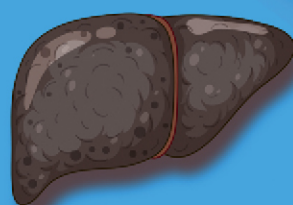
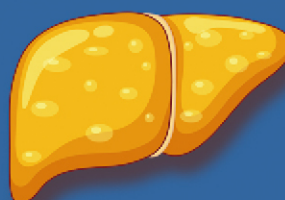
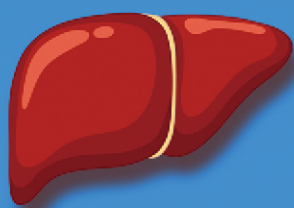


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Update on the treatment navigation for functional cure of chronic hepatitis B: Expert consensus 2.0

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As new evidence emerges, treatment strategies toward the functional cure of chronic hepatitis B are evolving. In 2019, a panel of national hepatologists published a Consensus Statement on the functional cure of chronic hepatitis B. Currently, an international group of hepatologists has been assembled to evaluate research since the publication of the original consensus, and to collaboratively develop the updated statements. The 2.0 Consensus was aimed to update the original consensus with the latest available studies, and provide a comprehensive overview of the current relevant scientific literatures regarding functional cure of hepatitis B, with a particular focus on issues that are not yet fully clarified. These cover the definition of functional cure of hepatitis B, its mechanisms and barriers, the effective strategies and treatment roadmap to achieve this endpoint, in particular new surrogate biomarkers used to measure efficacy or to predict response, and the appropriate approach to pursuing a functional cure in special populations, the development of emerging antivirals and immunomodulators with potential for curing hepatitis B. The statements are primarily intended to offer international guidance for clinicians in their practice to enhance the functional cure rate of chronic hepatitis B. (*Clin Mol Hepatol* 2025;31(Suppl):S134-S164)

Keywords: Chronic hepatitis B; HBsAg; Consensus; Antiviral Agents; Immunologic Factors

INTRODUCTION

Owing to the substantial global progress towards hepatitis B virus (HBV) elimination goals, the worldwide prevalence of chronic HBV infection declined over time,¹ particularly in children younger than 5 years. However, chronic hepatitis B (CHB) and its complications, cirrhosis and hepatocellular carcinoma (HCC), remain a significant public health threat globally, with 254 million people chronically infected and 1.1 million HBV-related deaths worldwide as of the latest estimates.² Currently, the landscape for chronic HBV therapy is evolving. The primary focus of HBV treatment is to achieve sustained off-treatment clearance of hepatitis B surface antigen (HBsAg), a milestone generally signifying a functional cure of HBV infection. Functional cure is recognized as the clinically optimal treatment goal for CHB due to its association with improved clinical outcomes, and is the only practically achievable endpoint that allows for the discontinuation of treatment. Research to achieve a functional cure for HBV infection includes exploring combinations of existing or new agents that target different steps of the viral life cycle or enhance the host's antiviral immune response. Moreover, standardized and

validated assays for novel virologic and immunologic markers toward better elucidating the mechanisms of action, defining HBV cure, measuring efficacy or predicting response are approved or in development. These studies provide the evidence for updating recommendations. This current version updates previous guidance³ after rigorous review of the latest available evidence.

DEFINITION OF FUNCTIONAL CURE AND ITS KEY CHALLENGES

Clinical significance of functional cure for chronic hepatitis B

The clinical significance of a “functional cure” for CHB is immense, given the long-term adverse outcomes of chronic HBV infection. Chronic HBV infection is a major cause of liver cirrhosis and HCC worldwide. Successful treatment can lead to regression of liver fibrosis and even partial reversal of cirrhosis, especially if the intervention occurs in the early stage of liver disease. A functional cure would prevent the disease progression of the advanced stages of

Abbreviations:

ASO, antisense oligonucleotide; atMB, atypical memory B; cccDNA, covalently-closed-circular DNA; CHB, chronic hepatitis B; CpAM, core protein allosteric modulator; DAA, directly acting antivirals; EOT, end of treatment; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; NA, nucleos(t)ide analogue; NAP, nucleic acid polymer; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; Peg-IFN, pegylated interferon; pgRNA, pregenomic RNA; rcDNA, relaxed circular DNA; siRNA, small interfering RNA; TDF, Tenofovir disoproxil fumarate; TLRs, Toll-like receptors

liver disease,⁴ thereby reducing the risk of liver-related morbidity and mortality and improving long-term outcomes. CHB patients require long-term management, including regular monitoring, medication, and potentially liver transplantation in advanced cases. A functional cure would thus substantially reduce the economic burden on healthcare systems and patients by eliminating the need for ongoing treatment and hospitalization.⁵ HBV infection is particularly prevalent in regions with inadequate access to healthcare and vaccination programs. Achieving a functional cure would contribute to the global effort to eliminate CHB as a public health threat by reducing the pool of infected individuals and preventing new infections. In addition, a functional cure could help reduce social stigma and promote greater acceptance and inclusion of individuals living with HBV. To sum up, the clinical significance of functional cure for CHB includes profound clinical, social, and economic benefits, offering hope for millions of individuals affected by this virus.

Definition of functional cure for chronic hepatitis B and endpoints of treatment

Current anti-HBV therapy can improve serologic, virologic, and histologic endpoints but is not considered curative. HBV cure is categorized as complete sterilizing cure, functional cure, and partial cure. The sterilizing cure, representing the ultimate therapeutic goal for CHB, is characterized by the complete elimination of both episomal covalently-closed-circular DNA (cccDNA) and integrated viral DNA fragments. However, the eradication of HBV remains elusive due to the lack of therapies that effectively target the cccDNA. Functional cure or clinical cure of CHB is defined as sustained HBsAg loss and undetectable serum HBV DNA, with or without hepatitis B surface antibody (HBsAb) seroconversion 24 weeks after the completion of treatment. Although cccDNA may still be present, it is not transcriptionally active.⁶ Guidance reported by EASL-AASLD HBV Treatment Endpoints Conference Faculty has recommended sustained HBsAg loss in addition to HBV DNA less than the lower limit of quantitation 24 weeks off-treatment as the preferred primary endpoint for phase III trials of chronic HBV treatment.^{7,8} The advancements in understanding of HBV molecular biology and antiviral immune responses have shed light on novel approaches and combinations to

treat CHB. Functional cure of CHB is becoming a realistic and feasible therapeutic goal with the treatment concept of integrating the suppression of HBV replication and viral protein production, with restoration of the host immune response to HBV. Partial cure of CHB, defined as off-treatment sustained hepatitis B e antigen (HBeAg) negative and undetectable HBV DNA with HBsAg positive at low levels (HBsAg level <100 IU/mL), is considered an acceptable intermediate endpoint on the pathway to a functional cure.

Consensus statement:

1. The optimal and achievable goal and primary endpoint for anti-HBV treatment is functional cure, which is defined as sustained serum HBsAg loss and undetectable serum HBV DNA, with or without HBsAb seroconversion 24 weeks after the completion of antiviral therapy.

Obstacles to curing hepatitis B from the virological and immunologic perspectives

Chronic HBV infection results from a complex interplay between viruses and the host immunity. HBV genome forms an episomal mini-chromosome, the so-called cccDNA in the nucleus of infected hepatocytes. cccDNA serves as the reservoir of chronic HBV infection and can be established by both de novo infection and intracellular replenishment of relaxed circular DNA (rcDNA). The half-life of cccDNA varies from a few weeks to several years depending on multiple factors including the micro-environment of the infected hepatocytes. Accumulating evidence indicates low-level ongoing HBV infection in the liver under nucleos(t)ide analogue (NA) treatment. HBV DNA, particularly the S fragments, have been observed to integrate into the host genome.⁹ The integration occurs early in infection and is involved in HBV pathogenesis depending on the integration site on host cell genome. Notably, a significant proportion of serum HBsAg is now known to be generated from the integrated HBV S gene fragment in CHB patients, particularly in HBeAg negative individuals. Elimination of HBV cccDNA and integrated HBV DNA fragment would lead to complete HBV cure, but it remains challenging and is an elusive therapeutic goal.^{10,11}

The liver is a tolerogenic organ where persistent viral infection can easily establish. HBV does not induce innate

immune-related genes during entry and expansion, suggesting it is a stealth virus.¹² Consistently, HBV core proteins cannot activate Toll-like receptors (TLRs).¹³ Although there are a large amount of HBsAg empty particles in the blood of CHB patients,¹⁴ these circulating HBsAg do not stimulate peripheral blood mononuclear cells to express antiviral cytokines.¹⁵ HBsAg is thought to suppress host immune responses. It can promote autophagic degradation of intrahepatic TAK1 and TAB2, resulting in inhibition of NF- κ B signaling.¹⁶ HBsAg negatively regulates downstream signaling of TLR2, TLR3 and TLR9 in dendritic cells, monocytes, and macrophages.¹⁷⁻²⁰ Moreover, weakened natural killer cell function is caused by HBsAg in CHB patients via down-regulation of stimulator of IFN genes.^{21,22}

