

Toward a Precision Cure for Chronic Hepatitis B: Convergence of RNA Silencing, Gene Editing, Immune-Reset Therapies, and Artificial Intelligence-Guided Diagnostics

Saniya Sanjaysinh Patil¹, Siddhi Shivaji Powar¹, Shruti Vilas Patil¹, Prathamesh Pundlik Khade²

¹Doctor of Pharmacy (Fourth Year Pharm.D), Vasantidevi Patil Institute of Pharmacy, Kodoli,

²Assistant Professor, Vasantidevi Patil Institute of Pharmacy, Kodoli.

Corresponding author: saniyapatil0573@gmail.com

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Abstract

Chronic hepatitis B virus (HBV) infection remains a major global health challenge, affecting over 250 million individuals and causing more than one million deaths annually from cirrhosis and hepatocellular carcinoma. Although current antiviral therapies effectively suppress viral replication, they rarely achieve a functional cure because covalently closed circular DNA (cccDNA) and integrated HBV DNA persist within hepatocytes. Consequently, lifelong treatment is often required, highlighting the urgent need for curative therapeutic strategies. Recent advances in molecular therapeutics, immunotherapy, and artificial intelligence (AI) have created new opportunities for precision HBV management. This narrative review critically evaluates emerging therapeutic approaches, including RNA interference, antisense oligonucleotides, gene-editing technologies, immune-reset therapies, rational combination regimens, biomarker-guided treatment, and AI-enabled precision diagnostics, with emphasis on their potential to achieve a durable functional cure. A comprehensive review of peer-reviewed literature published between 2015 and 2026 was conducted using PubMed, the Cochrane Library, and ClinicalTrials.gov. Clinical trials, mechanistic studies, and expert consensus guidelines focusing on novel HBV therapeutics, biomarkers, and AI applications were systematically evaluated, while non-peer-reviewed reports were excluded. Recent Phase III evidence demonstrates that the RNA-targeting agent bupirovirsen significantly improves sustained hepatitis B surface antigen (HBsAg) loss and functional cure rates compared with current standard therapy. Gene-editing platforms, including PBGENE-HBV, represent promising strategies for directly targeting cccDNA and integrated HBV DNA, although their long-term safety and efficacy remain under investigation. Immune-reset therapies involving therapeutic vaccines, Toll-like receptor agonists, immune checkpoint inhibitors, and engineered T-cell therapies have shown encouraging potential to restore antiviral immunity, particularly when combined with direct-acting antiviral agents. Furthermore, emerging biomarkers such as quantitative HBsAg, hepatitis B core-related antigen (HBcrAg), and serum HBV RNA, integrated

with AI-based predictive models, facilitate personalized treatment selection, response monitoring, and prognostic assessment. Collectively, current evidence suggests that the future of chronic HBV management lies in precision combination therapy integrating deep viral suppression, targeted gene editing, immune restoration, and AI-guided clinical decision-making. Although important challenges related to delivery systems, long-term safety, affordability, and global accessibility remain, these multidisciplinary advances provide a realistic pathway toward scalable functional cure strategies and support progress toward achieving the World Health Organization's hepatitis elimination goals.

Keywords

Chronic hepatitis B; Functional cure; RNA interference; Antisense oligonucleotides; Gene editing; CRISPR; Bepirovirsen; cccDNA; Artificial intelligence; Precision medicine; Biomarkers; Immunotherapy.

1. Introduction

1.1 Global Burden and WHO 2030 Elimination Targets

Chronic hepatitis B virus (HBV) infection remains a major global health challenge, affecting approximately 254–296 million individuals worldwide and causing over 1.1 million deaths annually from cirrhosis and hepatocellular carcinoma (HCC). Despite substantial progress through universal infant vaccination, improved prevention strategies, and declining paediatric HBsAg prevalence, HBV continues to impose a considerable clinical and economic burden. Less than 10% of infected individuals receive appropriate diagnosis and antiviral treatment, creating a significant gap in the cascade of care. Consequently, achieving the World Health Organization (WHO) target of eliminating viral hepatitis as a public health threat by 2030 will require innovative therapeutic strategies capable of delivering sustained viral control or cure rather than long-term viral suppression alone.^{1,2}

1.2 Functional Cure: The Current Therapeutic Endpoint

The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) define a functional cure as sustained hepatitis B surface antigen (HBsAg) loss, with or without anti-HBs seroconversion, accompanied by undetectable serum HBV DNA following completion of finite therapy.³ This endpoint differs from a sterilising cure, which requires complete elimination of covalently closed circular DNA (cccDNA) and integrated HBV DNA from infected hepatocytes. Because these viral reservoirs persist despite prolonged antiviral therapy, functional cure has emerged as the most realistic and clinically meaningful therapeutic goal.^{4,5}

1.3 Limitations of Current Standard Therapy

Nucleos(t)ide analogues push HBV DNA down to undetectable levels in most patients who take them consistently, but HBsAg clearance is rare - seroclearance rates sit in the low single digits even after years of treatment. Pegylated interferon-alfa does somewhat better on functional cure, though the rate varies widely between populations and comes with real toxicity^{8,9}. Neither approach touches cccDNA or integrated DNA, which is exactly why relapse after

stopping treatment is close to universal, and why the risk of HCC persists even in patients whose virus has been suppressed for years ^{4,6}.

