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Review Article

Toward a Functional Cure for Hepatitis B

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Current treatment of chronic hepatitis B virus (HBV) infection, pegylated interferon-α (pegIFN-α) and nucleos(t)ide analogue (NA), can suppress HBV replication, reverse liver inflammation and fibrosis, and decrease risks of cirrhosis and hepatocellular carcinoma, but hepatitis B surface antigen (HBsAg) loss is rare. Functional HBV cure is defined as undetectable HBsAg and unquantifiable serum HBV DNA for at least 24 weeks after a finite course of therapy. This requires suppression of HBV replication and viral protein production as well as restoration of immune response to HBV. Direct-acting antivirals targeting virus entry, capsid assembly, viral protein production and secretion are in clinical trials. In parallel, immune modulatory therapies to stimulate HBV-specific immune response and to remove immune blockade are being tested. Clinical trials of direct-acting antivirals alone or immune modulatory therapies alone have not been successful in achieving HBV cure. Recent combinations of direct-acting antivirals and immune modulatory therapies have shown promising results particularly with combinations that included pegIFN-α. These results need to be confirmed in larger studies with longer follow-up, and further work is needed to develop simpler regimens with fewer drugs that can be administered orally and safely. While there is a strong desire to develop finite therapies that can achieve HBV cure, safety is paramount and new therapies must provide incremental value compared to standard of care, which is predominantly long-term NA therapy. **(Gut Liver 2024;18:593-601)**

Key Words: Direct-acting antivirals; Hepatitis B surface antigen loss; Immune modulatory therapies; Nucleos(t)ide analogues; Pegylated interferon-α

INTRODUCTION

Current treatment of chronic hepatitis B virus (HBV) infection comprises pegylated interferon-α (pegIFN-α) or nucleos(t)ide analogues (NAs), used as monotherapy. Both pegIFN-α and NA can suppress HBV DNA replication, decrease liver inflammation, reverse liver fibrosis, and decrease risk of cirrhosis, hepatocellular carcinoma, and liver-related deaths. However, HBV remains in the liver and hepatitis B surface antigen (HBsAg) remains in the circulation even after HBV DNA has been undetectable in serum for many years, and virological relapse is universal when treatment is stopped. This review article will describe the challenges in eradicating HBV, summarize the efficacy of new HBV direct-acting antivirals and immune modulatory therapies in clinical trials, and discuss the strategies needed to achieve HBV cure.

CHALLENGES TO HBV CURE

HBV replicates at a rapid rate with daily production of HBV virions estimated to be 1 trillion (10^{12}). In addition to complete virions, HBV produces subviral particles that consist of surface proteins only. These subviral particles are incapable of replication or infection, but they are >1,000-fold more abundant than complete virions and the vast amount of circulating HBsAg has been attributed to cause immune exhaustion in chronic HBV infection. Recovery of HBV-specific T-cell immune responses had been demonstrated in patients with spontaneous, pegIFN-α- or NA-induced hepatitis B e antigen (HBeAg) or HBsAg

loss[1,2] and more recently in some patients who experienced marked decrease in HBsAg levels during treatment with short interfering RNA (siRNA). These data suggest that HBV-specific immune responses can be restored at least in some patients after HBV DNA replication and HBsAg production are suppressed.

A major challenge to HBV cure is the presence of covalently closed circular DNA (cccDNA), which can be derived both from incoming virions and from intracellular recycling of nucleocapsids.[3] The cccDNA serves as a transcriptional template for all HBV RNAs including pregenomic RNA (pgRNA) which is reverse transcribed into HBV DNA and messenger RNAs which are translated into viral proteins. *In vitro* studies suggest IFN has direct effects on cccDNA enhancing its degradation and/or decreasing its transcription,[4] accounting for a higher rate of HBeAg and HBsAg loss compared to NA therapy. NAs do not have direct inhibitory effects on cccDNA; thus, cccDNA concentrations are minimally decreased even after many years of NA therapy.[5]

A further challenge is that HBV DNA can be integrated into host DNA. Integrated HBV DNA is not replication competent, but full-length S gene is usually preserved and can be a source of circulating HBsAg, particularly in HBeAg-negative patients.[6] Thus, HBV cure will require sustained suppression of both cccDNA and integrated HBV DNA transcription as well as restoration of HBV-specific immune response to maintain immune control.