The liver is regarded as a “graveyard” for T cells, as it represents a specific site for T cell dysfunction and exhaustion.²³ HBV core or polymerase-specific CD8⁺ T cells are classically maintaining exhausted phenotype.²⁴ Mechanistically, hepatocyte-primed T cells differentiate into exhausted cells rather than effector cells.²⁵ Of note, the frequency of HBsAg-specific CD8⁺ T cells is decreased in CHB patients after they reach adulthood.²⁶ Correspondingly, HBsAg-induced monocytic myeloid-derived suppressor cells were found to mediate thymic clonal deletion of these T cells.²⁷ As thymic tolerance is established in children with vigorous thymus, this might be a potential mechanism for age-related outcome of HBV exposure. Peripheral B cell subsets showed low expression of TLR9 in CHB patients.²⁸ In these patients, HBsAg-specific B cells were demonstrated as an atypical memory B (atMB) phenotype, which lost the capability to differentiate into plasma cells and to secrete antibodies.^{29,30} In these atMB cells, CD138 and B cell maturation antigen that are crucial for plasma cell survival are not detected, but B-cell receptor signaling, endoplasmic reticulum pressure and apoptotic pathways are significantly up-regulated.³¹

Immune exhaustion, a phenomenon commonly observed in chronic HBV infection, is regarded as a significant host barrier to achieving a functional cure of CHB. This phenotype of exhaustion, which arises from persistent antigen exposure, is marked by the expression of checkpoint receptors and a progressive loss of effector functions.³² Understanding the mechanisms underlying immune exhaustion in CHB is crucial for developing novel immunotherapeutic strategies.³³

Current settings of anti-HBV treatment and potential pathways to achieving HBV cure

Currently, antiviral regimen includes two classes of drugs: immunomodulators, such as pegylated interferon- α (Peg-IFN), and directly acting antivirals (DAA), such as NAs.³⁴⁻³⁷ Although potent NA can achieve virologic response during therapy, the response is generally not sustained off-treatment. Due to the tenacity of cccDNA and absence of direct effect of NA on cccDNA, CHB patients face a high risk of relapse after NA withdrawal, which in turn may deteriorate to hepatic decompensation or even catastrophic life-threatening events without close monitoring and timely retreatment. Therefore, lifelong treatment may be required to maintain viral suppression in the majority of patients, particularly in HBeAg-negative patients. However, there are concerns with indefinite NA therapy, for example, financial burden and medication adherence. Peg-IFN exerts dual effects, through promoting the activity of host immune cells and inducing the production of interferon-stimulated genes, which encode direct antiviral effector proteins.³⁸ Furthermore, Peg-IFN can also inhibit HBV transcription and reduce the production of viral antigens through enhancing degradation of HBV pregenomic RNA (pgRNA) and core particles or by modifying epigenetic regulation of cccDNA.^{39,40} The finite duration of Peg-IFN treatment can result in modest reduction in serum HBsAg concentration and durable off-treatment response, however, only in a proportion of patients.

Effective and coordinated innate and adaptive branches of immunity is indispensable for the control of HBV infection,⁴¹ therefore, a promising target for therapeutic strategies is immune modulation to restore dysfunctional HBV-specific immunity. Persistent exposure to high HBV viremia and antigen burden creates a tolerogenic intrahepatic and extrahepatic environment in CHB.⁴² The duration of HBsAg exposure associates with the level of anti-HBV immune response, strategies to restore anti-HBV immune responses should consider younger patients.²⁶ Therapeutic reduction of viral load and antigenemia by effective DAA may provide a window of opportunity to break the immune tolerance and mobilize the immune response against HBV, subsequently, the administration of immunomodulators restores the exhausted immune responses. The suppression of viral load induced by NAs may restore the impaired adaptive im-

immune response, and leverage the immunomodulatory effects of Peg-IFN.⁴³⁻⁴⁶ This mechanism provides a rationale for combining Peg-IFN and NA to generate additive or synergistic effects, potentially leading to a functional cure of hepatitis B.^{43,47,48}

Consensus statement:

2. The major challenges of HBV cure include the lack of available drugs to eliminate cccDNA and integrated HBV DNA, and host's inability to restore the exhaustion of HBV-specific immunity.

3. The mechanistic rationale for combining direct-acting antivirals (e.g., NAs) and immunomodulators (e.g., Peg-IFN) is that these two classes of drugs have differential antiviral mechanisms, and that viral suppression mediated by NAs subsequently enhances the immunologic response to Peg-IFN.

TREATMENT STRATEGIES AND ROADMAP FOR FUNCTIONAL CURE OF CHB

Combining Peg-IFN and oral antiviral therapy

As aforementioned, a combination therapy with oral NAs and Peg-IFN is an interesting modality to accelerate functional cure. Peg-IFN can enhance the immune system in CHB patients and reduce HBV replication from NAs effects, consequently eliminating the cccDNA from liver. There are several treatment strategies of a combination therapy including “de novo strategy”, “add-on combination” or “switch-to therapy”.

As shown in Table 1, the “de novo” combination of Peg-IFN and low potency NAs in naïve CHB patients had no additional advantages over Peg-IFN monotherapy. Interestingly, a combination of Peg-IFN with potent NA such as tenofovir demonstrated a better response compared with Peg-IFN monotherapy.⁴⁹ Moreover, patients with genotype A achieved the highest rates of HBsAg loss with this combination therapy. However, current guidelines do not recommend the “de novo” combination therapy for CHB patients.

Most of studies of “add-on” strategy, as shown in Table 1,⁵⁰⁻⁶² provide the benefit of a declination of HBsAg level. However, the HBsAg clearance rate is still low in a short-term fol-

low-up. The “switch-to” strategy, also highlighted in Table 1, had benefits in finite treatment duration and may potentiate HBsAg loss. However, favorable parameters in the candidates are the pre-requisite, this includes low baseline HBsAg level and low on-treatment HBsAg level. The major drawback is the concern of HBV flare after treatment cessation, particular in those with advanced fibrosis or cirrhosis.

Meta-analyses indicated that combination therapy with Peg-IFN and NA could significantly improve the probability of HBsAg loss compared to NA monotherapy.^{63,64} However, one showed that combination therapy failed to induce higher HBsAg loss rates compared to IFN monotherapy, and the other suggested that sequential strategy was more superior than de novo strategy in achieving HBsAg loss. A prospective randomized controlled trial in HBeAg-positive naïve patients showed that compared with tenofovir disoproxil fumarate (TDF) alone and de novo combination, the addition of Peg-IFN in TDF-treated group might be an effective strategy for HBsAg loss.⁶⁵ This finding supports the clinical benefit of sequential administration of NA followed by Peg-IFN in CHB patients.

Efforts have also been made to determine the best approach using Peg-IFN for those already on stable NA. A previous study in HBeAg-negative NA-treated patients suggested that the “switch to” strategy might be superior to the “add-on” strategy in reducing HBsAg levels. NA cessation in the “switch-to” strategy might activate the host immune response, which could help boost the effects of Peg-IFN.⁶⁶ A meta-analysis showed that the pooled estimates of HBsAg loss rate for “switch-to” strategy were significantly higher than that of “add-on” strategy.⁶⁴ SWAP trial suggests that add-on Peg-IFN regimen is preferred to switch-to due to the improved safety and similar efficacy. Both strategies achieved comparable HBsAg loss in the HBeAg-negative participants, but switch arm demonstrated a higher risk of viral reactivation and clinical relapse (13.6% overall, 27% in HBeAg-positive), making this strategy inadvisable for HBeAg positive patients.⁶⁷ A recent randomized controlled trial of HBeAg-positive entecavir (ETV)-treated patients with HBsAg <3,000 IU/mL, HBeAg <200 signal-to-cutoff ratio (S/CO) reported that switch-to or add-on Peg-IFN led to comparable HBsAg reduction at week 48.⁶⁸ In a study investigating factors associated with virological relapse after switching to Peg-IFN in ETV-treated patients, HBeAg positivity rate was significantly higher in patients with viro-