1.4 Scope and Objectives of This Review

This review critically evaluates recent advances in HBV cure research published between 2015 and 2026, integrating evidence from peer-reviewed mechanistic studies, clinical trials, and registered ongoing studies. Particular emphasis is placed on RNA interference therapies, antisense oligonucleotides, capsid assembly modulators, gene-editing technologies, immune-directed therapies, therapeutic vaccines, combination treatment strategies, and artificial intelligence-enabled diagnostics. The review further discusses the translational challenges and future directions required to achieve a safe, durable, and globally accessible functional cure for chronic HBV.

2. HBV Biology and Current Standard of Care

2.1 HBV Genome Organization and Viral Life Cycle

HBV is a partially double-stranded DNA virus belonging to the **Hepadnaviridae** family. Following hepatocyte entry, relaxed circular DNA is transported to the nucleus and converted into covalently closed circular DNA (cccDNA), which functions as a stable episomalminichromosome and serves as the transcriptional template for all viral RNAs. Viral proteins and pregenomic RNA are synthesized in the cytoplasm, followed by reverse transcription within nucleocapsids and secretion of mature virions together with abundant non-infectious HBsAgsubviral particles that contribute to immune evasion (Figure 1).^{5,6}

2.2 cccDNA Persistence and Integrated HBV DNA

Persistent HBV infection is sustained by the remarkable stability of nuclear cccDNA and by integration of HBV DNA into the host genome. While integrated viral DNA cannot produce infectious virions, it remains an important source of HBsAg expression and contributes to genomic instability and hepatocarcinogenesis. These persistent viral reservoirs represent the principal barriers to HBV cure and therefore constitute major therapeutic targets for next-generation antiviral strategies. ^{4,5,6}

2.3 Host Immune Dysfunction During Chronic HBV Infection

HBV infection is characterized by profound impairment of both innate and adaptive immune responses, including exhaustion of HBV-specific CD8⁺ T cells, dysfunctional natural killer cells, impaired antigen presentation, and persistent exposure to high circulating HBsAg levels. Recent evidence indicates that reducing viral antigen burden can partially restore antiviral immune function, providing a strong biological rationale for combination therapies that simultaneously suppress viral replication and enhance host immune responses. ⁷

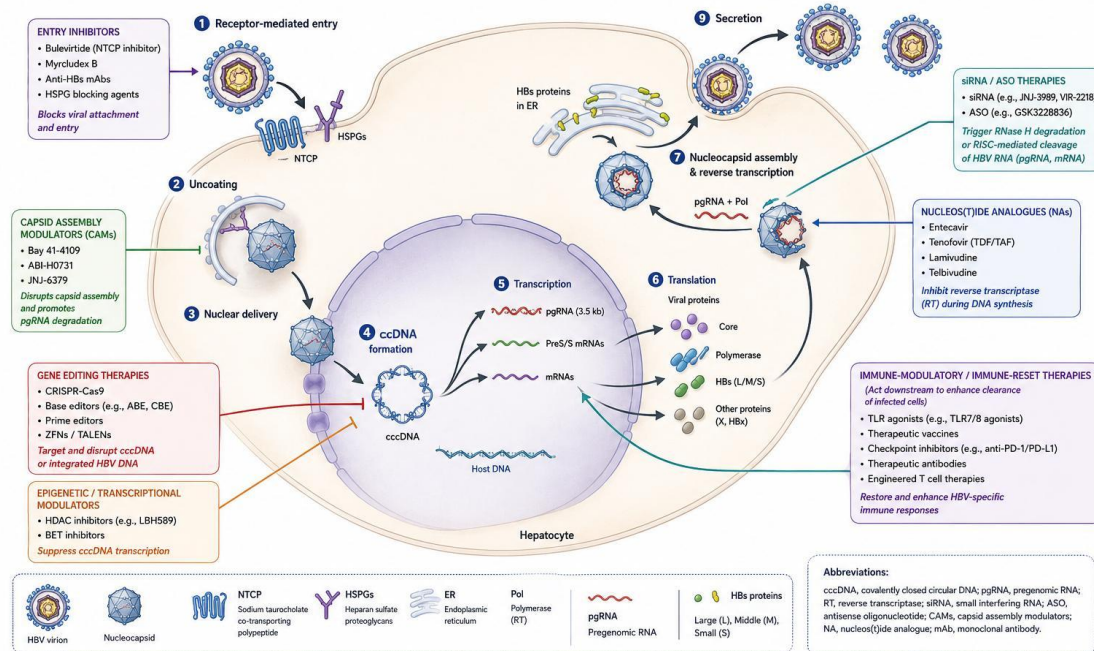


Figure 1: Schematic of the HBV life cycle

(Receptor-mediated entry, uncoating, nuclear delivery, cccDNA formation, transcription, translation, nucleocapsid assembly with reverse transcription, envelopment, and secretion)

