]

Treatment indications and timing

Not all patients with CHB require immediate antiviral therapy (see Fig. 2) for treatment indications (adapted from 2025 EASL guidance).[4] Untreated patients must be regularly assessed to detect disease progression and to make sure that they are regularly reviewed for initiation of antiviral therapy, to improve disease outcomes (Fig. 3).

Importantly, delaying treatment in individuals perceived as being in the 'immune-tolerant' phase can lead to missed therapeutic windows, particularly in older adults or those with metabolic dysfunction-associated steatotic liver disease (MASLD), which exacerbates fibrosis progression.[12–14]

Table 2
Factors determining choice of NA.

Nucleos(t)ide analogue (NA)	Indication for choice of NA
Entecavir	• Renal insufficiency • Osteopenia/osteoporosis • Hypophosphataemia
Tenofovir disoproxil fumarate (TDF)	• Pregnancy • HIV co-infection • Hepatocellular carcinoma

Treatment options and monitoring

First-line therapies include:

- Nucleos(t)ide analogues (NAs): tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and entecavir. These agents have a high genetic barrier to resistance and are well tolerated (see Table 2). TAF does not currently have a marketing authorisation in the UK for use in CHB.
- Pegylated interferon-α (PEG-IFNα): This finite-duration therapy enhances host immune responses and may lead to HBeAg or HBsAg loss, particularly in younger, HBeAg-positive patients with high ALT and low viral load.[15]

Table 3
Biomarkers in CHB.

Biomarker	Actions
Quantitative HBsAg (qHBsAg)	• Correlates with cccDNA activity in HBeAg-positive disease, but in HBeAg-negative phases HBsAg is largely derived from integrated HBV DNA, with weaker correlation to cccDNA. • Partly correlates with disease phase. • Useful in predicting IFN response and in identifying candidates for NA discontinuation.
HBV core-related antigen (HBcrAg)	• Composite of three proteins encoded by the HBV precore/core gene: hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg), and the 22 kDa precore protein (p22cr). HBcAg is translated from the pregenomic RNA, while HBeAg and p22cr are derived from the precore RNA. • Correlates with intrahepatic cccDNA and replicative capacity. • Performed well as a point-of-care test for high viraemia in low- and middle-income countries.[20]
HBV RNA	• Surrogate for pre-genomic RNA (pgRNA) and ongoing viral transcription. • Strong predictor of HBeAg seroconversion. • Can remain detectable even when DNA is suppressed by NAs, providing a window into residual activity and risk of reactivation.

While NAs achieve excellent virological control, HBsAg loss occurs in <5% of treated individuals over 5–10 years.[4] Long-term therapy is often required, especially in those with cirrhosis or high risk of relapse. Patients should be monitored every 3–6 months with ALT, HBV DNA and renal function (particularly for TDF). Although now rarely used outside a clinical trial setting, those on IFN require frequent evaluation for cytopenias, mood disturbances and autoimmune phenomena. Untreated patients also require surveillance for disease phase transitions and fibrosis progression.

Treatment discontinuation

Discontinuation of antiviral therapy should only be considered by those experienced in the management of hepatitis B. Cessation of NAs may be considered in certain circumstances, including:

- non-cirrhotics: following confirmed loss of HBsAg[16]
- compensated cirrhosis: loss of HBsAg with confirmed seroconversion to anti-HBs or sustained loss of HBsAg following 12 months of consolidation therapy.[4]

Cessation of NA therapy is not recommended in HBeAg-positive patients. In patients with decompensated cirrhosis, the evidence for NA discontinuation is weak, and most guidelines recommend indefinite continuation irrespective of anti-HBs seroconversion, given the high risk of relapse and hepatic decompensation. While isolated reports describe sustained remission following anti-HBs seroconversion, cessation is not routinely advised outside of research settings. A significant evolution in the 2025 EASL guidance is the provision of structured criteria for stopping NA therapy in selected non-cirrhotic, HBeAg-negative patients with:

- ≥3 years of undetectable HBV DNA
- qHBsAg <100 IU/mL (Asian populations) or <1,000 IU/mL (Caucasian populations)
- capacity for close post-treatment follow-up.[4]

Patients should be monitored with HBV DNA, ALT and qHBsAg every 1–3 months during the first year after NA discontinuation. HBcrAg and HBV RNA may provide additional insight into residual viral activity and relapse risk. Approximately 20–30% of patients may achieve sustained off-treatment control, and a smaller proportion may achieve HBsAg loss, representing a functional cure.[17–19] Treatment discontinuation requires careful discussion with the patient and frequent monitoring thereafter. It is best considered in a supervised setting.

Biomarkers in CHB management

Biomarkers have transformed the landscape of HBV management (see Table 3).