Apart from the biological challenges, HBV cure therapies must demonstrate incremental value and comparable safety to standard of care which is predominantly long-term NA monotherapy. The second-generation NAs, entecavir and tenofovir, are administered orally once daily, have excellent safety profile and <1% risk of antiviral drug resistance after ≥10 years of continuous therapy. Entecavir and tenofovir disoproxil fumarate are available as generics and are readily available and affordable in most countries. Thus, the bar for new therapies to show incremental value is high. In addition, there is a risk of hepatic decompensation when all drugs including NA are discontinued as had been reported in a recent trial of HBV cure therapy.[7]

DEFINITION OF HBV CURE

HBV cure has been categorized as sterilizing, functional, and partial. Sterilizing cure, defined as the elimination of cccDNA as well as integrated HBV DNA is considered an ideal but unrealistic endpoint. Functional cure, defined as sustained (≥24 weeks posttreatment) HBsAg loss with or without seroconversion to hepatitis B surface antibody (anti-HBs) and undetectable HBeAg and serum HBV DNA after a finite course of therapy, is considered an achievable endpoint and the goal to strive for. Partial HBV cure, defined as HBsAg positive, HBeAg negative with undetectable serum HBV DNA after discontinuation of a finite course of treatment, is considered a suboptimal endpoint for HBV cure therapies. These definitions were first proposed at the 2016 American Association for the Study of Liver Diseases and European Association for the Study of the Liver HBV Treatment Endpoint Conference, reaffirmed at the 2019 conference, and refined at the 2022 conference.[8-10] At the 2022 conference, very few new therapies had resulted in HBsAg loss at the end of treatment raising concerns that sustained HBsAg loss off-treatment might be aspirational. Thus, a revised definition of partial cure, HBsAg decreased to <100 IU/mL, HBeAg negative, and HBV DNA below quantification, sustained for at least 24 weeks off-treatment was embraced as an acceptable intermediate step toward functional HBV cure.

Low end-of-treatment HBsAg level is the best predictor of HBsAg loss after NA withdrawal and on-treatment HBsAg decline is a strong predictor of HBsAg loss during pegIFN-α therapy.[11,12] Low baseline HBsAg level is a predictor of HBsAg loss with many new HBV therapies in clinical trials.[13] However, there are no data on the likelihood of HBsAg loss after HBsAg level is reduced to low levels when treatment that directly targets HBsAg production, secretion or binding is stopped. Follow-up week 24 was selected as the timepoint to assess sustained response because durability of spontaneous, pegIFN-α- or NA- associated HBsAg loss is ~90% if undetectable HBsAg is confirmed on follow-up testing ≥24 weeks later[14,15] but this timepoint may not be appropriate for treatments with long duration of action. Indeed, among the small number of patients who had achieved HBsAg loss at the end of treatment in ongoing trials of new antivirals, 50% or more reverted back to HBsAg positive by follow-up week 24.[13]

New HBV markers such as HBV RNA and hepatitis B core-related antigen had been shown to be inferior to HBsAg level as predictors of HBsAg loss in studies of pegIFN-α and NA. The utility of these markers in predicting HBsAg loss with HBV cure therapies has not been demonstrated in part due to the limited number of patients achieving HBsAg loss.

CURRENT TREATMENT RARELY RESULTS IN HBsAg LOSS

1. Interferon monotherapy

After a 48-week course of pegIFN-α treatment, 20% to

25% of patients achieve a sustained decrease in HBV DNA levels, with HBsAg loss increasing from 2%–3% at the end of treatment to 8%–14% after 3 to 5 years posttreatment follow-up.[16-18] However, HBsAg loss is mainly observed in genotype A[19] which is rare in endemic regions.

2. NA monotherapy

NAs are more effective than pegIFN-α in inhibiting HBV DNA replication but only 2% to 5% of patients lost HBsAg after 10 years of continuous treatment.[18] Although virologic relapse is universal when NA is stopped prior to HBsAg loss, not all patients experience clinical relapse. Furthermore, some studies found that discontinuation of NA in HBeAg-negative patients who have completed more than 2 to 3 years treatment with undetectable serum HBV DNA have higher rates of HBsAg loss compared to those who continued NA.[20,21] This paradoxical finding first reported in retrospective studies has now been confirmed in two prospective randomized controlled trials in Europe with almost exclusively White patients but not in two other trials in North America with predominantly Asian patients.[22-25] Indeed, Asian patients with HBsAg level <100 IU/mL at the time of NA discontinuation have lower likelihood of HBsAg loss than White patients with HBsAg level <1,000 IU/mL at the time of NA discontinuation.[26] Thus, NA withdrawal will have minimal global impact as a strategy toward HBV cure.

3. Combination of IFN and NA

Most studies evaluating de novo combination of IFN-α and NA have not shown an improvement in HBsAg loss. Two meta-analyses showed that IFN-α add-on to NA or switching from NA to IFN-α in selected patients may increase HBsAg loss[27,28] but IFN-α is associated with many side effects and contraindicated in some patients, and the results in these selected patients may not be generalized.

HBV CURE THERAPIES IN CLINICAL TRIALS

New drugs are needed to achieve HBV cure. They include direct-acting antivirals targeting different steps in the HBV lifecycle and immune modulators aimed to stimulate HBV-specific immune response or to remove immune blockade (Figs 1 and 2).[29-31] Results of the key trials are summarized below.