2.4 Current Standard Therapy

Two regimens dominate current practice. Nucleos(t)ide analogues - mainly entecavir and tenofovir disoproxil or alafenamide - inhibit reverse transcription potently and are generally well tolerated, but most patients need to stay on them indefinitely. Pegylated interferon-alfa can be given for a fixed duration and adds an immunomodulatory effect, but flu-like symptoms, cytopenias, and neuropsychiatric side effects limit its use to a minority of eligible patients ^{8,9}. Neither drug touches cccDNA or integrated DNA, and that gap is the starting point for everything discussed in the rest of this review (Table 1).

Table 1: Current Standard Therapies for Chronic HBV

Therapy Class	Agent(s)	Mechanism	Advantages	Limitations
Nucleos(t)ide analogues	Entecavir, tenofovir DF/AF	Reverse-transcriptase inhibition	Potent DNA suppression; oral; well tolerated	Indefinite therapy; rare HBsAg loss; no cccDNA effect
Pegylated interferon-alfa	Peg-IFN- α 2a	Immunomodulation + direct antiviral	Finite course; occasional durable functional cure	Flu-like symptoms, cytopenias; contraindicated in decompensated cirrhosis

3. Direct-Acting Antiviral Strategies

3.1 RNA Interference and Antisense Oligonucleotide Therapies

Unlike nucleos(t)ide analogues, which only interrupt reverse transcription, RNA interference offers a way to actually shut down viral protein production. Small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) degrade HBV transcripts coming from both cccDNA and integrated DNA, working through RNase-H1 or the RISC/Argonaute-2 pathway. Because that mechanism reaches transcripts from both viral reservoirs, it produces reductions in HBsAg and other viral antigens that nucleos(t)ide analogues simply cannot achieve ^{9,10}.

3.2 Clinical Development of RNA-Targeting Agents

The furthest along in this class is bepirovirsen, an ASO that targets all HBV mRNAs. It moved from the phase 2b B-Clear study into the pivotal phase 3 B-Well 1 and B-Well 2 trials, which together enrolled more than 1,800 participants and were published in the New England Journal of Medicine in 2026. Roughly one-fifth of treated participants reached functional cure - sustained HBsAg loss with undetectable HBV DNA - after a fixed 24-week course, and that figure rose to about a quarter among people who started with lower baseline HBsAg. HBV DNA suppression held below the limit of quantification through week 72 in most responders, versus essentially no placebo recipients ^{11,12}. Adding pegylated interferon after bepirovirsen, tested in the phase 2b B-Together design, cut post-treatment relapse further ¹³. A handful of other siRNA candidates - elebsiran and imdusiran among them - have shown comparably strong HBsAg declines in phase 2 work, especially when paired with pegylated interferon ¹⁴. Long-term follow-up of earlier-generation siRNA cohorts also backs up the durability angle, with a meaningful share of patients maintaining low HBsAg years after treatment ¹⁵.

3.3 Capsid Assembly Modulators

Capsid assembly modulators work differently again: they block pregenomic RNA from being packaged into new capsids, which cuts off one route by which cccDNA gets replenished. The best-studied example, bersacapavir, was tested alongside an siRNA and nucleos(t)ide analogues in the phase 2b REEF-1 trial, spanning roughly 470 participants across 19 countries. Combination arms hit protocol-defined treatment-stopping criteria more often than nucleos(t)ide analogue monotherapy by week 48, while monotherapy arms ran into viral breakthrough and resistance - a result that argues fairly strongly for using this class in combination rather than alone ¹⁶.

3.4 Entry Inhibitors and Nucleic Acid Polymers

A different approach altogether is to stop the virus from getting into hepatocytes in the first place. Entry inhibitors block the sodium-taurocholate co-transporting polypeptide (NTCP) receptor that HBV shares with hepatitis D virus (HDV), preventing new infection and limiting viral spread. This class is already established in HDV treatment and is now being explored as an HBV combination partner rather than a monotherapy ⁶.

3.5 Neutralising Monoclonal Antibodies

Broadly neutralising antibodies take a related but distinct tack. VIR-3434, the furthest along in development, targets a conserved epitope in the HBsAg antigenic loop and neutralises HBV across genotypes more potently than hepatitis B immunoglobulin. It has also been engineered to trigger Fc-mediated immune effector function, an added layer being tested in early human trials¹⁷.

3.6 Emerging Direct-Acting Antiviral Targets

Behind the agents already in clinical testing sits a broader pipeline of next-generation siRNA and combination oligonucleotide constructs, engineered with chemical modifications meant to improve hepatocyte uptake, cut down on off-target immune activation, and extend how long the drug stays active in the liver. The goal is deeper, more durable antigen suppression than first-generation agents deliver, though most of these constructs are still awaiting clinical validation^{9,10}.

