

Review

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Functional cure of chronic hepatitis B virus infection: current therapeutic regimens

Yi-Wei Shi^{1,2,3,#}, Rui Pu^{1,2,3,#}, Yi-Bo Ding^{1,2,3,#}, Wen-Bin Liu^{1,2,3}, Zi-Shuai Li^{1,2,3}, Jia-Yi Zhao^{1,2,3}, Yi-Fan Chen^{1,2,3}, Guang-Wen Cao^{1,2,3}

¹Department of Epidemiology, Second Military Medical University, Shanghai 200433, China.

²Key Laboratory of Biological Defense, Ministry of Education, Second Military Medical University, Shanghai 200433, China.

³Shanghai Key Laboratory of Medical Bioprotection, Second Military Medical University, Shanghai 200433, China.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Guang-Wen Cao, Department of Epidemiology, Second Military Medical University, Shanghai 200433, China. E-mail: gcao@smmu.edu.cn

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Abstract

Hepatitis B virus (HBV) infection remains a major cause of hepatocellular carcinoma (HCC). It is estimated that 254 million people are chronically infected with HBV, with 1.1 million deaths projected in 2025. Functional cure, defined as sustained loss of hepatitis B surface antigen (HBsAg), is important for the prevention of HCC. While nucleos(t)ide analogs maintain viral suppression in over 95% of patients, HBsAg clearance is achieved in only 2%-11%. The functional cure rate with interferon therapy is highly variable in different populations, ranging from 2% to over 40%. Consequently, functional cure remains the primary focus of novel therapeutic development. Here, we analyze the virological and immunological barriers to functional cure and summarize current therapeutic methods. Among these, novel RNA-interference-based therapeutics reduce HBsAg to below 10% of baseline in most patients. However, monotherapy with these agents results in HBsAg loss in fewer than 10% of cases. However, sequential interferon or immunomodulatory agents raise the HBsAg loss to 15%-30%. To achieve the > 50% cure rate likely required for the World Health Organization's 2030 elimination goals, we analyze promising strategies focused on multi-target combination approaches and precision-medicine frameworks.

Keywords: Hepatitis B virus, functional cure, novel therapeutic methods, combination strategies, special populations



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INTRODUCTION

Hepatitis B virus (HBV) infection remains one of the most critical global public-health challenges. In 2025, the World Health Organization (WHO) estimated that 254 million individuals were chronically infected with HBV, resulting in approximately 1.1 million annual deaths due to cirrhosis and hepatocellular carcinoma (HCC)^[1]. The burden remains highly concentrated, with three-quarters of cases located in the Western Pacific (97 million), Africa (65 million) and South-East Asia (61 million)^[2]. Universal infant vaccination has reduced early childhood HBV infections below 0.1%. Nevertheless, over 90% of existing chronic infections were acquired perinatally or in early childhood^[3]. Without intervention, HBV-related mortality is projected to increase by 39% between 2015 and 2030^[4]. In China, for example, 32% of chronically infected men and 9% of women are predicted to succumb to HCC before the age of 75 years^[5].

Long-term suppression of HBV replication through antiviral therapy has been proven to significantly reduce the risk of HCC and liver-related mortality, serving as a critical tertiary prevention strategy. Recent studies demonstrated that nucleos(t)ide analogs (NAs) fail to eradicate the viral covalently closed circular DNA (cccDNA) and integrated HBV fragments^[6-9]. Consequently, fewer than 5% of patients achieve hepatitis B surface antigen (HBsAg) loss after stopping therapy^[6-9]. This low rate represents a critical barrier to functional cure (sustained HBsAg seroclearance off-therapy), defined as sustained HBsAg loss [< 0.05 international units per milliliter (IU/mL)] and undetectable HBV DNA (< 10 IU/mL) for at least 24 weeks off-therapy^[10-13]. Ultra-sensitive HBsAg assays (lower limit of detection ≤ 0.005 IU/mL) are increasingly needed to accurately measure profound antigen suppression and predict relapse^[14]. Expert Consensus 2.0 outlines a two-stage curative paradigm. The first stage uses small interfering RNA (siRNA) or antisense oligonucleotides (ASOs) to suppress antigens and reverse immune tolerance. The second stage employs pegylated interferon (Peg-IFN), therapeutic vaccines, or programmed-death-1 (PD-1)/PD-ligand-1 (PD-L1) inhibitors to prime adaptive immunity. Phase II trials (NCT02981602, NCT04225715) of this sequential approach achieved HBsAg seroclearance rates of 15%-30%^[15-17]. In this review, we summarize the virological and immunological barriers to functional cure, evaluate combination regimens [Table 1], and propose a framework to achieve $\geq 50\%$ functional-cure rates, a threshold which is likely required to meet WHO 2030 targets.

BARRIERS TO FUNCTIONAL CURE

Virological barriers

cccDNA serves as the key viral reservoir that sustains lifelong HBV infection. Organized as an epigenetic minichromosome complexed with histones and host factors, cccDNA resides in the hepatocyte nucleus and displays a half-life of weeks to years. Because NAs act only on the reverse transcription of pre-genomic RNA, they do not prevent intracellular recycling of relaxed-circular DNA that continuously replenishes the cccDNA pool^[6,7,18-21]. Single-cell sequencing studies confirmed that a low level of transcriptionally active cccDNA persists in the liver under NAs therapy^[22]. This persistence explains the high rate of virological relapse after treatment withdrawal. Additionally, the S region of the HBV genome can integrate into the host genome early in infection via non-homologous end joining. These integrated fragments can continuously express HBsAg and constitute one of the main sources of serum HBsAg in hepatitis B e antigen negative (HBeAg-negative) chronic hepatitis B (CHB) patients^[23-25]. During chronic infection, high levels of HBV DNA and HBsAg establish an antigen-tolerant environment, which impairs adaptive immune responses^[26,27]. HBV also evades immune surveillance through genomic mutations. For instance, deletions in the pre-S/S regions can yield false-negative HBsAg tests or facilitate immune escape^[28]. The coexistence of cccDNA and integrated DNA in hepatocytes poses a major obstacle to viral eradication, as current therapies do not effectively target both reservoirs^[29-31]. To address the virological barriers, therapeutics precisely target multiple key steps of the HBV life cycle [Figure 1].