1. Direct-acting antivirals

1) Entry inhibitors

Bulevirtide, a synthetic lipopeptide corresponding to the HBV preS1 region, blocks entry of HBV into hepatocytes via the sodium taurocholate co-transporting polypeptide receptor, preventing infection of uninfected hepatocytes. Bulevirtide monotherapy in chronic HBV/hepatitis D virus infection had minimal effect on HBsAg levels with greater decline when combined with pegIFN-α, whether this is true for chronic HBV monoinfection remains to be determined.[32]

2) Capsid assembly modulators

Capsid assembly modulators (CAMs) are small molecules that can be administered orally. First generation CAMs primarily act by interfering with capsid formation resulting in aberrant or empty capsids thereby decreasing pgRNA packaging and HBV DNA replication. Second-generation CAMs achieve higher intracellular concentrations necessary to block capsid disassembly (cccDNA establishment) and intracellular recycling of capsids (cccDNA replenishment) and may decrease HBV protein production.

Clinical trials of a combination of CAM and an NA have shown an additive effect in decreasing HBV DNA and pgRNA levels but minimal effect on HBeAg and HBsAg levels.[29,30] The phase 2 trial of vebicorvir plus entecavir showed more rapid and profound decline in HBV DNA

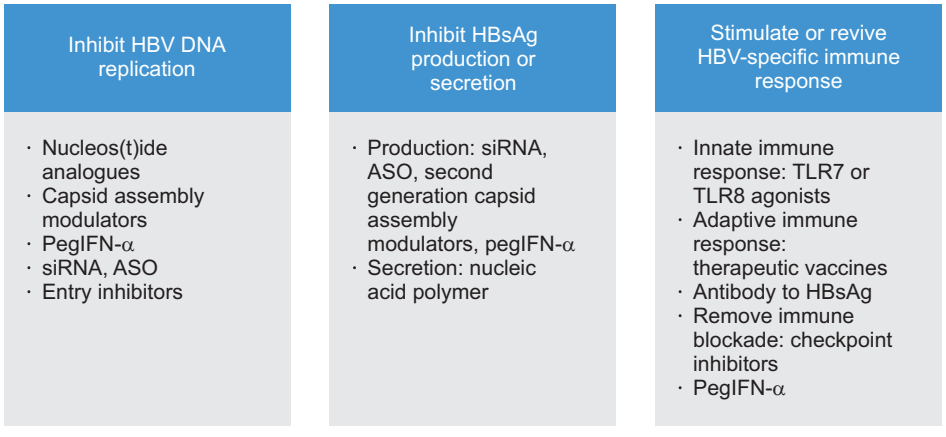

Fig. 1. Steps toward achieving hepatitis B virus (HBV) cure. HBV cure requires suppression of HBV DNA replication and HBV protein particularly hepatitis B surface antigen (HBsAg) production, and stimulation or revival of HBV-specific immune response. Several classes of drugs targeting each step are in clinical trials. pegIFN-α, pegylated interferon-α; siRNA, short interfering RNA; ASO, antisense oligonucleotides; TLR7, Toll-like receptor 7; TLR8, Toll-like receptor 8.