Table 2: Direct-Acting Antiviral Agents and Capsid Assembly Modulators

Class	Representative Agent(s)	Mechanism	Trial / Phase (Journal, Year)
ASO	Bepirovirsen	Degrades all HBV transcripts	B-Well 1/2, Phase 3 (N Engl J Med, 2026)
siRNA	VIR-2218 (elebsiran)	RNAi vs pgRNA/S transcripts	Phase 2 + Peg-IFN (Lancet GastroenterolHepitol, 2024)
siRNA	JNJ-73763989	RNAi, pan-HBV RNA	REEF-1, Phase 2b (Lancet GastroenterolHepitol, 2023)
Capsid assembly modulator	Bersacapavir (JNJ-56136379)	Empty-capsid induction; blocks cccDNA replenishment	REEF-1, Phase 2b (Lancet GastroenterolHepitol, 2023)
Neutralising mAb	VIR-3434	Anti-HBsAg antigenic-loop neutralisation + Fc effector activity	Preclinical/early-phase (J Hepitol, 2023)

4. Gene Editing Strategies for HBV Cure

4.1 CRISPR-Cas Gene Editing

If cccDNA and integrated DNA are the real reservoirs of persistence, the most direct fix is to cut them out. CRISPR-Cas9 and related RNA-guided nucleases, along with engineered meganucleases, can be programmed to cleave both directly, triggering double-strand breaks that degrade the viral genome or knock out essential reading frames. This is the one strategy on this list that goes after the root cause rather than working around it, which is precisely what nucleos(t)ide analogues and RNA-silencing agents cannot do^{4,10}.

4.2 Base Editing and Prime Editing

Base and prime editors offer a gentler variant of the same idea: they can correct or disrupt short stretches of viral DNA without creating a double-strand break at all. That matters because double-strand breaks carry a known risk of large chromosomal deletions or translocations at on- and off-target sites, a safety concern that has dogged first-generation nuclease editors. Base and prime editing sidesteps that specific problem while, in principle, still disabling transcription from cccDNA and integrated sequences. The catch is that these platforms remain earlier in preclinical development for HBV, and no human trials have been registered yet ¹⁰.

4.3 Epigenome Editing and CRISPR Interference (CRISPRi)

A third option skips DNA cutting altogether. CRISPRi-based epigenetic silencing recruits repressive chromatin modifiers to cccDNA, switching off transcription without touching the DNA sequence itself. It is an attractive middle ground — durable suppression with, potentially, a cleaner off-target safety profile than either nuclease- or base-editing approaches ¹⁰.

4.4 First-in-Human Clinical Evidence (PBGENE-HBV and ELIMINATE-B)

The first gene-editing candidate to reach human testing for chronic HBV is PBGENE-HBV, an in vivo meganuclease designed to cleave cccDNA and disable integrated HBV DNA simultaneously within hepatocytes. It is now in first-in-human dose-escalation testing under the registered ELIMINATE-B protocol (ClinicalTrials.gov identifier NCT06680232) ¹⁸. At the time of writing, detailed efficacy and safety results have not appeared in a peer-reviewed publication. The registered protocol calls for sequential dose-escalation cohorts with HBsAg decline and safety as the primary outcomes, so any conclusions about how well this approach actually works should wait for that peer-reviewed data ¹⁸.

4.5 Delivery Systems, Safety, Off-Target Effects, and Regulatory Challenges

None of this works without getting the editing machinery into hepatocytes, and lipid nanoparticles and adeno-associated virus vectors remain the two main options for doing that. Several questions are still open, though: how much off-target editing occurs, what the long-term genotoxicity looks like, how immunogenic the viral capsid components turn out to be, and whether a one-time intervention actually stays durable. Answering those will take pharmacovigilance well beyond the standard phase 1-2 safety window ^{4,10}.

5. Immune-Reset Therapies

5.1 T-Cell Exhaustion and Immune Tolerance

Suppressing the virus is only half the problem. Getting to functional cure seems to also require rebuilding HBV-specific immunity, not just knocking down viral load — which is why immune-reset strategies are usually paired with a direct-acting agent that lowers antigen burden first. This sequential or combination logic runs through most of what follows in this section ^{7,8}.

5.2 Therapeutic Vaccines

Protein-based, DNA-based, and mRNA-based therapeutic vaccines all aim to reawaken HBV-specific T- and B-cell responses in a host that has already been exposed to the virus for years. In mouse work, sequential mRNA vaccination combined with other direct-acting agents achieved functional cure in a recombinant AAV8-1.3HBV carrier model — an encouraging early signal for quadruple-combination regimens, though it still needs to be confirmed in humans ²⁵.