Table 1. Therapeutic landscape for CHB functional cure

Therapeutic category	Mechanism of action	Specific regimen	Primary efficacy endpoints	Efficacy data	Key advantages	Major limitations	Ref.
I. Current standard of care							
NAs	Competitively inhibit HBV DNA polymerase and reverse transcriptase, terminating viral DNA synthesis and replication	ETV, TDF, TAF	Viral suppression (undetectable HBV DNA), HBsAg clearance	Viral suppression in > 95% of patients; HBsAg clearance in < 5%	High efficacy in viral suppression, reduces HCC risk, improves liver histology	Does not eliminate cccDNA, frequent relapse after cessation, often requires lifelong therapy	[49-57]
Peg-IFN	Direct antiviral and immunomodulatory activity, epigenetically suppresses cccDNA transcription	Peg-IFN α , weekly injections	HBeAg loss/seroconversion, HBsAg clearance	HBeAg loss and undetectable HBV DNA in ~30% of HBeAg-positive patients. HBsAg clearance up to 40% in inactive carriers	Finite treatment duration, no lifelong treatment required, potential for sustained immune control	Subcutaneous injection, multiple adverse reactions (flu-like symptoms, depression, etc.) Efficacy depends on baseline HBsAg level and HBeAg status. Not suitable for decompensated cirrhotic patients	[37, 62-66, 69-72,76]
II. Traditional combination strategies							
<i>De novo</i> combination (NA + Peg-IFN)	Combines viral suppression of NAs with immune-mediated clearance of Peg-IFN	Simultaneous initiation of NA and Peg-IFN	HBsAg clearance	-	-	No proven advantage over monotherapy or sequential approaches	[82-87]
Switch strategy (NAs $\rightarrow$ Peg-IFN)	Stops NAs and switches to Peg-IFN after virologic suppression to activate immunity	Discontinue NAs, initiate Peg-IFN	HBsAg clearance	HBsAg clearance rates of 8.5%-14% at week 48 in HBeAg-negative patients with baseline HBsAg < 100 IU/mL	Potential for HBsAg clearance	High risk of virologic relapse and clinical hepatitis flare (2%-4%)	[73-76]
Add-on strategy (NA + Peg-IFN)	Maintains NAs therapy while adding Peg-IFN for immunomodulation	Continue NAs, add Peg-IFN	HBeAg seroconversion, HBsAg clearance	HBsAg clearance rates of ~7% in HBeAg-positive patients, 20% in those with baseline HBsAg < 1,500 IU/mL	Lower risk of virologic relapse (9% vs. 26%) and hepatitis flare (1.2% vs. 6.8%) compared to switch strategy	Efficacy still depends on baseline HBsAg level. Injection-related side effects, requires monitoring	[77-81]
III. Novel antiviral agents							
siRNA	Degrades viral mRNA via RNA-induced silencing complex, blocking translation of all HBV proteins	IR-2218 (elebsiran), Xalnesiran, Imdusiran	HBsAg reduction, HBsAg clearance	Monotherapy reduces HBsAg by > 1 log ₁₀ , but HBsAg loss $\leq$ 10%, rebound common after cessation	Potent reduction of HBsAg and other viral antigens	Low HBsAg loss rate as monotherapy, antigen rebound	[88-94]
ASO	Hybridizes to HBV RNA and recruits RNase H1 to degrade viral transcripts, some have TLR8 agonist activity	Bepirovirsen, 300 mg weekly for 24 weeks	HBsAg clearance	HBsAg loss in 9%-10% of patients after 24 weeks. 16%-25% in those with baseline HBsAg $\leq$ 3 log IU/mL	Higher monotherapy clearance rate than siRNA. Finite-duration monotherapy can directly elicit functional cure. Effective for HBsAg expressed by integrated DNA	Limited efficacy in patients with high baseline HBsAg, rebound possible	[88, 93-98]
CAMs	Disrupts HBV capsid assembly/disassembly, preventing pgRNA encapsidation and cccDNA replenishment	JNJ-56136379	Viral load reduction, HBsAg reduction	Preclinical studies show marked viral load decline, monotherapy rarely achieves functional cure	Lower HBsAg, epigenetically silence cccDNA	Limited efficacy as monotherapy	[100, 102]