Table 1. Combination strategies with Peg-IFN and NA

	Regimen	Study design	Participants	HBsAg response
De novo strategy				
HBsAg-positive CHB patients	Peg-IFN-2a alone (n=271), Peg-IFN-2a plus lamivudine (n=271), lamivudine alone (n=272) for 48 weeks	Multicenter, double-blind, randomised controlled trial ⁵⁰	814 patients with HBsAg-positive chronic hepatitis B, mostly from Asian (87%)	HBsAg seroconversion after 24 weeks of follow-up: Peg-IFN-2a alone: 2.95% Peg-IFN-2a in combination with lamivudine: 2.95% lamivudine monotherapy: 0.00% ($P=0.004$ for both comparisons with lamivudine) HBsAg loss at the end of treatment (week 52): combination therapy: 7% monotherapy group: 5% (comparison was not significant)
	Peg-IFN-2b plus lamivudine (n=130), Peg-IFN-2b monotherapy (n=136), for 52 weeks	Multicenter, double-blind, randomised controlled trial ⁵¹	307 HBsAg-positive patients with chronic hepatitis B	HBsAg loss after 24 weeks of follow-up, combination therapy: 2.79% Peg-IFN-2a alone: 3.95% lamivudine alone: 0.00% (both comparisons with lamivudine were significant)
	Peg-IFN-2a alone (n=177), Peg-IFN-2a plus lamivudine (n=179), lamivudine alone (n=181) for 48 weeks	Multicenter, double-blind, randomised controlled trial ⁵²	537 HBsAg-negative chronic hepatitis B	HBsAg loss at week 72, group A: 9.1% group B: 2.8% group C: 0.0% group D: 2.8% group A vs. group B ($P=0.002$), or group C ($P<0.001$) or group D ($P=0.003$) group B vs. group C ($P=0.466$) or group D ($P=0.883$) In the genotype A, CHB patients had the highest HBsAg loss and trended toward to HBsAg-positive patients. A post hoc analysis study at week 120 follow-up ⁵³ HBsAg loss at week 120: group A: 10.4% group B: 3.5% group C (120-week tenofovir): 0.0% group D: 3.5% group A vs. group C ($P<0.001$) or group D ($P=0.002$)
HBsAg-negative CHB patients	Peg-IFN-2b plus lamivudine (n=130), Peg-IFN-2b monotherapy (n=136), for 52 weeks	Multicenter, double-blind, randomised controlled trial ⁵¹	307 HBsAg-positive patients with chronic hepatitis B	HBsAg loss at week 72: Peg-IFN plus TDF: 11.5% Peg-IFN: 5.7% TDF: 0.0% Peg-IFN plus TDF vs. Peg-IFN ($P=0.143$) Peg-IFN plus TDF or Peg-IFN alone vs. TDF ($P=0.000$ or $P=0.010$) A reduction of HBsAg level $>1.5 \log_{10}$ IU/mL at week 24 from baseline can predict the 72-week HBsAg loss with an AUROC curve of 0.846
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Both HBsAg-positive and negative CHB patients	Tenofovir disoproxil fumarate (TDF) plus Peg-IFN for 48 weeks (group A) (n=186) TDF plus Peg-IFN for 16 weeks followed by TDF for 32 weeks (group B) (n=184) TDF for 120 weeks (group C) (n=185) Peg-IFN for 48 weeks (group D) (n=185)	Multinational, open-label, randomized, controlled trial ⁴⁹	740 HBsAg-positive or -negative patients with chronic hepatitis B, with three-quarter Asian patients	HBsAg loss at week 72, group A: 9.1% group B: 2.8% group C: 0.0% group D: 2.8% group A vs. group B ($P=0.002$), or group C ($P<0.001$) or group D ($P=0.003$) group B vs. group C ($P=0.466$) or group D ($P=0.883$) In the genotype A, CHB patients had the highest HBsAg loss and trended toward to HBsAg-positive patients. A post hoc analysis study at week 120 follow-up ⁵³ HBsAg loss at week 120: group A: 10.4% group B: 3.5% group C (120-week tenofovir): 0.0% group D: 3.5% group A vs. group C ($P<0.001$) or group D ($P=0.002$)
HBsAg-negative CHB patients	Peg-IFN plus TDF for 48 weeks (n=104) Peg-IFN alone for 48 weeks (n=106) TDF alone for 144 weeks (n=120)	Real-world clinical cohort of Chinese patients with CHB ⁵⁴	330 patients with CHB	HBsAg loss at week 72: Peg-IFN plus TDF: 11.5% Peg-IFN: 5.7% TDF: 0.0% Peg-IFN plus TDF vs. Peg-IFN ($P=0.143$) Peg-IFN plus TDF or Peg-IFN alone vs. TDF ($P=0.000$ or $P=0.010$) A reduction of HBsAg level $>1.5 \log_{10}$ IU/mL at week 24 from baseline can predict the 72-week HBsAg loss with an AUROC curve of 0.846
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Table 1. Continued

Regimen	Study design	Participants	HBsAg response
Add-on strategy			
Early “add-on” Peg-IFN to NA (Defined as starting NA before Peg-IFN less than 1 year)			
HBeAg-positive CHB patients	Open-label, multicenter, randomized controlled trial (ARES study) ⁵⁵	175 HBeAg-positive CHB patients	During randomized therapy from week 24 to 48, decline in HBsAg: add-on arm: $-0.3 \log \text{ IU/mL}$ Entecavir monotherapy: $-0.01 \log \text{ IU/mL}$ ($P<0.001$) During long-term follow-up, ⁵⁵ add-on therapy group had a reduction of HBsAg level more than 1 log significantly higher than entecavir group (59% vs. 28%, $P=0.02$)
Late “add-on” Peg-IFN to NA (Defined as starting NA before Peg-IFN more than 1 year)			
HBeAg-positive CHB patients	Open-label, multicenter, randomized controlled trial (PEGON) ⁵⁶	77 HBeAg-positive patients with compensated liver disease who were treated with entecavir/tenofovir for >12 months and had an HBV DNA load of <2,000 IU/mL	A decline in the HBsAg level of $>0.5 \log \text{ IU/mL}$ at week 72: Peg-IFN add-on group: 26% NA monotherapy: 8% ($P=0.038$)
HBeAg-negative CHB patients	Open-label, multicenter, randomised, controlled trial from French ⁵⁷	183 HBeAg-negative CHB and negative HBV DNA while on stable NA for at least 1 year	HBsAg loss at week 96 Peg-IFN-2a plus NA: 7.8 NA only: 3.2% ($P=0.15$) The baseline HBsAg level correlated with HBsAg clearance.
Both HBeAg-positive and negative CHB patients	Prospective cohort study from Japan ⁵⁸	83 CHB Patients receiving maintenance TDF therapy with HBsAg level >800 IU/mL	A rapid decrease in HBsAg at 96 weeks: add-on arm: 41% TDF monotherapy: 2% ($P<0.001$)
Switch-to strategy			
HBeAg-positive CHB patients	open-label, multicenter, randomized controlled trial (OSST study) ⁵⁹	197 HBeAg-positive CHB patients who had received entecavir for 9–36 months, with HBeAg <100 PEIU/ml and HBV DNA $\leq 1,000$ copies/mL	HBsAg loss at week 48: Peg-IFN-2a: 8.5% Entecavir: 0.0% In entecavir-treated patients with HBeAg loss and had HBsAg <1,500 IU/mL at time of switching had a higher chance of HBsAg loss (22.2%). On-treatment predictors, HBsAg levels at 12 weeks after switching <200 IU/mL predicted great chance of HBsAg loss (77.8%), HBsAg level $\geq 1,500 \text{ IU/mL}$ predict poor response (1.7%) after switch therapy. A 1-year follow-up of the OSST study reported sustained HBsAg loss was documented in 6 of 7 (85.7%) patients 1-year post-treatment. ⁶⁰

Table 1. Continued

Regimen	Study design	Participants	HBsAg response
HBsAg-negative CHB patients	Open-label, multicenter, randomized, controlled trial (New Switch Study)	303 HBsAg-positive patients who achieved HBeAg loss and HBV DNA <200 IU/mL with previous NA treatment	HBsAg loss at the end of treatment: 48-week Peg-IFN treatment duration: 14.4% 96-week Peg-IFN treatment duration: 20.7% ($P=0.1742$) HBsAg loss at the end of 48-week follow-up: 48-week Peg-IFN treatment duration: 9.8% 96-week Peg-IFN treatment duration: 15.3% ($P=0.1670$) Baseline HBsAg <1,500 IU/mL and week 24 HBsAg <200 IU/mL were associated with the highest rates of HBsAg loss at the end of both 48- and 96-week treatment (51.4% and 58.7%, respectively). ⁶¹
HBsAg-negative CHB patients	Open-label, multicenter, randomised, controlled trial (Endeavor study) ⁶²	92 Patients who achieved virological suppression and HBeAg loss with entecavir treatment	HBsAg loss at week 48 group I: 3.70% group II: 3.03% group III: 9.38% the comparison was not statistically HBsAg decline at week 48: group I: 0.13 log ₁₀ IU/mL group II: 0.74 log ₁₀ IU/mL group III: 0.85 log ₁₀ IU/mL $P<0.05$ for group1 vs. group 2 or group 3

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antibody; NA, nucleos(t)ide analogue.

logical relapse than in those without.⁶⁹ Collectively, add-on Peg-IFN may be preferable to switch-to Peg-IFN in NA-treated CHB patients, especially HBeAg-positive patients.

Consensus statement:

4. Sequential combination therapy using potent NA followed by Peg-IFN improves the HBsAg loss rate in patients with detectable HBV DNA compared to NA monotherapy.