5.3 Toll-Like Receptor Agonists

Selgantolimod, an oral TLR8 agonist, takes a more indirect route by switching on innate antiviral pathways: it induces interleukin-12 and activates natural killer and mucosal-associated invariant T cells. In a phase 2 trial, it produced modest declines in HBsAg and HBeAg, with a small proportion of virologically suppressed participants achieving HBsAg loss ^{19,20}.

5.4 Immune Checkpoint Inhibitors

PD-1/CTLA-4 blockade is already established in HBV-related HCC, and it is now being explored, more cautiously, as a way to restore exhausted HBV-specific T-cell function in chronic infection itself. The caution is warranted — hepatotoxicity and flare risk mean dose-finding outside oncology populations needs to move slowly ²¹.

5.5 Engineered and Adoptive Cell Therapies

HBV-specific TCR-engineered T cells, built using mRNA electroporation combined with lentiviral transduction, have shown both antitumour and antiviral activity in patients with recurrent HBV-related HCC after liver transplantation, notably without triggering acute liver failure despite killing HBsAg-positive hepatocytes on target ²². A related programme, SCG101 TCR-T, is testing similar constructs specifically for HBV-related HCC ²⁴. Meanwhile, CAR-T platforms originally built for B-cell malignancies have already been given safely to patients with HBV-associated cirrhosis under antiviral prophylaxis - useful real-world safety data for whatever HBV-directed cellular therapies come next ²³.

5.6 Cytokine-Based Immune Modulation

The clearest clinical evidence for sequential cytokine-based immune modulation so far comes from the phase 2b B-Together design, in which bepirovirsen followed by pegylated interferon-alfa achieved functional cure in a meaningful minority of participants with lower baseline HBsAg — direct support for the deep-suppression-then-immune-consolidation model this review keeps returning to ¹³. IL-12 and IL-15 have not been tested this way yet: what evidence exists for chronic HBV is still confined to preclinical work and adjacent indications, with no registered human trials specifically evaluating either cytokine in HBV cure regimens ⁸.

Table 3: Gene Editing and Immune-Reset Therapies

Modality	Target/Agent	Clinical Evidence	Benefit	Challenge
Gene editing (meganuclease)	PBGENE-HBV	Registered Phase 1 (ELIMINATE-B, NCT06680232)	Directly targets cccDNA and integrants	Durability, off-target/long-term safety unresolved; efficacy not yet peer-reviewed
TLR8 agonist	Selgantolimod	Phase 2 (J Hepatol, 2023)	Innate immune activation; oral	Modest effect size alone
Checkpoint inhibitor	Nivolumab, ipilimumab	Phase 2, HBV-related HCC (J Cancer Res ClinOncol, 2023)	Reverses T-cell exhaustion	Hepatotoxicity/flare risk outside oncology indications
TCR-T cell therapy	SCG101; HBV-TCR-T	Phase 1 (Clin Cancer Res, 2025)	Directly eliminates HBsAg+ hepatocytes/HCC	On-target hepatotoxicity; manufacturing complexity
Therapeutic vaccine	Sequential mRNA vaccination	Preclinical, rAAV8-1.3HBV mouse model (Acta Pharm Sin B, 2026)	Restores HBV-specific adaptive immunity	Human efficacy unproven

6. Rational Combination Regimens

6.1 Direct-Acting Antiviral Combinations

Stacking nucleos(t)ide analogues with siRNA/ASO agents and capsid assembly modulators goes further than any single agent can on its own. The REEF-1 phase 2b trial demonstrated this directly: combination regimens hit protocol-defined treatment-stopping criteria more often than nucleos(t)ide analogue monotherapy¹⁶.

6.2 RNA Silencing Plus Immunotherapy

Adding pegylated interferon-alfa on top of an RNA-silencing backbone boosts both HBsAg decline and immune restoration beyond what either drug achieves alone. Elebsiran plus pegylated interferon-alfa-2a outperformed elebsiran monotherapy on HBsAg reduction in a phase 2 study, and the B-Together design -sequential bepirovirsen then interferon -cut post-treatment relapse in the same way^{13,14}.

6.3 Capsid Modulators Combined with Immune-Reset Therapies

There is a reasonable case, still mostly theoretical, for pairing capsid assembly modulators with immune-reset agents like TLR8 agonists or therapeutic vaccines. The logic runs like this: capsid modulators suppress cccDNA

replenishment and reduce circulating viral particles, which lowers the antigen burden that has been keeping HBV-specific T cells suppressed, potentially clearing the way for checkpoint- or agonist-driven immune activation to actually work. What is missing is a trial that tests this pairing directly rather than inferring it from separate arms of different studies -most of the current evidence is indirect in exactly that way ^{16,19}.