Entry inhibitor	Competitively blocks NTCP receptor on hepatocytes, preventing HBV/HDV entry	Bulevirtide	HBsAg reduction	Modest HBsAg reduction as monotherapy, significant declines when combined with Peg-IFN in co-infected patients	Targets viral entry, valuable in combination	Limited effect on HBsAg alone	[104]
NAPs	Interferes with assembly/secretion of subviral HBsAg particles, directly reducing circulating HBsAg	REP 2139	HBsAg seroconversion	In triple combination with Peg-IFN and tenofovir, HBsAg seroconversion rates ~60%	Potent HBsAg reduction	Limited clinical data, unproven long-term efficacy. Mechanism not fully elucidated	[108]
IV. Immunomodulatory therapies							
Pattern recognition receptor agonists	Activates innate immune signaling (e.g., TLR pathways), driving type I interferons and pro-inflammatory cytokines	Vesatolimod (TLR7 agonist), Ruzotolimod (TLR7 agonist), Selgantolimod (TLR8 agonist)	HBsAg reduction	Monotherapy yields modest HBsAg reductions or low seroconversion rates	Activates innate immunity and bridges to adaptive immunity	Insufficient to break deep tolerance under high antigen load	[106-109]
ICIs	Blocks PD-1/PD-L1 axis to reverse T-cell exhaustion and restore antiviral T-cell function	Envafolelimab (anti-PD-L1), Nivolumab (anti-PD-1)	HBsAg clearance	Envafolelimab: 21.1% HBsAg clearance in patients with baseline HBsAg < 100 IU/mL. Nivolumab: HBsAg reduction in 11/12 subjects, one HBsAg loss	Revives exhausted T cells, effective in low-antigen settings	Efficacy dependent on low antigen load, safety concerns in some populations	[106]
Therapeutic vaccines	Breaks immune tolerance, elicits robust HBV-specific T- and B-cell responses	BR11-179 (HBsAg + Pre-S1 + Pre-S2), VTP-300 (ChAdOx1/MVA vectors)	HBV-specific T-cell responses, HBsAg reduction	Induces HBV-specific CD4 ⁺ /CD8 ⁺ T-cell responses and neutralizing antibodies. Larger HBsAg reduction when combined with siRNA/ICIs	Resets immune memory, designed for chronic infection	Limited efficacy as monotherapy, requires combination	[113, 114]
Prophylactic vaccines	Prevents infection by inducing neutralizing antibodies	Recombinant HBV vaccines, 0-1-6 month schedule	Protective anti-HBs antibodies	In neonates of HBsAg+/HBeAg+ mothers, vaccine + HBIG reduces chronic carrier rate to 6% vs. 88% in controls	Highly efficacious and safe, primary prevention	Not curative, used for prophylaxis only	[115]
Monoclonal antibodies	Neutralizes HBV particles and enhances antigen presentation via Fc engineering	VIR-3434 (Fc-engineered human mAb)	HBsAg reduction	Single doses produce rapid HBsAg drops (~2 log ₁₀ IU/mL), but durability limited	Rapid antigen reduction, quickly reduces viral load	Short-lived effect, requires combination regimens	[116]
T-cell engineering therapies	Genetically engineers T cells with HBV-specific TCRs or CARs for precise cytotoxicity against infected hepatocytes	TCR-T (targeting HBV core antigen), CAR-T (targeting HBV surface antigen)	Viral replication control	Preclinical and early-phase studies show potential for eradicating viral reservoir	Potential to target and eliminate infected cells	Safety and persistence hurdles, early-stage development	[117, 118]
V. Novel combination regimens							
ASO + NAs combination	ASO lowers HBsAg and viral proteins, NAs suppress replication	Bepirovirsen + ETV/TDF	HBsAg decline or loss	Significant HBsAg reduction or clearance in some NA-experienced patients with acceptable safety	Dual action may reawaken exhausted immunity	Requires further validation in phase III trials	[97]
siRNA + Peg-IFN	siRNA depletes antigens, lifting immune suppression; Peg-IFN provides antiviral and immunostimulatory effects	VIR-2218/Xalnesiran + Peg-IFNα	HBsAg clearance	HBsAg loss rates of 15%-23%	Strong synergy, higher functional cure rates	Sequential therapy required	[126, 127]

ASO → Peg-IFN sequential	ASO reduces antigen load, followed by Peg-IFN to consolidate response and reduce relapse	Bepirovirsen (24 weeks) → Peg-IFN	HBsAg clearance, reduced relapse	Reduces post-treatment relapse and consolidates HBsAg loss	Improves durability of response	Complex sequential regimen	[128]
siRNA + therapeutic vaccine	siRNA drives HBsAg to low levels, vaccine mimics acute infection to expand multispecific T and B cells	Imdusiran (AB-729) + VTP-300	HBsAg clearance	Stronger HBV-specific CD4 ⁺ /CD8 ⁺ T-cell response after siRNA pretreatment	Paradigm of “antigen-down, immunity-up”	Still in early development	[129, 134]
siRNA + innate agonist	Simultaneously silences viral genes and activates innate immunity (e.g., TLR agonists)	Xalnesiran + Ruzotolimod (TLR7 agonist)	HBsAg decline	Synergistically reduces HBsAg, prolongs RNA silencing effect	Jointly breaks immune tolerance	Optimal dosing and sequencing under investigation	[127, 130, 131, 135]
siRNA + ASO combination	Complementary mechanisms: siRNA degrades all viral transcripts, ASOs recruits RNase H1 to cleave HBV RNA	REP 2139-Mg (ASO) + ARB-1467 (siRNA)	HBsAg decline	Safe and well tolerated; induces deeper and more durable HBsAg declines	Complementary action enhances antigen reduction	Awaiting large, stringent RCTs	[125]

CHB: Chronic hepatitis B; NAs: nucleos(t)ide analogs; HBV: hepatitis B virus; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; HBsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; cccDNA: covalently closed circular DNA; Peg-IFN: pegylated interferon; HBeAg: hepatitis B e antigen; IU/mL: international units per milliliter; siRNA: small interfering RNA; mRNA: messenger RNA; ASO: antisense oligonucleotide; RNase H1: ribonuclease H1; TLR: Toll-like receptor; CAMs: capsid assembly modulators; pgRNA: pregenomic RNA; NTCP: sodium taurocholate cotransporting polypeptide; HDV: hepatitis D virus; NAPs: nucleic-acid polymers; REP: replication-competent virus; ICIs: immune-checkpoint inhibitors; PD-1: programmed-death-1; PD-L1: PD-ligand-1; MVA: modified vaccinia virus ankara; HBIG: hepatitis B immunoglobulin; TCR-T: T-cell receptor-engineered T cell; CAR-T: chimeric antigen receptor T cell; ETV: entecavir; TDF: tenofovir disoproxil fumarate; RCTs: randomized controlled trials.

Immunological barriers

The liver is an immune-tolerant organ, providing a permissive environment for the persistence of HBV. HBV infection can suppress the interferon signaling pathway in hepatocytes, reducing the production of antiviral effector molecules^[26,32]. In early infection, HBV barely induces type I or III interferon responses or the expression of interferon-stimulated genes^[11,33]. Viral proteins further contribute to immune evasion through multiple mechanisms. For example, non-infectious HBsAg subviral particles can inhibit Toll-like receptor (TLR) 2/3/9 signaling in dendritic cells and monocytes/macrophages. This suppression reduces nuclear factor κ B (NF- κ B) activation and interferon (IFN)- α production. HBsAg can also block the NF- κ B activation and IFN- α production^[34]. Additionally, HBeAg can induce the expansion of intrahepatic regulatory T cells, fostering a local immunosuppressive microenvironment^[35].