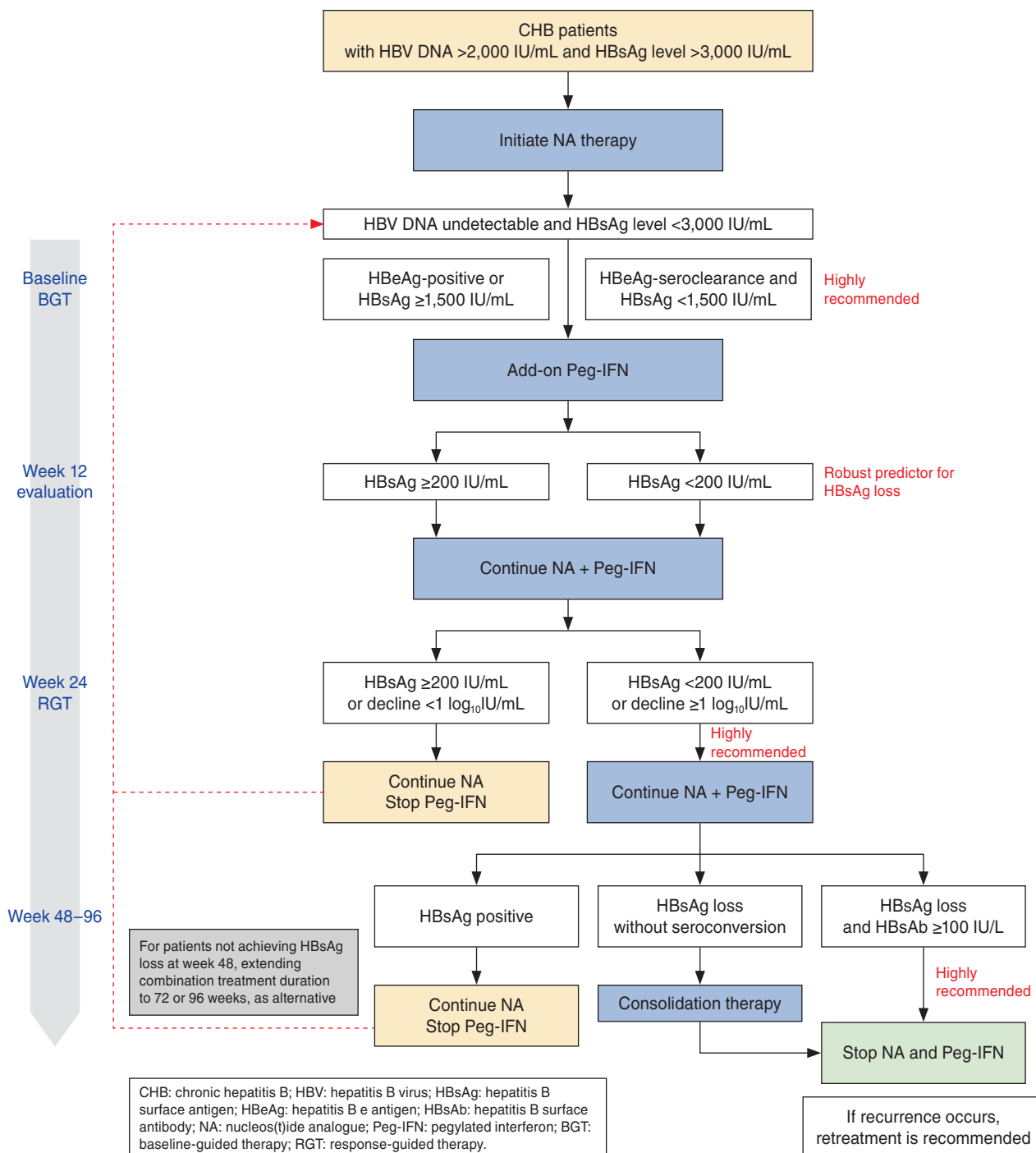


Figure 1. Navigation for combination of NA and Peg-IFN towards functional cure of hepatitis B.

5. For virally-suppressed patients on stable NA therapy, add-on Peg-IFN may be preferred over switch-to Peg-IFN, as it has similar HBsAg loss rates and reduces the risk of relapse in NA-treated patients with chronic hepatitis B, particularly in those who are HBeAg-positive.

Treatment navigation for functional cure by combination of NA and Peg-IFN

Based on the latest evidence, we propose an updated treatment navigation for sequential combination therapy with DAA (e.g., NA) and immunomodulator (e.g., Peg-IFN), which integrates strategies of baseline-guided therapy and response-guided therapy (Fig. 1). Specifically,^{70,71} for patients with high HBsAg levels (>3,000 IU/mL) and detectable HBV DNA, NA should be initiated first to suppress viral replication, thereby reducing viral load burden. Once the patients achieve undetectable HBV DNA, low HBsAg levels, especially $\leq 1,500$ IU/mL, and negative HBeAg, Peg-IFN can be subsequently administered to restore anti-HBV immunity. At week 24 of Peg-IFN-based treatment, individuals with HBsAg levels of ≥ 200 IU/mL or decline of $< 1 \log_{10}$ IU/mL had a minimal chance of achieving HBsAg loss, therefore, stopping Peg-IFN therapy or alternative treatment may be considered.

Although the durability of HBsAg loss is generally high, there exists a debate about whether and when the treatment can be stopped in the patients with HBsAg loss. A long-term follow-up study showed that at year 5 of follow-up, 18% of patients treated with Peg-IFN and NA combination therapy had durable HBsAg loss and 88% of them had developed HBsAb.⁷² Controversy remains over whether HBsAb development is requisite for functional cure, as HBsAg loss is sustained in most patients with or without HBsAb seroconversion in follow-up with currently approved therapies but will need to be confirmed with therapies in development.⁸ High level of HBsAb (> 100 U/mL) is strongly associated with low risk of recurrence.^{73,74} Studies have shown that a consolidation Peg-IFN treatment of ≥ 12 –24 weeks after HBsAg loss may improve the durability of this response.⁷⁵ Therefore, once HBsAg loss is achieved without HBsAb seroconversion, a consolidation Peg-IFN treatment or additional therapy such as hepatitis B vaccine^{76,77} may be considered to maintain the HBsAg loss and improve HBsAb responses, eventually leading to a stable

functional cure. For patients experiencing recurrence after cessation of Peg-IFN-based therapy, retreatment may be effective and HBsAg loss rate has been shown to be 80%.⁷³

Consensus statement:

6. The roadmap integrating strategies of baseline- and response-guided therapy based upon HBsAg kinetics can guide treatment decision on combination therapy with NA and Peg-IFN.

7. Low baseline HBsAg level ($< 1,500$ IU/mL) and HBeAg loss under NA therapy, as well as early on-treatment HBsAg decline may predict which patients are likely to achieve HBsAg loss with combination treatment.

8. Individuals with HBsAg levels of ≥ 200 IU/mL or decline of $< 1 \log_{10}$ IU/mL at week 24 had a minimal chance of achieving HBsAg loss, therefore, stopping Peg-IFN therapy or alternative treatment may be considered.

9. Once HBsAg loss is achieved without HBsAb development, a consolidation Peg-IFN treatment ≥ 12 weeks or additional therapy such as vaccine may be considered to maintain the HBsAg loss and achieve a stable functional cure.

Discontinuation of NA in selected patients

Several trials, including FINITE study etc., have shown that finite NA therapy prior to HBsAg loss in non-cirrhotic HBeAg-negative patients is a feasible approach to functional cure with definite treatment.⁷⁸⁻⁸¹ A study in non-cirrhotic HBeAg-negative patients showed that discontinuation of ETV therapy led to more 5-year cumulative incidences of HBsAg loss (13%) without an increased risk of HCC compared to those continuing ETV. The best candidates for NA withdrawal are virally suppressed, HBeAg-negative, noncirrhotic patients with low HBsAg levels, specifically Caucasians with $< 1,000$ IU/mL and Asians with < 100 IU/mL.⁸² Although study proposed that NA discontinuation-associated relapse may be an integral part of the stop-to-cure approach and ultimately triggers HBsAg loss,⁸³ cessation of NA therapy prior to HBsAg loss will expose patients to the risk of off-treatment relapse, or even decompensation, such treatment decision should be made with caution, and based upon a full assessment of the indi-

vidual patient's benefit/risk.⁸⁴ Strict surveillance and long-term follow-up after the discontinuation of NA therapy are recommended to prevent deterioration. Further studies are needed to fine-tuning the strategy, including research for the optimal duration of consolidation therapy, timing to stop, and timing to start retreatment.

Consensus statement:

10. Cessation of long-term NA therapy prior to HBsAg clearance in HBeAg-negative patients with low HBsAg levels (<100 IU/mL) may be an alternative approach to func-

tional cure. However, such treatment decision should be made with caution, and strict surveillance and long-term follow-up after the discontinuation of NA therapy is recommended to prevent deterioration.