6.4 Phase 3 Evidence and Regulatory Progress

Of everything discussed in this review, bepirovirsen has travelled furthest through the regulatory pipeline. It went from phase 2b (B-Clear) to the pivotal phase 3 B-Well 1 and B-Well 2 programmes, published in the New England Journal of Medicine in 2026 - the first RNA-targeted therapeutic to report phase 3 functional-cure data in chronic HBV ^{11,12}. Together with the sequential-interferon B-Together design, these trials now set the benchmark that later combination regimens, gene-editing-anchored ones included, will be measured against ^{11,13}.

6.5 Predictors of Sustained Functional Cure and Treatment-Free Remission

Some biomarkers do a reasonably good job of predicting who will stay cured. Baseline and on-treatment levels of quantitative HBsAg, HBcrAg, and serum HBV RNA all track with the likelihood of sustained HBsAg loss and low relapse risk after stopping treatment. In the Hepatitis B Research Network's Immune Active cohort, for instance, patients with undetectable serum HBV RNA at end-of-treatment were substantially more likely to sustain partial cure than those with quantifiable HBV RNA ³⁶. HBcrAg performs similarly well, showing high pooled sensitivity for predicting virological relapse after nucleos(t)ide analogue withdrawal ²⁸.

6.6 Personalised Combination Therapy

No single mechanism predicts response reliably across all patients, so the field has been moving away from one-size-fits-all regimens toward sequencing combinations based on each patient's baseline antigen burden, genotype, and immune profile. Recent expert consensus guidance on functional-cure treatment navigation has now formalised this approach (Figure 2) ³¹.

Figure 2. Integrated Precision Cure Strategies for Chronic Hepatitis B

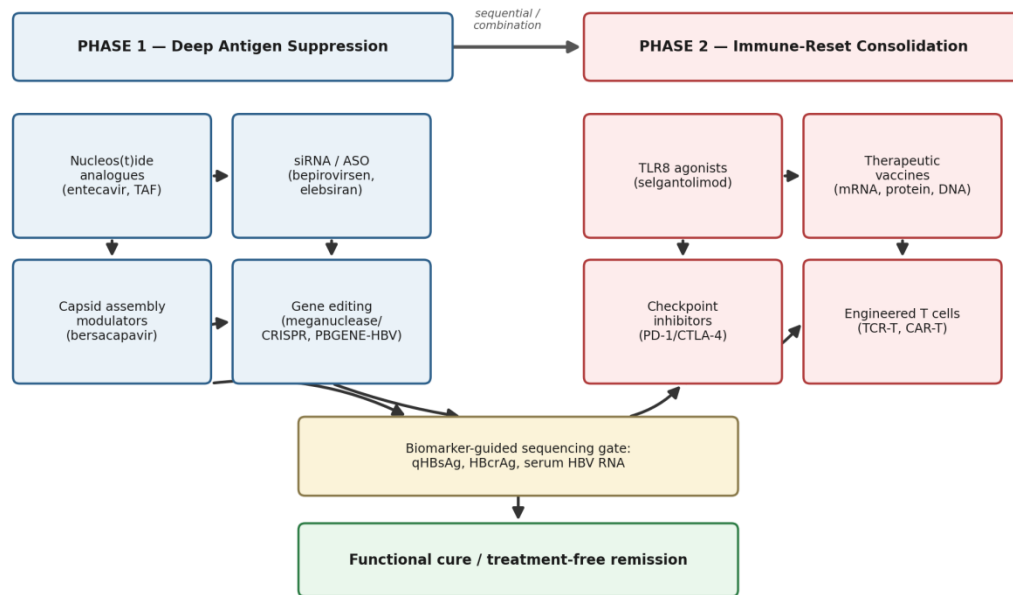


Figure 2: Integrated precision cure strategy combining Phase 1 deep antigen suppression (nucleos(t)ide analogues, siRNA/ASO, capsid assembly modulators, gene editing) with Phase 2 immune-reset consolidation (TLR8 agonists, therapeutic vaccines, checkpoint inhibitors, engineered T cells), sequenced through a biomarker-guided gate toward functional cure or treatment-free remission.

7. Biomarkers and AI-Guided Precision Diagnostics

7.1 Biomarkers of Viral Activity

Quantitative HBsAg is still the workhorse endpoint biomarker for functional cure, since it reflects total transcriptionally active cccDNA and integrated DNA combined³. Two newer markers are increasingly used alongside it. HBcrAg, a composite of core-related viral proteins, tracks intrahepatic cccDNA transcriptional activity more closely than either HBsAg or HBV DNA, and recent meta-analyses put its pooled sensitivity and specificity for relapse prediction at 0.81 and 0.72^{27,28}. Serum HBV RNA — essentially encapsidated pregenomic RNA circulating in serum — does something similar, reflecting cccDNA transcriptional activity and predicting both HBeAg seroconversion and treatment response^{26,27}. HBV DNA is still the standard measure of active replication, and direct quantification of intrahepatic cccDNA by liver biopsy remains the closest thing to a gold standard, though its invasiveness confines it largely to research settings³⁶.