In CHB, sustained high-level HBsAg induces profound immune tolerance, impairing both humoral and cellular antiviral immunity. The failure to generate anti-HBs (hepatitis B surface antibody) is strongly associated with the inability to achieve functional cure^[26,36,37]. Within the adaptive immune system, chronic HBV infection leads to profound exhaustion of virus-specific CD8⁺ T cells. These cells co-express multiple immune checkpoint molecules and have impaired effector functions^[38-40]. Single-cell sequencing studies have revealed that these T cells adopt a terminally exhausted phenotype in the liver microenvironment, which positively correlates with the transcriptional activity of cccDNA^[41]. Moreover, persistent high levels of HBsAg can induce thymic clonal deletion, significantly reducing the peripheral pool of HBsAg-specific CD8⁺ T cells^[42]. In B cells, HBsAg-specific B cells exhibit an atypical memory B cell phenotype,

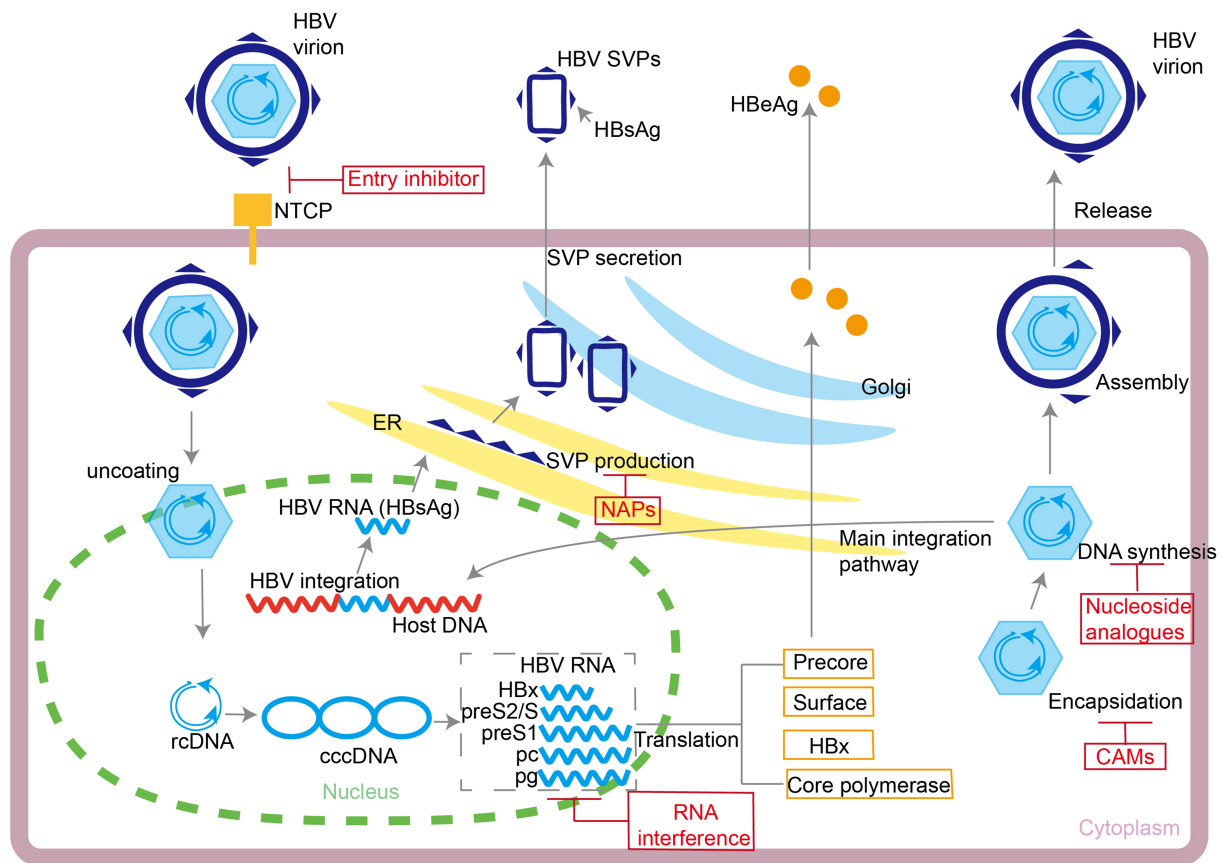


Figure 1. HBV life cycle. The HBV life cycle and the sites of action of entry inhibitors, NAs, RNAi therapeutic agents, CAMs, and NAPs are shown. HBV: Hepatitis B virus; NAs: nucleos(t)ide analog; RNAi: RNA interference; CAMs: capsid assembly modulators; NAPs: nucleic-acid polymers; NTCP: sodium taurocholate cotransporting polypeptide; SVPs: subviral particles; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; ER: endoplasmic reticulum; rcDNA: relaxed circular DNA; cccDNA: covalently closed circular DNA.

which impairs their differentiation into plasma cells and diminishes their capacity to secrete antibodies^[43-45]. This vicious cycle of viral persistence, sustained antigen burden, and immune exhaustion represents the major host barrier to achieving a functional cure^[11,45-48].

CURRENT TREATMENT STRATEGIES

Mechanism and clinical efficacy of NAs

NAs serve as the first-line antiviral agents and the foundation of CHB management, capable of maintaining viral suppression in over 95% of adherent patients^[49]. They competitively inhibit the HBV DNA polymerase and reverse transcriptase, thereby terminating viral DNA synthesis and replication^[49,50]. By suppressing HBV DNA levels, NAs reduce HBV-related HCC development, which constitutes their primary therapeutic mechanism^[51]. Current international guidelines recommend entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide as preferred first-line therapies for CHB, given their high and comparable efficacy. Combining ETV with other NAs may further enhance serum HBV DNA suppression^[51,52].