New treatment approaches and potentially curative regimens

Although sequential combination therapy with Peg-IFN and NA improves HBsAg loss rates compared to NA monotherapy, this benefit is largely limited to selected patients, specifically those with low HBsAg levels. The way to

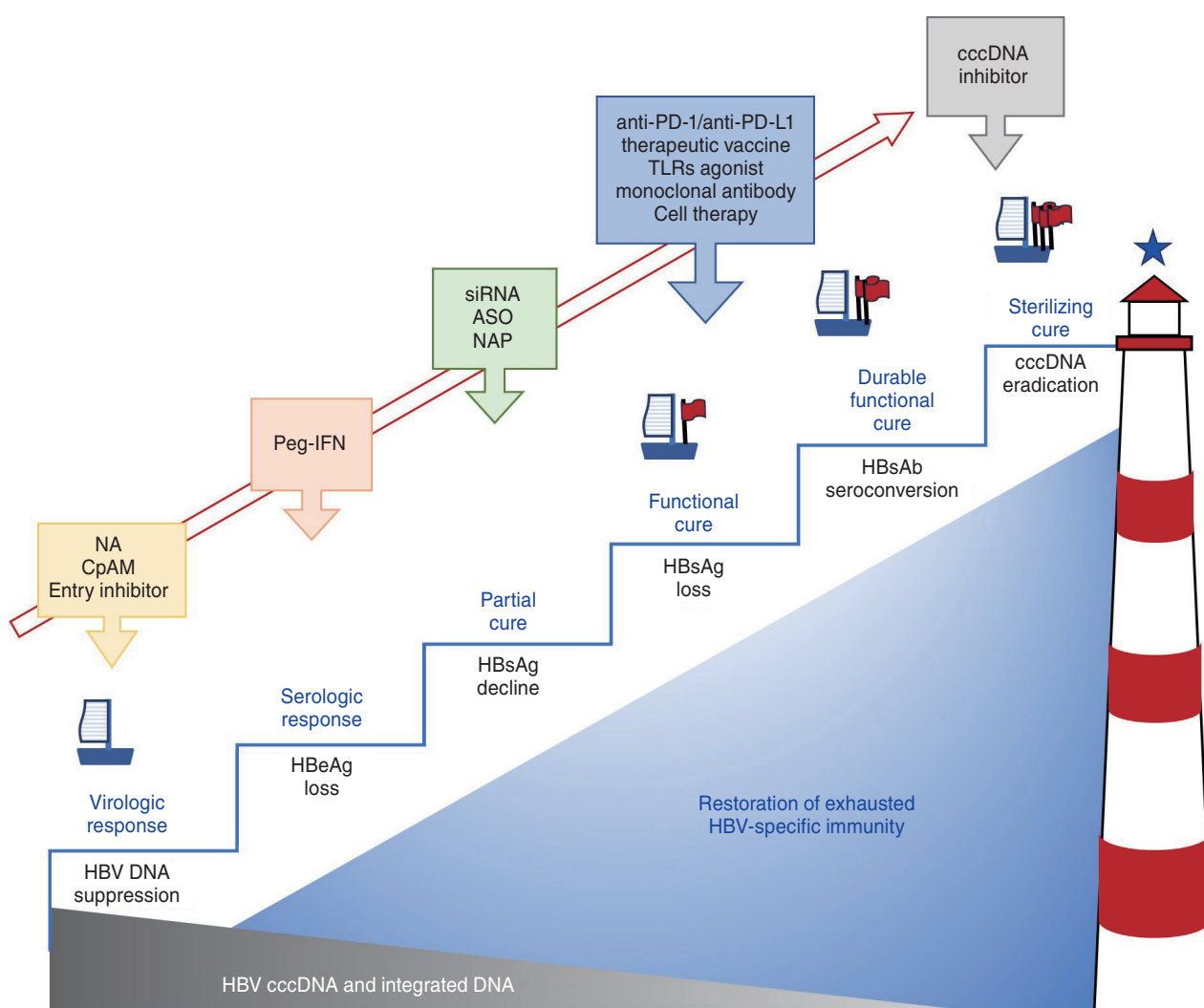


Figure 2. Proposed navigations for novel combination towards functional cure of hepatitis B. NA, nucleos(t)ide analogue; Peg-IFN, pegylated interferon- α ; siRNA, small interfering RNA; ASO, antisense oligonucleotide; CpAM, core protein allosteric modulator; PD-1, Programmed Death-1, PD-L1, Programmed Death-Ligand 1; NAP, nucleic acid polymer; TLR, Toll-like receptor; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody.

achieve functional cure is by using direct antiviral agents to reduce the circulatory HBsAg to an undetectable level, thereby allowing reawakening of the dysfunctional immune system in the hosts (Fig. 2). Novel DAAs acting against different viral replicative steps have been explored. The foremost ones are HBV RNA interfering agents including small interfering RNA (siRNA) and antisense oligonucleotide (ASO).⁸⁵ They knock down HBV gene expression through degradation of the pgRNA and mRNAs for HBV DNA and viral protein syntheses mediated by the RNA induced silencing complex and RNase H1, respectively. Because of the overlapping genomic arrangement of HBV, a single trigger usually targeting the X genomic region is able to knock down all the HBV RNA activities. The currently active investigational siRNAs include AB-729 (Imdusiran), JNJ-3989, RG-6346 (Xalnesiran), and VIR-2218. When they were given 4–8 weekly for 12 to 48 weeks, there was >1 log₁₀ IU/mL HBsAg reduction in 90% of subjects and reaching the nadir HBsAg <100 IU/mL in 50% of subjects.^{86–88} These HBsAg reductions were sustainable up to 48 weeks or longer after the treatments were stopped. However, all studies using siRNAs have not been associated with HBsAg loss. On the other hand, short term treatment of an ASO (Bepivirose) given for 4 weeks has already been shown to be associated with transient loss of HBsAg in 4 out of 16 patients (treatment-naïve/NA-treated).⁸⁹ The follow-up phase II study of this agent showed that 9% of NA-treated and 10% of treatment-naïve patients achieved HBsAg seroclearance after 24 weeks of treatment.⁹⁰ Alanine transaminase (ALT) flares, usually followed by HBsAg reduction signifying immune mediated response, were observed in both siRNA and ASO treatments.

Another group of DAAs is the core protein allosteric modulators (CpAMs). They affect the viral nucleocapsid assembly which is essential for pgRNA encapsidation. Hence, they have dual modes of action, i.e., depletion of complete virion formation and depletion of replenishment of cccDNA in the nucleus of hepatocytes. There are two classes of CpAMs: Class I (class A) CpAMs form aberrant nucleocapsids; Class II (class E) CpAMs form empty nucleocapsids. Many studies have shown that CpAMs were able to exert greater HBV DNA reduction when combined with NAs compared to NAs alone.^{91,92} Additionally, CpAMs have a profound reduction of HBV RNA levels. In the early generation of CpAMs, there was very minimal/modest HBsAg re-

duction in treatment-naïve HBeAg positive patients.^{91,92} These early generation CpAMs may also have the concern of drug resistance development when they were given without NAs.⁹¹ The latest more potent CpAMs, e.g., ALG 000184, were associated with a clinically meaningful HBsAg reduction⁹³ in HBeAg positive treatment-naïve patients without emergence of drug resistance when they were given without NAs.

In addition to the above two novel classes of DAAs, there are two other different classes of DAAs with different mechanisms of action, namely the virus entry inhibitor, e.g., bulevirtide (Myrcludex B), and the viral protein export inhibitor, e.g., nucleic acid polymers (NAPs) - REP-2139 and REP-2165. The former competes with the pre-S2 sequence of HBV for engaging the sodium taurocholate co-transporting polypeptide, the main hepatocyte receptor for viral entry. HBsAg reduction effect was mainly seen in the 48-week study using bulevirtide and Peg-IFN where 24.4% of patients achieved HBsAg decline by >1 log₁₀ IU/mL or HBsAg loss in HBV HDV co-infected population.⁹⁴ However, when it was given alone, there was no significant reduction of HBsAg at week 48 in HBV-HDV co-infected patients.⁹⁵ NAP also showed HBsAg responses when combined with Peg-IFN and tenofovir.⁹⁶ With 48 weeks of this triple therapy, 87.5% of patients achieved HBsAg reduction >1 log₁₀ IU/mL and, 60% achieved HBsAg seroconversion.