7.2 Machine Learning for Diagnosis and Prognosis

A recent meta-analysis pooled several machine learning approaches — including least absolute shrinkage and selection operator regression and gradient boosting with SHapley Additive exPlanation (SHAP) interpretability —

that combine baseline and on-treatment biomarkers to predict functional cure under pegylated interferon therapy, and found clinically useful discrimination held up across multi-centre cohorts ³⁰.

7.3 AI-Based Prediction of Treatment Response

Prediction does not stop at the point of cure. PLAN-B-CURE, for instance, uses post-seroclearance variables like age, sex, diabetes, cirrhosis, albumin, and platelet count to forecast liver-related outcomes after HBsAg loss, which is a useful reminder that risk stratification still matters even once a patient appears cured ²⁹. On the imaging side, AI models built on CT-derived radiomic features have been validated specifically for predicting incident HCC in chronic HBV patients ³².

7.4 Genotype- and Host-Stratified Precision Medicine

Not every patient's biology behaves the same way. HBV genotype, host genetic factors, sex, and age all shift the odds of spontaneous or treatment-induced HBsAgseroclearance, and the latest expert consensus guidance now explicitly recommends folding these host- and virus-level variables into individualised treatment navigation rather than defaulting to a single regimen for everyone ³¹.

7.5 Digital Twins and AI-Driven Clinical Decision Support

A more forward-looking idea is the digital twin — a patient-specific computational model built to simulate an individual's physiology and likely response to treatment. The concept is already gaining traction elsewhere in hepatology, with early applications in surgical planning and steatotic liver disease. Applying it to chronic HBV cure regimens is still mostly conceptual at this stage; nobody has actually deployed it clinically yet ²⁴.

7.6 Toward an Integrated Precision Cure Model

Put the pieces together — serologic biomarkers, imaging, host and genotype data, machine learning risk scores — inside a single clinical decision-support framework, and what emerges is a genuine path toward individualised sequencing, timing, and monitoring of combination cure regimens (Figure 3, Table 4).

Table 4: Biomarkers and Artificial Intelligence Applications in Precision HBV Management

Biomarker / Tool	What It Reflects	Clinical / AI Application	Key Evidence
Quantitative HBsAg	Total transcriptionally active cccDNA + integrated DNA	Treatment-response monitoring; functional-cure endpoint	Cornberg et al., J Hepatol 2020
HBcrAg	Intrahepatic cccDNA transcriptional activity	Predicts relapse after NA cessation; HCC risk stratification	Meta-analysis, pooled AUC 0.83 for relapse prediction (2025)
Serum HBV RNA	Encapsidatedpregenomic RNA; cccDNA transcriptional activity	Predicts HBeAgseroconversion, relapse risk, early treatment response	Wang et al., J Hepatol 2016; Kosaka et al., J Gastroenterol 2025

Intrahepatic cccDNA (biopsy-based)	Direct reservoir quantification	Research-grade gold standard; not routinely clinical	Coffin, Zhou, Terrault, Gastroenterology 2019
Machine learning (SHAP-interpretable models)	Multivariable integration of baseline/on-treatment markers	Predicts functional cure probability under Peg-IFN; individualised counselling	Ye et al., Virol J 2024; Zhang et al., HepatolInt 2024
Post-cure ML risk model (PLAN-B-CURE)	Host/clinical variables after HBsAgseroclearance	Predicts liver-related outcomes after functional cure	Hur et al., J Hepatol 2025
AI imaging biomarkers	CT-based radiomic features	HCC risk prediction in chronic HBV	Cheung et al., J Hepatol 2024