Despite effectively suppressing viral replication and improving liver histology, NAs fail to eliminate cccDNA, leading to frequent relapse after cessation^[6,8,53-57]. Most patients require lifelong NAs therapy, as virologic relapse is frequent following treatment cessation^[58]. Patients with drug-resistant virologic breakthrough have a higher risk of developing HCC than those with sustained virologic response^[59]. This

indicates that uncontrolled HBV replication persists in some patients despite NAs therapy. The relative efficacy of different NAs in reducing HCC risk remains debated^[51,60], while treatment adherence and duration are also critical factors. Therefore, NAs therapy is essentially a long-term, and often lifelong, viral suppression strategy. Its core clinical value lies in maintaining viral suppression to prevent or delay disease progression and to establish a stable baseline for future curative interventions.

Immunomodulatory effects of interferon therapy

Unlike NAs, interferons inhibit viral replication but also enhance host immune responses^[47,61]. Peg-IFN exhibits both direct antiviral and immunomodulatory activity, and can epigenetically suppress cccDNA transcription^[62-66]. Its longer half-life (80-90 h) and more stable pharmacokinetics compared with standard interferon have made Peg-IFN the preferred clinical formulation^[7,37,67,68]. Given these properties, recent research has focused on identifying which patients are most likely to benefit from Peg-IFN therapy. In a cohort study of 190 patients, Peg-IFN treatment significantly reduced liver-related mortality in CHB and compensated cirrhosis, with the best long-term outcomes observed in those achieving HBsAg loss^[69]. Peg-IFN induces HBeAg seroconversion and undetectable HBV DNA in approximately 30% of patients, with HBsAg clearance rates reaching up to 40% in inactive carriers^[70,71]. One clinical trial enrolled HBeAg-negative patients who had achieved suppressed viremia on NAs therapy^[37]. In patients with a low baseline HBsAg level (< 1,500 IU/mL), adding 48 weeks of Peg-IFN significantly increased the HBsAg clearance rate from 2% to 12%. Similarly, in treatment-naïve HBeAg-positive patients, a multicenter randomized trial study (NCT00877760) demonstrated that a sequential strategy of ETV followed by Peg-IFN achieved a higher HBeAg seroconversion rate (16%) than ETV monotherapy did (5%)^[72]. However, not all combinations are successful. One clinical trial (NCT01532843) found that TDF plus Peg-IFN induced a greater HBsAg decline but no significant difference in HBsAg clearance at 72 weeks post-treatment compared with TDF monotherapy^[73]. These findings underscore that baseline patient characteristics are key determinants of interferon efficacy.

Clinical evidence for combination strategies

To address the limitations of monotherapy, various combination strategies have been developed. These aim to integrate the potent viral suppression of NAs with the immune-mediated clearance induced by interferon. To overcome the limitations of monotherapy, various combination approaches have been explored to synergize the potent viral suppression of NAs with the immune-mediated clearance induced by interferon. The switching strategy entails a transition from NAs to Peg-IFN in patients who have achieved virologic suppression. In HBeAg-negative patients with baseline HBsAg levels below 100 IU/mL, this approach leads to HBsAg clearance rates of 8.5%-14% at week 48. However, the risk of virologic relapse and clinical hepatitis flare is high, especially in HBeAg-positive or advanced fibrosis patients^[73-75]. Severe hepatitis flares occur in 2%-4% of cases, limiting broad application^[76].

In contrast, the add-on strategy maintains NAs therapy while introducing Peg-IFN. In ETV-suppressed patients, the addition of Peg-IFN significantly increases HBeAg seroconversion and HBsAg decline. Among those with baseline HBsAg levels below 1,500 IU/mL, HBsAg clearance rates reach 20%^[77]. In HBeAg-positive patients, the add-on strategy achieves HBsAg clearance rates of approximately 7% of cases. Despite this similar efficacy, the add-on strategy substantially reduced risk of virologic relapse (9% vs. 26%) and hepatitis flare (1.2% vs. 6.8%) compared to the switch strategy, establishing it as the preferred approach in this population^[74,78-80]. *De novo* combination has not proven superior to sequential strategies and is not recommended by current guidelines^[81-86].

NOVEL CURATIVE STRATEGIES AND DRUG ADVANCES

RNA-interference-based therapeutics (siRNAs and ASOs)

RNA interference (RNAi), primarily comprising siRNAs and ASOs, suppresses the expression of all HBV proteins by targeting viral messenger RNA (mRNA). Preclinical studies demonstrate their capacity for simultaneous suppression of replication, antigen expression and cccDNA transcriptional activity^[87]. RNAi technology targets HBV mRNA and thus prevents synthesis of all viral proteins, including HBsAg, HBeAg and the polymerase^[88]. As a potent antiviral approach, RNAi reduces HBsAg by more than 1 log₁₀ IU/mL. However, monotherapy results in HBsAg loss in fewer than 10% of patients and is often followed by rebound^[16,89-92].

ASOs degrade target mRNA through the Ribonuclease H1 (RNase H1) pathway. The pivotal phase IIb B-Clear trial (NCT03365947) revealed that 28%-29% of participants achieved HBsAg below the limit of detection at end-of-treatment, with comparable rates in both NA-treated and NA-naïve cohorts. However, only 9%-10% of participants achieved the primary endpoint of sustained HBsAg/DNA loss 24 weeks post-treatment. This result indicated that approximately two-thirds of initial responders experienced virologic rebound^[93,94]. This rebound phenomenon underscores the fragility of ASO-induced functional cure without immune consolidation. Among patients with baseline HBsAg ≤ 3 log₁₀ IU/mL, the sustained rate improved to 16%-25%, yet relapse remained dominant^[95]. Bepirovirsen also possesses Toll-like receptor 8 (TLR8)-agonist activity that activates innate immunity and augments antiviral responses, providing an immunologic basis for functional cure in a subset of patients^[96]. siRNAs and ASOs are both RNA-interference agents, yet their mechanisms diverge. siRNAs load into RNA-induced silencing complex to cleave viral mRNA and block translation of all HBV proteins^[92,95], whereas ASOs form DNA-RNA heteroduplexes that recruit RNase H1 to degrade viral mRNA. Certain ASOs additionally stimulate immunity through TLR8^[87].