There are several novel agents targeting different immune cells or pathways which are rendered defective by HBV. TLR agonists, e.g., TLR7 and TLR8 agonists, have been tried under different regimens. Vesatolimod (TLR7 agonist) treated for 12 weeks did not result in HBV DNA and HBsAg reduction.⁹⁷ Ruzotolimod, another TLR7 agonist given every other day for a total of 42 days, showed mild mean reduction of 0.14 log IU/mL in HBsAg levels in NA-treated patients.⁹⁸ Selgantolimod, a TLR8 agonist treated for 24 weeks in NA-treated patients, was associated with 5% (2/39) of HBsAg seroconversion.⁹⁹

Targeting Programmed Death-1 (PD-1) or its ligand, Programmed Death-Ligand 1 (PD-L1), is another possible treatment to enhance the adaptive immunity through T cell activation. Initial positive results were seen in a study using 2 doses of nivolumab (anti-PD-1) with/without therapeutic vaccine.¹⁰⁰ Subsequent study using an anti-PD-L1, envafolumab given biweekly for 24 weeks in patients with baseline HBsAg levels <100 IU/mL was associated with HBsAg

reduction of $>1 \log_{10}$ IU/mL in 42.1% of patients and with HBsAg loss in 21.1% of patients.¹⁰¹

Not until recently, therapeutic vaccine stimulating host immune responses against HBV has revived its attention in the field. Novel therapeutic vaccines including BR11-179 comprised of HBsAg, Pre-S1 and Pre-S2; and VTP-300 comprised of HBsAg, Pre-S1, Pre-S2, modified polymerase and core have shown some positive results. Treatment using BR11-179 with or without IFN was associated with restoration of IFN-gamma production and mounting of HBsAb response although there was no observable HBsAg reduction.¹⁰² On the other hand, VTP-300 given with or without nivolumab were associated with meaningful HBsAg reduction in patients with lower baseline HBsAg <100 IU/mL.¹⁰³

Another novel group of immunomodulatory agents is monoclonal antibodies e.g., VIR-3434. One dose of VIR-3434 was associated with immediately HBsAg reduction of $2 \log$ IU/mL.¹⁰⁴ However, HBsAg rebound was seen early at day 29 after single dosing. VIR-3434 is postulated to have several actions including inhibition of viral entry, enhanced virus delivery to dendritic cells and enhanced T cell presentation and stimulation.

In addition, a possible immunotherapeutic approach to create a functionally intact population of HBV-specific T cells against HBV may be T cell engineering through T cell receptor gene transfer or use of chimeric antigen receptor T cells.^{105,106}

To date, single novel DAA has not yet resulted in high rate of functional cure. There are many ongoing studies combining different DAAs with or without immunomodulators. Examples of these include combination of Imdusiran (siRNA) with VTP-300 (therapeutic vaccine),¹⁰⁷ VIR 2218 (siRNA) with Peg-IFN,¹⁰⁸ Xalnesiran (siRNA) with Peg-IFN or with Ruzotolimod (TLR-7 agonist)¹⁰⁹; and Bepirovirsen followed by Peg-IFN.¹¹⁰ In general, the HBsAg loss could be achieved in approximately 15–23% at 24-week post-treatment by the latter 3 regimens. However, the higher efficacy is usually observed in patients with lower baseline HBsAg levels, i.e., $<1,000$ IU/mL. More future studies using different agents and combination strategies to achieve a higher functional cure rate inclusive of patients with high baseline HBsAg levels are urgently needed.

The potential curative strategy for hepatitis B virus infection in special populations

The curative strategy has been explored in special populations infected with chronic HBV including those with low-level viremia, metabolic dysfunction-associated steatotic liver disease (MASLD), liver cirrhosis, HCC, renal impairment, coinfections and children (Table 2).^{111–160} Shared decision making, following comprehensive discussions outlining the potential benefits and risks of Peg-IFN-based curative therapy, is advised for all candidate patients in the special populations.

Contraindications to Peg-IFN-based therapy

Clinicians should be aware of the contraindications to Peg-IFN-based therapy prior to its initiation. Peg-IFN use in patients with decompensated cirrhosis may precipitate hepatic failure or severe bacterial infections, thus is absolutely contraindicated.¹⁶¹ Although the impact of IFN on pregnancy is controversial,¹⁶² female patients of childbearing age should undergo a pregnancy test before Peg-IFN-based therapy. Furthermore, patients with active psychiatric disorders, a history of suicidal ideation, autoimmune diseases, or other severe systemic illnesses are contraindicated. Given the significant potential for adverse effects associated with Peg-IFN, thorough patient counseling and shared decision making are recommended to facilitate the development of individualized treatment plans for all patients.

Consensus statement:

11. Shared decision making, following comprehensive discussions outlining the potential benefits and risks of Peg-IFN-based curative therapy, is advised for all candidate patients in the special populations.

12. Patients with decompensated cirrhosis, pregnancy, active psychiatric disorders, a history of suicidal ideation, autoimmune diseases, or other severe systemic illnesses are contraindicated to Peg-IFN-based curative therapy and NA monotherapy should be recommended.

Table 2. The potential curative strategy for hepatitis B virus infection in special populations

Special populations	Relevant studies
Inactive HBsAg carriers (IHCs), CHB patients with low-level viremia, and indeterminate-phase or Grey Zone patients	• Although “inactive carrier” disease phase is associated with a favorable prognosis, it has been replaced by other terms in several current guidelines, as the risk of spontaneous reactivation and the potential risk of disease progression and HCC development are not negligible.¹¹¹ • Current guidelines do not recommend antiviral therapy for IHCs. However, IHCs may achieve high rates of HBsAg loss, whether receiving Peg-IFN therapy alone or in combination with NA.¹¹²⁻¹¹⁴ Thus, Peg-IFN-based treatment is a therapeutic option to achieve functional cure. • A five-year follow-up study showed that HBsAg loss over time in HBeAg-negative patients with HBV DNA <20,000 IU/mL was not influenced by combination treatment with NA and Peg-IFN.¹¹⁵ • Persistent low-level viremia during NA monotherapy is associated with a higher risk of liver cirrhosis or HCC.¹¹⁶⁻¹¹⁸ Therefore, treatment adjustments such as switching to or adding another preferred NA that can induce maintained virological response, or adding Peg-IFN can be considered. • In some HBeAg-negative patients with low-level viremia, transcriptionally active HBV integration may lead to ubiquitous HBsAg expression independent of HBV replication.¹¹⁹ • HCC risk in persistently indeterminate CHB was substantially higher than inactive CHB.¹²⁰ Antiviral treatment could reduce the risk of HCC and liver-related mortality among CHB patients in the indeterminate phase.¹²¹
CHB in children and adolescents	• Blocking mother-to-child transmission has significantly reduced HBV infection prevalence in children.^{122,123} However, less developed countries indicate a significant burden of HBV infection among children. • The chronicity of HBV infection is much higher in children than in adults following acute HBV infection.¹²⁴ Previous guidelines recommended antiviral therapy for children with active hepatitis B, whereas no therapeutic interventions have been recommended for pediatric immune-tolerant CHB. • The functional cure rate in HBeAg-positive CHB children significantly decreases with increasing age when they receive antiviral therapy.¹²⁵⁻¹²⁷ • The recently released expert consensus recommends initiating antiviral treatment as early as possible for children with CHB,¹²⁸ aiming to slow disease progression and reduce the disease burden in China.
Patients with metabolic dysfunction-associated steatotic liver disease (MASLD)	• HBV infection and MASLD are two major causes leading to liver cirrhosis and HCC.¹²⁹⁻¹³¹ In Asia, there is a growing trend towards coexistence of MASLD in individuals with CHB.¹³¹ • Concurrent MASLD may enhance HBsAg seroclearance and suppress HBV replication, irrespective of antiviral therapy.¹³²⁻¹³⁸ However, the potential long-term adverse effects of hepatic steatosis on the liver, such as the development of liver fibrosis or HCC^{130,139} should not be overlooked. • The impact of hepatic steatosis on efficacy of antiviral therapy for CHB is controversial. Several studies have demonstrated that hepatic steatosis may diminish the effectiveness of antiviral treatment and is significantly associated with treatment failure,^{140,141} but others suggest that hepatic steatosis does not affect treatment response.^{142,143} • Existing clinical studies on the functional cure of CHB have often excluded patients with concurrent MASLD, resulting in a lack of scientific data tailored to the treatment of this specific population. Comprehensive evaluations are essential to delineate the effects of concurrent MASLD on the functional cure in CHB patients receiving combination therapy. • The management of these patients should aim not only for a functional cure for HBV but also the effective control of MASLD. A recent study indicates that chronic hepatitis B and C outweigh MASLD in the associated risk of cirrhosis and HCC. This underscores the need to prioritize treatment of chronic viral hepatitis before addressing MASLD.¹³⁹