Figure 3. AI-Guided Precision Cure Model for Chronic Hepatitis B

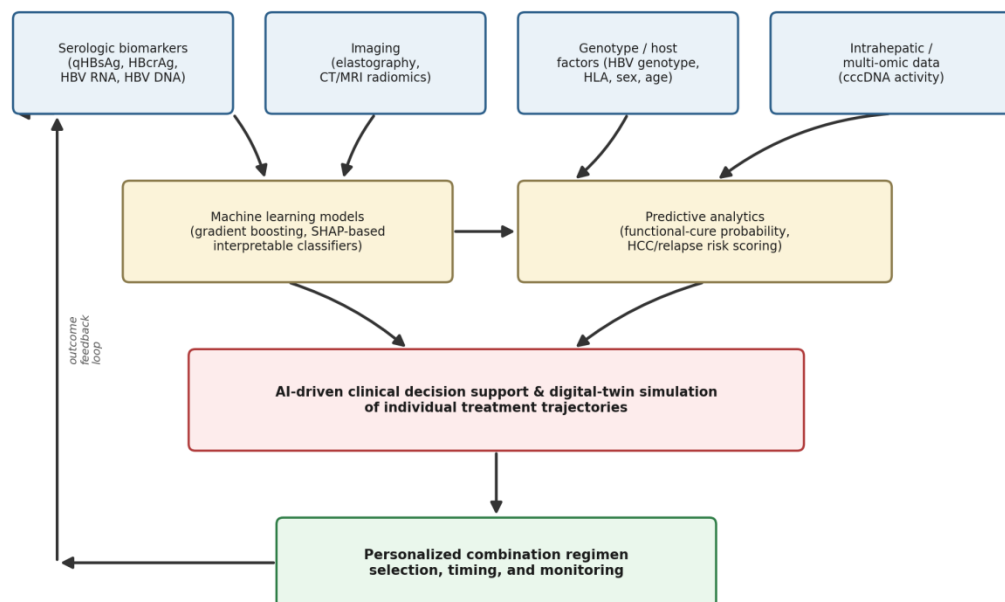


Figure 3: AI-guided precision cure model integrating serologic biomarkers, imaging, and genotype/host data through machine learning-based predictive analytics into clinical decision support and digital-twin simulation, informing personalised combination regimen selection with outcome-based feedback.

8. Challenges and Future Directions

8.1 Scientific and Clinical Barriers

For all the progress described above, no current modality actually eliminates cccDNA and integrated HBV DNA from every infected hepatocyte — even the most advanced RNA-silencing and gene-editing candidates achieve functional cure in only a minority of patients. There is also a measurement problem: biomarker thresholds for deciding when to

stop treatment are not well standardised across populations or assay platforms, and adding HBV RNA or HBcrAg to models built on host, clinical, and HBV DNA factors has so far only nudged predictive accuracy up modestly. That limits how well any of these models generalise across different patient groups^{4,28,36}.

8.2 Safety, Delivery, Cost, and Global Accessibility

Gene-editing and cell-therapy platforms depend on hepatocyte-targeted delivery — mostly lipid nanoparticles and adeno-associated viral vectors — whose long-term genotoxicity, integration risk, and immunogenicity are not yet fully worked out over multi-year follow-up. There is a more practical problem too: engineered T-cell products and viral-vector-delivered nucleases are expensive and complicated to manufacture, and the worry is that these therapies stay out of reach in the high-burden, resource-limited settings across Africa and the Western Pacific, where most chronic HBV infection actually occurs. Simplified, lower-cost delivery and manufacturing will need to be developed alongside the science itself, not as an afterthought^{1,4,22}.

8.3 Special Populations

A few patient groups need separate consideration. HBV-HDV coinfection, present in an estimated 5-10% of HBsAg carriers, drives a faster, more aggressive disease course, and prophylaxis strategies built for HBV alone do not automatically translate⁶. In HBV-HIV coinfection, tenofovir-containing antiretroviral regimens with activity against both viruses are the recommended approach — using an HBV monotherapy-active agent like lamivudine or emtricitabine on its own risks selecting for HBV resistance — and coinfecting patients carry a higher HCC risk than HBV mono-infection even when HBV is fully suppressed^{33,34}. Liver transplant recipients are a third special case: before combination prophylaxis existed, HBV recurrence rates ran as high as 80-100%, with roughly half of untreated recurrences proving fatal within two years. Adding hepatitis B immunoglobulin (HBIG) alongside nucleos(t)ide analogues brought recurrence down to under 10%, and increasingly, centres are moving to HBIG-sparing, high-potency nucleos(t)ide analogue monotherapy in lower-risk patients, which cuts both cost and the logistical burden of long-term immunoglobulin dosing³⁵.

8.4 Lessons from Emerging Entry-Inhibitor and Antibody Therapies

HDV treatment has already provided a useful proof of concept here: blocking viral entry through NTCP meaningfully reduces antigen burden even without touching cccDNA directly. That is encouraging for HBV, where entry inhibitors and neutralising antibodies look better positioned as combination partners than as standalone cures^{6,17}.

8.5 Progress Toward WHO 2030 Elimination Targets

None of the science reviewed here substitutes for the basic public health work of diagnosing and treating more people — WHO 2030 elimination targets will not be hit without substantially higher coverage than exists today. But the two goals reinforce each other: a functional cure that actually works at scale would shrink the population that needs indefinite therapy, which makes the public health targets more achievable, not less^{1,2}.

8.6 Future Outlook

If there is a single most plausible route to a scalable functional cure, it probably looks like this: deep antigen suppression, whether through siRNA/ASO, capsid assembly modulators, or gene editing, followed by immune-reset consolidation using TLR agonism, checkpoint blockade, or engineered T cells — with biomarker- and AI-guided diagnostics doing the work of sequencing and monitoring rather than a one-size-fits-all protocol^{13,31}.

9. Conclusion

Bepirovirsen's phase 3 result is the first time an RNA-based therapeutic has come close to clinically meaningful, finite-duration functional cure rates in chronic HBV. PBGENE-HBV, meanwhile, is already in registered first-in-human testing, though its efficacy data have not yet cleared peer review. Getting from here to a precision cure that works at population scale will take more combination-regimen trial evidence, biomarker- and AI-based patient stratification that is actually standardised, and — just as importantly — equitable global access to whichever of these technologies ultimately proves out.

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