RNAi therapies, including siRNAs and ASOs, potently suppress the HBV transcriptome, thereby reducing viral antigen production and establishing a virological foundation for breaking immune tolerance. Nevertheless, whether using siRNAs or ASOs, monotherapy achieves HBsAg loss in fewer than ten percent of patients, and antigen rebound is frequent after treatment cessation^[90,96]. Future therapeutic strategies therefore pursue the combination of RNAi and immunomodulation. A priming phase employing siRNAs or ASOs to reduce HBsAg below 100 IU/mL is followed by Peg-IFN, therapeutic vaccines, or PD-1/PD-L1 inhibitors to reactivate host immunity and secure durable control, aiming for substantially higher rates of functional cure^[16,97].

Nucleocapsid inhibitors

Nucleocapsid inhibitors are among the most representative direct-acting antivirals. They can be classified into two categories based on their mechanism of action: (1) core protein allosteric modulators that induce the formation of aberrant capsids and (2) assembly inhibitors that prevent capsid formation entirely. They disrupt HBV capsid assembly and disassembly, exerting dual inhibitory effects at multiple critical steps of the viral life cycle^[98]. These agents act on two fronts: they prevent pre-genomic RNA from being packaged into capsids and block the subsequent reverse transcription step, curtailing the production of new virions. They also inhibit newly formed relaxed circular DNA from reaching the nucleus, thereby blocking replenishment of the cccDNA pool^[99]. Beyond direct interference with capsid formation, select capsid assembly modulators (CAMs) promote viral clearance through non-cytopathic mechanisms. Allosteric modulation of core protein activates cellular stress pathways including apoptosis, facilitating selective elimination of the viral reservoir^[98]. When combined with other lifecycle-targeting drugs, such as siRNAs or polymerase inhibitors, nucleocapsid inhibitors produce synergistic suppression^[99]. Pre-clinical studies show marked viral-load declines, yet monotherapy rarely achieves a functional cure^[100]. Multiple candidates have now entered clinical trials as key components of combination regimens^[27]. Pairing with RNAi therapeutics

or immunomodulators may yield more comprehensive antiviral activity^[45]. Next-generation capsid inhibitors lower HBsAg and can epigenetically silence cccDNA^[16,96,99].

Entry inhibitors and nucleic-acid polymers

Beyond strategies that directly target viral mRNA, agents that hit other lifecycle nodes - entry inhibitors and nucleic-acid polymers (NAPs) - offer additional avenues. The entry inhibitor Bulevirtide competitively blocks the sodium taurocholate cotransporting polypeptide (NTCP) receptor on hepatocytes, preventing HBV/hepatitis D virus (HDV) entry. Bulevirtide monotherapy has only a modest effect on HBsAg. However, in HBV/HDV coinfection, adding bulevirtide to Peg-IFN drives significant HBsAg decline, highlighting its value in combination^[101]. NAPs act later in the lifecycle. Their exact mechanism has not been fully elucidated; however, they appear to interfere with assembly and/or secretion of sub-viral surface-antigen particles, directly and robustly lowering circulating HBsAg. When combined with Peg-IFN and tenofovir in a triple regimen, clinical studies have reported HBsAg seroconversion rates of ~60%, illustrating the considerable promise of this class in curative combinations^[102].

Immunomodulators

Pattern-recognition-receptor agonists

Pattern-recognition-receptor (PRR) agonists reshape adaptive immunity by triggering innate signaling cascades such as TLR pathways. TLR-8 agonists, for example, reduce the frequency of terminally exhausted HBV-specific CD8⁺ T cells and promote the activation of myeloid cells^[103,104]. Intracellular sensors TLR-7 and TLR-8 recognize viral RNA motifs. This activates the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway. This triggers the production of type I IFN and pro-inflammatory cytokines, which not only initiate innate immune responses but also play a key role in bridging to adaptive immunity. In one clinical trial (NCT04225715), sequential administration after a PRR agonist enhanced immunological responses^[99]. However, clinical data indicate that monotherapy with Vesatolimod (TLR-7 agonist), Ruzotolimod (TLR-7 agonist), and Selgantolimod (TLR-8 agonist) yields only modest HBsAg reductions or low seroconversion rates^[105-107], indicating that innate-immune activation alone is insufficient to break deep tolerance under high antigen load. These agents are therefore considered adjuvant components within combination strategies.

Immune-checkpoint inhibitors

Immune-checkpoint inhibitors (ICIs) reverse T-cell exhaustion by targeting the PD-1/PD-L1 axis. The PD-1/PD-L1 pathway is central to the functional shutdown of HBV-specific T cells. Blocking this inhibitory signal reactivates antiviral T-cell function. Preclinical evidence suggests that combining ICIs with antioxidants or phenolic compounds can further restore the activity of HBV-specific CD8⁺ T-cell *in vitro*^[104]. Early clinical data with PD-1/PD-L1 inhibitors alone have demonstrated potential efficacy. In a study of envafolelimab (anti-PD-L1), 21.1% of patients (baseline HBsAg < 100 IU/mL) achieved HBsAg seroclearance, while an additional 21.0% achieved a significant HBsAg reduction of > 1 log₁₀ IU/mL without clearance at the 24-week endpoint^[108]. Another clinical trial of nivolumab (anti-PD-1) in HBeAg-negative, virally-suppressed CHB patients demonstrated acceptable safety, with 11 out of 12 subjects showing HBsAg reductions, including one instance of HBsAg loss accompanied by an alanine aminotransferase (ALT) flare^[109]. By preventing PD-1 on T cells from engaging PD-L1 on antigen-presenting cells or hepatocytes, these inhibitors release the inhibitory signal and revive cytotoxicity. HBV-specific CD8⁺ T cells in chronic infection are terminally exhausted and exhibit high PD-1 expression. PD-1 inhibitors partially recover their interferon-gamma (IFN- γ) secretion and cytolytic capacity, especially when antigen load is first lowered by siRNAs^[12,104,109]. These findings provide preliminary evidence that ICIs can contribute to functional cure, particularly in patients with low antigen levels.