These biomarkers, while not yet universally available in clinical practice, are increasingly employed in specialist centres and clinical trials.[10,20,21]

Special populations

- Pregnancy:
  - Those established on TDF therapy should continue. ETV or PEG-IFNa should be switched to TDF.
  - Antiviral prophylaxis with TDF from 28 weeks is recommended in those with HBV DNA ≥200,000 IU/mL. Neonates should receive birth-dose vaccine and HBIG within 12 h of delivery.
- TDF is safe to continue while breastfeeding. Risk of HBV transmission through breastfeeding is negligible if the newborn has received appropriate immunisation, even if maternal antivirals are discontinued.[22]
- Immunosuppressed patients should undergo HBsAg and anti-HBc screening. Those with positive HBsAg require prophylactic antiviral therapy, particularly with B-cell depleting agents. Virus in anti-HBc-positive, HBsAg-negative patients may also reactivate and they will require monitoring and/or prophylactic antiviral therapy in cases of B-cell depleting agent treatment.
- In HIV co-infection, dual-active ART regimens including tenofovir are essential to suppress both viruses.
- For HDV co-infection, bulevirtide is the first licensed agent, and further entry inhibitors and immunotherapies are under evaluation.

HCC surveillance

HCC remains the principal cause of death in CHB. While antiviral therapy reduces risk, it does not eliminate it. Surveillance with 6-monthly liver ultrasound (with or without AFP) is recommended, in HBsAg positive patients, for:

- all patients with cirrhosis
- those with intermediate/high risk based on PAGE-B, REACH-B or aMAP scores
- patients with metabolic risk factors (eg MASLD, diabetes) even with virological suppression.

Failure to maintain surveillance in at-risk individuals with low viral load or normal ALT represents a common and consequential error. For the minority of CHB patients who achieve HBsAg seroconversion, HCC surveillance should continue, particularly in those aged >50, who have cirrhosis or a family history of HCC, due to elevated risk.[23]

Emerging therapies

The future of CHB treatment lies in combination therapies that target multiple steps of the HBV life cycle (see Table 4). Such agents are currently in phase II/III trials and may ultimately enable finite, curative regimens.

Table 4
Examples of emerging therapies in CHB.[24]

Directly acting antivirals		
Drug classification	Examples	Mechanism
Small interfering RNA (siRNA)	VIR-2218 JNJ-3989	Inhibit translation and HBV replication by selectively targeting and forming complementary base pairs with mRNAs transcribed from the HBV genome.
Antisense oligonucleotide (ASO)	Bepirovirsen	Short, single-stranded nucleic acids targeting HBV mRNA, impeding viral translation, and generation of viral/subviral particles.
Core protein allosteric modulators (CpAMs)	Vebicorvir (ABI-H0731)	Disrupts viral replication through alteration of nucleocapsid assembly.
Immunotherapeutics		
TLR agonists	Selgantolimod (GS-9688)	TLR-8 agonist stimulates cytokine response. Activates NK cells and stimulates T-cell proliferation.
Therapeutic vaccines	GS-4774	Enhance antiviral immune response by stimulating production of IFN-γ, TNF and interleukin-2 by T cells.
Checkpoint inhibitors	Nivolumab	Anti-PD-1/PD-L1 drives reduction in HBsAg.

Key changes in CHB management in the past decade

Over the past decade, the landscape of CHB has shifted. This includes novel nomenclature, use of new biomarkers and updates in guidance for the initiation and cessation of therapy. The nomenclature for the disease phases has been updated, focusing on HBeAg positivity and presence of hepatitis, making the natural history of CHB easier to navigate for a wider audience.[25] The threshold for initiating treatment has been lowered, with recommendations for treatment initiation even without significant fibrosis and in phases without active hepatitis, which previously was not the case.[26] Novel biomarkers are being introduced and can provide additional insight into viral activity. They help to predict treatment response and risk of reactivation, allowing for earlier cessation of antiviral therapy. Novel biomarkers are also showing promise as point-of-care tests in low- and middle-income countries. New therapies are emerging that target different aspects of the viral life cycle and impact the immune response, and their use in combination may lead to curative regimens.

Conclusion

CHB remains a globally prevalent, potentially progressive condition with significant morbidity and mortality. The 2025 EASL guidelines reflect a transition towards biomarker-led, individualised therapy. Accurate diagnosis, staging and tailored treatment are essential to minimise complications and enhance patient outcomes. With the continued evolution of biomarkers and the advent of new therapeutic agents, clinicians must stay informed and responsive to advances in care.

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Declaration of competing interest

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

CRediT authorship contribution statement

Andrew G. Watson: Methodology, Investigation, Writing – review & editing, Visualization. **Akhilesh S. Mulay:** Methodology, Investigation, Writing – review & editing, Visualization. **Upkar S. Gill:** Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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