Table 2. Continued

Special populations	Relevant studies
CHB patients with liver cirrhosis	• Among CHB patients with liver cirrhosis, the primary therapeutic objective centers on reducing subsequent complications such as HCC development or mortality, rather than achieving functional cure.¹⁴⁴ • For patients with decompensated cirrhosis, immediate initiation of indefinite NA is strongly advised, while the use of Peg-IFN is contraindicated due to safety concerns. • In patients with compensated cirrhosis, NA is indicated for those with detectable serum HBV DNA levels; however, the long-term benefits of adjunctive Peg-IFN therapy remain uncertain. • Additionally, for well-compensated cirrhotic patients undergoing combination therapy, the optimal timing for discontinuing NA remains indeterminate. While a recent retrospective study suggests that withdrawal of NA monotherapy in cirrhotic patients may potentially facilitate HBsAg loss and enhance overall survival,¹⁴⁵ caution is warranted due to residual confounding factors¹⁴⁶ and the risk of serious adverse events such as acute flares,¹⁴⁷ necessitating further studies to validate the benefits of ceasing NA therapy prior to HBsAg loss in cirrhotic patients undergoing combination therapy.
CHB with HCC	• Patients with HCC due to underlying CHB should continue or receive lifelong prophylactic therapy with preferred NA through and following systemic anticancer therapies or potentially curative HCC therapy including liver transplantation.¹⁴⁸ • Patients who developed HCC after HBsAg loss were found to have comparable biological functions of HBV integration to HBsAg-positive patients with HCCs, with continuing pro-oncogenic effects of HBV integration. Therefore, CHB patients should remain under surveillance for HCC even after achieving HBsAg loss.¹⁴⁹ • Immune checkpoint inhibitors including anti-PD-1 and anti-PD-L1 may accelerate HBsAg loss in patients with cancer or HCC and baseline HBsAg <100 IU/mL.¹⁵⁰
CHB patients with renal impairment	• Renal abnormalities are prevalent among the CHB population, emphasizing the necessity for regular renal assessment in these patients.¹⁵¹ • Patients with suspected HBV-related renal involvement,¹⁵² including membranous nephropathy, membranoproliferative glomerulonephritis, polyarteritis nodosa, and mesangial proliferative glomerulonephritis, should promptly receive antiviral therapy. • Although the data regarding the optimal anti-HBV therapy for this subset of patients is limited,¹⁵³ add-on Peg-IFN to ETV seemed not to exacerbate renal function decline. Moreover, those with a baseline HBsAg level of less than 250 IU/mL may experience improved renal function following 48 weeks of therapy.¹⁵⁴ • Given the potential pathophysiological mechanisms involving viral antigens and immune complex deposition in HBV-related renal dysfunction, curative combination therapy should be considered in appropriate CHB patients with renal involvement to optimize therapeutic outcomes.
Patients with HBV- hepatitis C virus (HCV) coinfection	• The prevalence of HBV-HCV coinfection is expected to decline due to the favorable efficacy and safety profile of pan-genotypic DAAs against HCV. • Given the high rates of sustained virologic response (SVR),¹⁵⁵ immediate initiation of DAA therapy in those with detectable HCV RNA is justified. • Peg-IFN-based regimens are no longer recommended as the first-line therapy for those with HBV-HCV coinfection. However, following successful achievement of SVR for HCV, Peg-IFN-based curative therapy for HBV remains an aggressive approach aimed at functional cure. • Prophylactic NA during anti-HCV therapy is recommended because of the high risk of hepatitis B reactivation.¹⁵⁶ • Further investigation is necessary to ascertain whether the continuation rather than cessation of NA therapy, followed by add-on Peg-IFN, constitutes a safe and efficacious strategy for achieving HBsAg loss in patients with HBV-HCV coinfection who have completed anti-HCV therapy.

Table 2. Continued

Special populations	Relevant studies
Patients with HBV- hepatitis D virus (HDV) coinfection	- Approximately 5% of individuals infected with HBV are coinfecting with HDV,¹⁵⁷ however, only approximately 20% to 50% of them have been diagnosed.¹⁵⁸ Therefore, universal HDV screening is recommended for all patients who are positive for HBsAg.¹⁵⁹ - Chronic HBV-HDV coinfection leads to more rapidly progressive liver disease than chronic HBV monoinfection. - HBsAg loss sustained 24 weeks after the end of therapy with HBV DNA negativity is considered a functional cure for HBV-HDV coinfection. Therapeutic strategies leading to functional cure of HBV are ideal for HBV-HDV coinfection.^{8,160} - Peg-IFN is the current treatment of choice in HBV-HDV co-infected patients with compensated liver disease. - Entry-inhibitor Buleviride (BLV) is approved in Europe for the treatment of chronic hepatitis D. - Buleviride as well as prenylation inhibitor Isonafamib plus ritonavir with or without Peg-IFN have shown higher virological response rates but seldom lead to functional cure.^{158,160}

CHB, chronic hepatitis B; DAA, directly acting antivirals; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue.

MONITORING AND LONG-TERM FOLLOW-UPS

Predictor and monitoring

Serum HBsAg level may reflect active cccDNA and is a reliable marker to optimize Peg-IFN use. HBsAg kinetics within the first 24 weeks of Peg-IFN-based therapy are predictive of HBsAg loss and sustained response. Low baseline¹⁶³ and on-treatment^{164,165} HBsAg levels, or early strong HBsAg reductions¹⁶⁶ could help identify patients with a high probability of achieving HBsAg loss both in HBeAg-positive and HBeAg-negative patients.¹⁶⁷ ETV-treated patients with HBeAg loss and HBsAg <1,500 IU/mL at baseline had high chance of achieving HBsAg loss.⁵⁹ On-treatment HBsAg levels >200 IU/mL identify patients unlikely to benefit from Peg-IFN add-on and could be used as a potential response-guided strategy and stopping-rule for Peg-IFN therapy.¹⁶⁴ Different components of HBsAg, namely the large and medium HBsAg, decrease earlier than total HBsAg before HBsAg loss, and thus might be biomarker candidates for predicting cure of HBV infection.¹⁶⁸ Several studies demonstrated a correlation of ALT flares and HBsAg loss during Peg-IFN therapy.^{169,170} ALT ≤40 U/L at baseline or ALT levels ≥80 U/L at week 12 of Peg-IFN therapy was associated with HBsAg loss at week 24 post-treatment.¹⁷¹ In a post hoc analysis of randomized trials,¹⁷⁰ ALT flares during Peg-IFN treatment are associated with subsequent HBsAg decline and may predict HBsAg loss. Flares rarely occurred during Peg-IFN add-on therapy. A study developed scoring system integrating baseline HBsAg level <1,000 IU/mL, HBsAg decline >0.5 log₁₀ IU/mL at week 12 and ALT flare at week 12 to predict HBsAg loss either by add-on or switch-to Peg-IFN in NA-suppressed patients.¹⁷² End of treatment (EOT) HBsAg levels may predict HBsAg loss during post-treatment follow-up. EOT HBsAg level <10 IU/mL was predictive of HBsAg loss (52%) at 3-year post-treatment.¹⁷³ EOT HBsAb level may be correlated with sustained off-treatment HBsAg loss.^{174,175} EOT HBsAb levels >2 log₁₀ IU/L and hepatitis B core-related antigen (HBcrAg) levels <4 log₁₀ U/ml were associated with durable HBsAg loss at 24 weeks post-treatment.⁷⁴ A retrospective study indicated that HBeAg¹⁷⁶ negativity at EOT was associated with lower incidence of HBsAg reversion after Peg-IFN discontinuation, which is consistent with the findings

Table 3. Predictive potential of novel markers for HBsAg loss

Novel markers	Characteristics	Predictive potential for HBsAg loss
Virological markers		
HBcrAg	HBcrAg consists of HBeAg, HBcAg in Dane particles, and a truncated 22 kDa precore protein (p22cr) and phosphorylated HBcAg (pHBcAg) in empty Dane-like particles. ¹⁶¹ The levels of HBcrAg reflect HBV DNA levels in serum and liver, and cccDNA in the liver, thus HBcrAg may serve as a surrogate marker for predicting viral relapse after stopping NAs therapy. ¹⁶²⁻¹⁶⁵	Combining HBsAg (<10, 10–100 or >100 IU/mL) and HBcrAg (<2 log vs. ≥2 log) levels improved prediction of HBsAg loss after NA cessation. ¹⁶⁶ Recently developed highly sensitive HBcrAg could be suitable in predicting HBsAg loss after NA cessation. ¹⁶⁷
HBV RNA	Serum HBV RNA is encapsidated pgRNA and can be used as a potential biomarker reflecting the active transcription of intrahepatic cccDNA. ¹⁶⁸	EOT HBsAb levels >2 log ₁₀ IU/L and HBcrAg levels <4 log ₁₀ IU/mL were associated with durable HBsAg loss induced by Peg-IFN based therapy at 24 weeks post-treatment. ⁷⁴
Quantitative anti-HBc	The quantification of anti-HBc levels plays an important role in the diagnosis and treatment monitoring of CHB. ¹⁹¹ Anti-HBc may be used as a marker for significant histological inflammation diagnosis, ¹⁹² natural history differentiation, ^{193,194} HBsAg seroconversion, ¹⁹⁵⁻¹⁹⁷ and clinical relapse after NA discontinuation therapy. ¹⁹⁸	Serum HBV RNA may be a potential predictor of viral rebound and HBsAg loss post NA treatment withdrawal. ^{188,189} A post hoc analysis of a randomized clinical trial of Peg-IFN based therapy indicated that HBV RNA and HBcrAg were weak predictors of HBsAg loss. ¹⁶⁵ HBcrAg and HBV RNA have a limited role in improving the prediction of HBsAg loss in CHB patients upon readily available markers. ¹⁹⁰
Immunological markers	The HBV-induced host immune response is pivotal in determining the outcome of HBV infection, progression of the disease, and the response to antiviral therapy. ²⁰²⁻²⁰⁶	Low levels of anti-HBc may be associated with HBsAg loss. Anti-HBc levels <3 log IU/mL was associated with undetectable HBV DNA and HBsAg loss occurred within 10 years in HBeAg negative patients. ¹⁹⁹ Lower level of anti-HBc IgG (<11 relative light unit) at baseline was associated with HBsAg loss during long-term NA therapy. ²⁰⁰ Patients with lower baseline anti-HBc (<0.1 IU/mL) had a significantly higher rate of HBsAg loss under Peg-IFN add-on treatment. ²⁰¹
Immunological markers	The HBV-induced host immune response is pivotal in determining the outcome of HBV infection, progression of the disease, and the response to antiviral therapy. ²⁰²⁻²⁰⁶	On-treatment development of anti-IFNα neutralizing antibodies during Peg-IFN treatment was associated with reduced quantitative HBsAg and qHBeAg declines. ²⁰⁷ Changes of NK-cell phenotype were associated with HBsAg seroconversion in patients treated with NA. ²⁰⁸ Several immunological markers associated with HBV control or viral relapse upon NA discontinuation have been proposed. ^{209,210} The presence of functional HBV-specific T cells has been suggested as a candidate immunological biomarker for the safe discontinuation of NA. ²¹¹ HBV-specific CD4 ⁺ T-cell responses induced by the targeted peptide possess specificities for HBsAg loss in CHB patients undergoing NA discontinuation. ²¹² Successful response to Peg-IFN correlates with an early significant restoration of impaired immune responses. ²¹³ An inverse relationship was observed between the trends of sPD-1/sPD-L1 and HBsAg loss during IFN and NAs combination treatment. ²¹⁴ Baseline HBsAb-specific B cells might be a predictive biomarker of HBsAg seroconversion in CHB patients treated with Peg-IFN. ²¹⁵