Therapeutic and prophylactic vaccines

Therapeutic vaccines are designed to break tolerance and elicit HBV-specific T- and B-cell responses. Next-generation candidates incorporate multiple viral antigens to broaden immune recognition. For example, a virus-like particle-based therapeutic vaccine (BR11-179) contains HBsAg, Pre S1 antigen (Pre-S1), and Pre S2 antigen (Pre-S2), while a therapeutic vaccination (VTP-300) uses chimpanzee adenoviral vector (ChAdOx1)/modified vaccinia Ankara (MVA) vectors to deliver HBsAg, polymerase, and core antigens. Unlike prophylactic vaccines, they are designed to reset immune memory and are usually combined with ICIs or RNAi drugs^[109,110]. When HBsAg has first been lowered, the combination of therapeutic vaccine plus ICI produces a significantly greater decline in HBsAg levels^[111].

In the absence of a curative regimen, prophylactic vaccination remains the most effective intervention to reduce global disease burden, mother-to-child transmission, and HCC. Four decades of randomized controlled trials (RCTs) and real-world data demonstrate that recombinant HBV vaccines are highly efficacious and safe. The first RCT involved HBsAg+/HBeAg+ mothers, who were randomized to receive either a plasma-derived hepatitis B vaccine or a placebo^[112]. The trial showed a reduction in the chronic carrier rate: 6% in the vaccine group *vs.* 88% in the placebo group, corresponding to a protective efficacy of 94%. A subsequent U.S. Centers for Disease Control and Prevention (CDC) multi-center RCT (NCT04465890) showed that a yeast-derived vaccine lowered the carrier rate to 4.8%, equivalent to plasma vaccine but with no difference in adverse events. This finding paved the way for recombinant vaccines^[112]. Until curative therapies become widely available, expanding prophylactic vaccine coverage remains the most cost-effective and fastest route to achieving the WHO 2030 target of a 90% reduction in incident HBV infections.

Monoclonal antibodies and T-cell engineering

Beyond the critical goal of lowering antigen load, a parallel strategy focuses on reconstituting HBV-specific immunity. A prime example is an antibody (VIR-3434), a fragment crystallizable (Fc)-engineered human monoclonal antibody. It potently neutralizes all HBV particles and, via its optimized Fc, enhances antigen presentation to dendritic cells, potentially activating dormant HBV-specific T cells. Single doses produce rapid HBsAg drops ($\sim 2 \log_{10}$ IU/mL)^[113]. The therapeutic effect is often transient, necessitating use within combination regimens.

T-cell engineering genetically modifies T cells to target HBV-infected hepatocytes. Autologous or allogeneic T cells are engineered *ex vivo* with HBV-specific T-cell receptors (TCR-Ts) or chimeric antigen receptors (CAR-Ts), granting precise cytotoxicity against infected hepatocytes. Unlike CAR-Ts that recognize only surface antigens, TCR-Ts can recognize both intracellular HBV-derived peptides presented via major histocompatibility complex class I molecules, offering a broader antigen spectrum and lower detection threshold. In HBV-related HCC, TCR-T therapy has demonstrated objective response rates of 17%-64% and a median overall survival of 33.5 months, significantly surpassing sorafenib (10.7 months)^[114]. However, current research in TCR-T and CAR-T therapies for HBV remains in preclinical and early-phase trials. Major obstacles include ensuring safety and achieving durable persistence *in vivo*. Despite these hurdles, engineered T cells offer a promising strategy for viral reservoir eradication^[115].

Novel adjuvant systems and small-molecule HBsAg secretion inhibitors

Next-generation adjuvants focus on enhancing antigen presentation and cytokine production. With natural killer T cells now recognized as key mediators of vaccine responsiveness, adjuvant design should engage both innate and adaptive immunity^[116]. Many therapeutic HBV vaccines are protein-based and require adjuvants. While the mechanism of alum remains incompletely defined, it is believed to involve the

induction of local inflammation and dendritic cell activation^[117]. New approaches employ TLR agonists as pathogen-mimetic motifs, using whole yeast as a natural adjuvant. This strategy requires no external adjuvant, likely because the recombinant hepatitis B core antigen (HBcAg) carries nucleic acids that act as TLR-3 agonists^[118]. Nano-delivery systems, such as polysaccharide emulsions, also provide potent immune stimulation^[119,120]. Combinations of TLR agonists with nano-carriers are now being evaluated to optimize the spatiotemporal orchestration of immune activation.

A new class of HBsAg inhibitors has emerged with a different mechanism. a hepatitis B virus expression inhibitor GST-HG131 is a small-molecule di-hydroquinolizinone that functions as an HBsAg expression inhibitor through a host-targeted mechanism different from siRNAs or ASOs^[121]. Rather than employing nucleic acids to directly bind HBV transcripts via sequence-specific hybridization, GST-HG131 selectively inhibits the host poly(A) polymerases domain containing 5 and 7. This inhibition prevents mRNA maturation, accelerating its degradation and consequently reducing HBsAg production.

CONVERGENCE OF NOVEL TECHNOLOGIES FOR HBV CURE

The functional cure of CHB necessitates combination therapies that simultaneously target viral replication and host immunity. Current evidence supports several rational combination strategies. Combining antivirals with complementary mechanisms can produce synergistic effects. siRNAs and ASOs both suppress viral transcripts but employ distinct pathways. Early-phase trials (NCT02233075, NCT02876419) indicate that this combination is feasible and can produce profound HBsAg reduction^[122]. The combination of NAs and ASOs exerts a synergistic effect through concurrent suppression of viral replication and antigen production. This dual action may disrupt the foundation of immune tolerance. A phase-II RCT (NCT04676724) evaluating bepirovirsen added to ongoing NAs therapy demonstrated significant HBsAg decline or loss in a subset of patients with acceptable safety^[97]. This evidence supports ASO-NAs combinations and informs the design of phase-III trials. Another sequential strategy of RNAi followed by immunomodulation has demonstrated strong synergy. This approach first employs siRNAs to deplete viral antigens, thereby alleviating immune suppression. Subsequently, Peg-IFN is administered to exert its dual antiviral and immunostimulatory effects. This approach has achieved HBsAg loss rates of 15%-23% in several clinical trials (NCT04778904)^[123,124]. Similarly, sequential therapy with the ASOs bepirovirsen followed by Peg-IFN has been shown to reduce post-treatment relapse and consolidate HBsAg loss, thereby improving durability^[125].

The combination of siRNAs and therapeutic vaccines represents a strategy of first reducing antigen load and then boosting immune responses. In this approach, siRNA agents first drive HBsAg to minimal levels. Subsequently, a vectored vaccine is administered to mimic acute-resolving infection^[126]. This sequence facilitates the expansion of T and B cells, enabling targeted clearance of residual infected hepatocytes. Combining siRNAs with innate immune agonists, such as the TLR-7 agonist, represents another strategy. This approach simultaneously silences viral genes and activates plasmacytoid dendritic cells to create an interferon-rich microenvironment, jointly breaking immune tolerance^[124]. The ability of RNAi-immunomodulator regimens to achieve rapid, deep HBsAg declines, sustain treatment effects, and curb viral rebound has prompted their investigation in multiple active trials (NCT04676724)^[97,127,128].

However, emerging evidence underscores that not all combination strategies yield additive effects, and safety concerns warrant careful consideration. Certain combinations, such as pairing siRNAs with CAMs, demonstrated no additive benefit over monotherapy in reducing HBsAg^[129]. These findings underscore that the novel therapeutic regimens must be carefully balanced based on mechanistic synergy. Management measures for hepatitis flares or significant adverse events should be established to ensure data validity. If the

target population is extended to cirrhosis patients, the drug's safety and overall benefit-risk in decompensated cirrhosis populations should be evaluated. A key safety concern for anti-HBV drugs is recurrent ALT elevation, which can be classified into three main types. The first type is mediated by the host immune response and is accompanied by decreases in HBV DNA and serological marker levels. The second type is driven by enhanced viral activity. The third type results from adverse drug reactions. Multi-target combination therapy for CHB has emerged as a consensus approach; however, emerging evidence challenges the assumption that all combinations are synergistic.

FUTURE STRATEGIES TOWARD FUNCTIONAL CURE

Despite progress in reducing HBsAg, true functional cure of HBV faces two obstacles: persistence of cccDNA and deep immune tolerance. Future therapeutic strategies must aim to silence or eliminate the cccDNA reservoir and systematically restore HBV-specific immunity. Although RNAi can significantly reduce viral antigens, it does not directly target cccDNA. Therefore, current research is actively exploring combination therapies that couple RNAi with epigenetic silencers or gene editors^[130-133].

Personalized immunotherapy and timing will be critical. Evidence indicates that PD-1 inhibitors, TLR agonists, and therapeutic vaccines are most effective under low antigen load. This underscores the principle of reducing antigen to elevate immunity^[99,112,114]. Yet optimal dose, sequence and duration remain undefined. Single-cell sequencing, immune-repertoire profiling and systems-immunology models are needed to build predictive algorithms for precision intervention.

As curative strategies evolve, tailoring therapeutic regimens to special populations will become clinical practice. In specific populations, such as those with low-level viraemia, inactive carriers, or patients in the grey zone, Peg-IFN therapy can still achieve HBsAg loss^[22,134-139]. Furthermore, initiating treatment in children and adolescents maximizes the probability of a functional cure^[140-142]. Those with metabolic dysfunction-associated steatosis liver disease require simultaneous metabolic control to prevent progression^[143-150]. In contrast, cirrhotic or HCC patients should avoid Peg-IFN. Their management should emphasize long-term NAs maintenance and intensive surveillance^[2,151-153]. Additionally, Peg-IFN-based regimens may be preferable in patients with renal impairment. In cases of HBV/hepatitis C virus (HCV) or HBV/HDV coinfection, management should prioritize HCV eradication while maintaining effective suppression^[20,154-163].

Safety and global access pose major challenges. Early agents have been discontinued for toxicity^[164], underscoring the need for rigorous long-term safety databases. Furthermore, delivering high-cost innovations to low- and middle-income countries is essential if WHO's 2030 elimination target is to be met^[165,166]. In summary, the era of functional cure has begun; however, actual cure will require multidisciplinary convergence of virology, immunology, gene engineering and public-health policy. With continued innovation and optimization, CHB is set to be transformed from controllable to curable in the coming decade.

CONCLUSION

Functional cure of CHB remains an unmet clinical goal. NAs suppress viral replication but require lifelong therapy. Even after treatment cessation, HBsAg loss occurs in only 2%-11% of patients. The functional cure rate with interferon therapy is highly variable across populations, ranging from 2% to over 40%. RNAi potently lowers HBsAg, yet durable responses are achieved in fewer than 10% of patients. These limitations indicate that antigen reduction alone cannot reverse profound immune exhaustion. Sequential combination strategies, using RNAi followed by immunotherapy, have achieved 15%-30% functional cure rates. Future

progress depends on precision immunoprofiling, cccDNA-targeting gene editing, and multi-target drug development. However, approximately 75% of infected individuals live in low-income regions, making the delivery of affordable cures essential to meet WHO elimination targets.

DECLARATIONS

Authors' contributions

The work presented here was conducted collaboratively by all authors.

Developed the concept and designed the review: Shi YW, Pu R, Ding YB

Independently screened the full texts of eligible studies to confirm compliance with inclusion criteria, assess study quality, and extract data: Shi YW, Pu R, Ding YB, Liu WB, Li ZS, Zhao JY, Chen YF, Cao GW

Provided overall supervision and revision of the manuscript: Cao GW

All authors contributed to the manuscript drafting and revision, and approved the final version for submission.

Availability of data and materials

Not applicable.

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Conflicts of interest

Cao GW is the Editor-in-Chief of *Hepatoma Research*, and Liu WB is a member of the Junior Editorial Board of *Hepatoma Research*. Cao GW and Liu WB were not involved in any stage of the editorial process, including reviewer selection, manuscript handling, or decision-making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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