Table 3. Continued

Novel markers	Characteristics	Predictive potential for HBsAg loss
Genetic markers	Host genetic variations can affect the outcome of CHB patients.	
Single nucleotide polymorphisms		HBsAg-negative CHB patients carrying rs9277535 non-GG genotype had a higher likelihood of spontaneous HBsAg loss compared to those carrying G alleles. ²¹⁶ Patients with S267F variant on NTCP gene tended to have more sustained response with HBsAg loss at 24 weeks following Peg-IFN treatment. ²¹⁷ In HBsAg-positive genotype B patients, rs7574865 in STAT4 was found to be associated with functional cure of CHB by Peg-IFN treatment. ²¹⁸ IL28B polymorphisms may predict IFN-related HBsAg loss in genotype D HBeAg-negative patients. ²¹⁹ Rs7519753 C allele was associated with an increased probability of HBsAg loss in CHB patients post Peg-IFN treatment. ²²⁰ Combination of the IFN lambda 4 rs368234815 and rs117648444 genotypes predicted HBsAg clearance in HBeAg-negative CHB patients post IFN treatment. ²²¹

cccDNA, covalently-closed-circular DNA; CHB, chronic hepatitis B; EOT, end of treatment; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; NK, natural killer; Peg-IFN, pegylated interferon.

from a prospective study⁷⁵ in HBeAg positive CHB patients.

During long-term NA therapy, HBsAg level or its trajectories can predict HBsAg loss.^{177,178} HBsAg decline of $\geq 1 \log_{10}$ IU/mL at week 24 independently predicts HBsAg loss in HBeAg-positive patients treated with up to 5 years of TDF treatment.¹⁷⁹ EOT HBsAg thresholds are identified to determine when NA treatment can be ended with low risk of relapse and high probability of HBsAg loss.^{82,180}

Novel HBV biomarkers are in development to understand the natural history of HBV, improve the management of CHB patients, and to predict disease outcomes of CHB. The utility of these biomarkers in predicting HBsAg loss is shown in Table 3.¹⁸¹⁻²²¹

Before initiating Peg-IFN based therapy, measurement of key baseline parameters is required, such as HBsAg, HBeAg, and HBV DNA levels, routine blood test and biochemical markers, liver ultrasound and transient elastography, thyroid function, mental condition, autoimmune antibodies, fundus examination, a pregnancy test and routine diagnostic tests to exclude other conditions or comorbidities that could contraindicate Peg-IFN therapy, which is significant for determining the appropriate therapy and predicting treatment response. Monitoring these parameters shall be carried out periodically to assess adverse events and treatment effectiveness during therapy, which is essential for evaluating the severity of adverse events and whether there is response to therapy.

Consensus statement:

13. Before initiating combination therapy, measurement of key baseline parameters is required to guide the treatment decision and predict efficacy and safety. Monitoring needs to be carried out periodically to assess adverse events and treatment effectiveness during therapy.

Long-term follow-up

HBsAg loss is associated with favorable long-term outcomes and reduces the risk of HCC and liver-related complications.^{4,222,223} Although HBsAg loss typically demonstrates durability, HBsAg reversion or recurrence may occur in approximately 6% of the patients. Notably, the recurrence rate tends to be slightly higher at the 1-year follow-up than the overall recurrence rate.²²⁴ Closer attention

should be paid to patients with cirrhosis, older than 50 years at the time of HBsAg loss. Therefore, periodic follow-up visits should be performed once every 3 months in the beginning after cessation of treatment, and the time interval of the follow-up visits may be gradually extended. Furthermore, HBsAg and HBV DNA reversion can occur owing to reduced immune control of HBV infection. Patients with HBsAg loss should be evaluated annually for their HBsAg, HBV DNA, and ALT levels. Retreatment remains effective in these cases although HBsAg reversion is not a target for immediate re-treatment unless it is accompanied by elevated HBV DNA and ALT levels.

Although HBsAg loss can significantly reduce the risk of HCC, HCC can still develop in patients after HBsAg loss, even in those without cirrhosis, possibly due to occult HBV infection or HBV DNA integration. Closer attention should be paid to patients with cirrhosis because those patients who achieve HBsAg loss have a higher subsequent risk of HCC than those without cirrhosis (risk of 0.54% vs. 0.13% annually).²²⁵ Moreover, old age, sex, family history of HCC, alcohol consumption, diabetes, cirrhosis, albumin, and low platelet count may be independent risk factors for HCC after HBsAg loss.²²⁵⁻²²⁷ Surveillance for HCC should be performed every 3–6 months using alpha-fetoprotein and ultrasound, computed tomography or magnetic resonance imaging if necessary, and for esophageal varices using endoscopy if varices are detected at pre-treatment endoscopy. Patients with preexisting cofactors for liver disease (including alcohol consumption, obesity, and/or type 2 diabetes, and significant liver disease) may require additional assessments.

HBsAg loss can also significantly reduce liver-related complications. The incidence of hepatic decompensation decreases over time in patients after HBsAg loss owing to the regression of cirrhosis. However, the regression takes time, and a significant reduction in the risk of hepatic decompensation is observed after several years of HBsAg loss.^{225,228}

HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive agents and antitumor chemotherapy are at risk of HBV reactivation.³⁵ ALT, HBV DNA, and HBsAg levels should be assessed before initiating such treatments and closely monitored during and after treatment.

Consensus statement:

14. Despite HBsAg loss, it is essential to monitor HBsAg recurrence, HCC surveillance, and hepatic events. Regular assessment of HBV-related markers, including ALT, HBV DNA, and HBsAg levels, is necessary, especially when there is concern for HBV reactivation.

FUTURE PERSPECTIVES

Treatment thresholds in CHB are changing across all the major liver disease organizations driven by the overarching aim to reduce morbidity and mortality associated with chronic infection. The urgency of this unmet clinical need is underlined by the projected doubling of HBV-related HCC deaths by 2040.²²⁹ While broadening of treatment candidacy can mitigate the complications of CHB, and a growing body of cost-effective analyses support early treatment as a strategy to avert the development of HCC,^{230,231} functional cure remains the ultimate therapeutic goal.

This consensus update focuses on the latest developments in the functional cure program and illustrates the complex interplay between viral factors and immune dynamics to achieve HBsAg loss. We demonstrate that Peg-IFN still has an important role in achieving HBsAg loss in selected virally suppressed patients on NA therapy, while NA withdrawal can be an effective approach in those non-cirrhotic patients with low levels of HBsAg. However, the greatest focus is on the multifaceted strategy of depleting viral antigen with siRNA or ASO and creating the ideal immunological milieu to re-invigorate the host immunity.²³² We discussed the lead candidates from the latest clinical trials and the rationale for various combination regimens is deliberated. The progress made with novel HBV therapies over recent years has been made in tandem with our broader understanding of virological markers; HBcrAg, HBV RNA and HBcAb; and novel immunological parameters. These developments are critical for the progress of the field as these novel tools are likely to signpost the functional cure program. Finally, we acknowledge the changing clinical landscape ahead and in particular the management of multimorbid patients and specifically how MASLD may represent a new challenge in the management of CHB and potentially a barrier to functional cure. Future studies will

need to examine the impact of MASLD, both in isolation and with other metabolic risk factors, on CHB management and functional cure.

Authors' contributions

Conceptualization, QN and MFY; writing—original draft preparation, DW, JHK, TP, XJW, PTFK, MO, SHA, YT, GQW, ZHY, WHL, AK, FSW, MFY, and QN; writing—review and editing, all authors; supervision, QN and MFY; funding acquisition, DW and QN; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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