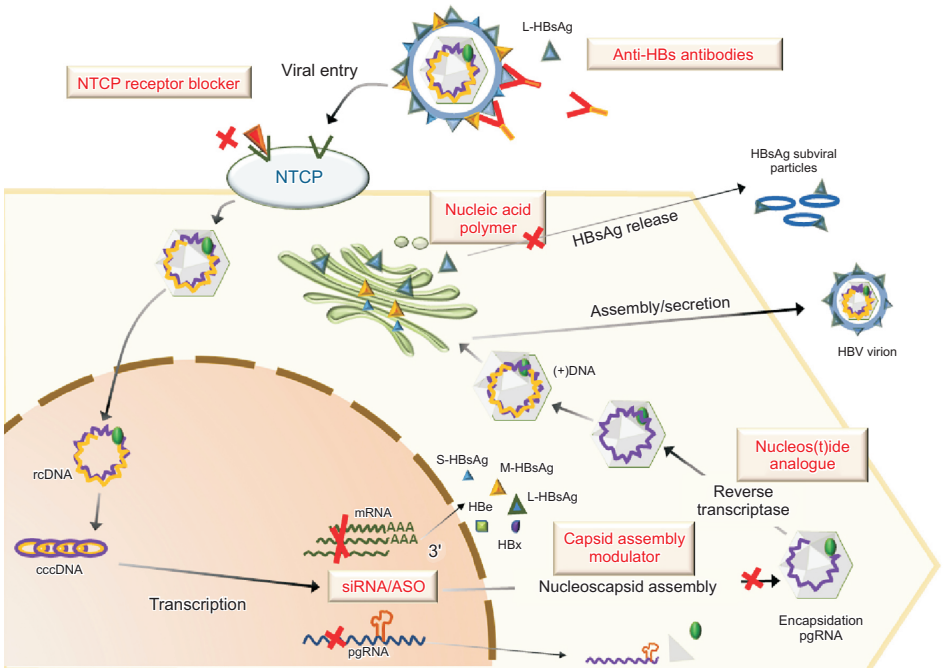

Fig. 2. Hepatitis B virus (HBV) lifecycle and targets for direct-acting antiviral drugs. Sodium taurocholate co-transporting polypeptide (NTCP) receptor blocker inhibits HBV entrance into hepatocyte. Short interfering RNAs (siRNA) and antisense oligonucleotides (ASO) interferes with translation of RNA transcribed from covalently circular DNA: messenger RNA and/or pregenomic RNA, and RNA transcribed from integrated HBV DNA. Capsid assembly modulators (CAM) interfere with capsid formation resulting in empty or aberrant capsids, decreasing pregenomic RNA packaging and HBV DNA replication. Nucleic acid polymer blocks subviral hepatitis B surface antigen (HBsAg) assembly and secretion, leading to HBsAg reduction. Vaccinal antibodies bind and neutralize circulating HBsAg and potentially restore exhausted HBV-specific immune response. Anti-HBs, hepatitis B surface antibody; rcDNA, relaxed circular DNA; cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA; mRNA, messenger RNA; HBe, hepatitis B e protein; HBx, hepatitis B X protein.

and pgRNA levels compared to entecavir alone but there was minimal decrease in HBsAg levels after 48 week treatment and most patients who met criteria for discontinuing treatment at week 72 had virologic relapse and many had hepatitis flares.[33] Addition of vebicorvir to GalNAc-siRNA (AB-729) plus NA did not result in greater decrease in HBsAg level compared to AB-729 and NA while addition of another CAM (JNJ-6379) to siRNA (JNJ-3989) and NA resulted in a smaller decrease in HBsAg level compared to siRNA and NA suggesting an antagonistic effect.[30]

Preliminary data from a small trial of a second-generation CAM (ALG-00184) with or without entecavir showed HBsAg decrease by >1 $\log_{10}$ in a few patients after 48 weeks treatment[34] providing hope that CAMs may have a role in HBV cure.

3) Post-transcription inhibitors

Small interfering RNAs (siRNA) and antisense oligonucleotides (ASO) silence HBV RNA thereby inhibiting HBV DNA replication and viral protein production.

Clinical trials of several GalNAc-conjugated siRNAs showed 2–3 $\log_{10}$ HBsAg decline after 3–4 doses lasting for 6 to 9 months posttreatment.[30] However, HBsAg decline plateaued around 16 to 20 weeks despite continued dosing to 48 weeks.[35] Mild alanine aminotransferase (ALT) elevation as well as upregulation of HBV-specific T cell activation markers in association with HBsAg decline was observed in some but not all patients.[36] To date, only 1 trial of siRNAs for up to 48 weeks with or without NA has reported off-treatment HBsAg loss.[37]

A phase 2 trial of bepirovirsen, an unconjugated ASO targeting all HBV RNAs showed a marked decrease in HBsAg level at week 24 in the highest dose (300 mg) group, with 26% and 29% having undetectable HBsAg at the end of treatment, and 9% and 10% having undetectable HBsAg as well as unquantifiable HBV DNA after 24 week post-treatment follow-up, in patients with versus without concurrent NA, respectively.[13] These results were superior to that of the same ASO with GalNAc-conjugation suggesting that bepirovirsen may act more as an immune modulator than an antiviral since it is predominantly taken up by macrophages and not hepatocytes.

4) S secretion inhibitors

Nucleic acid polymers can block the release of subviral particles from hepatocytes. One study showed that addi-

tion of REP-2139 or REP-2165 and pegIFN-α after lead-in NA resulted in HBsAg loss in 60% of patients at the end-of-treatment and in 35% after more than 6 months post-treatment.[38] However, there were only 40 patients in this trial, many patients had ALT flares, and results of confirmatory studies have not been reported.

2. Immune modulators

1) Innate immune response

Toll-like receptor (TLR) 7 and TLR8 agonists showed minimal clinical efficacy despite improvement in immune response. Addition of a TLR7 agonist, ruzolotolimod to an siRNA (xalnesiran) and NA resulted in HBsAg loss of 13% after 24 weeks of posttreatment follow-up compared to 3%–7% with xalnesiran and NA, but the response was inferior compared to the addition of pegIFN-α and HBsAg loss was only observed in patients with baseline HBsAg <1,000 IU/mL.[37]

2) HBV-specific T cell response

Past attempts with therapeutic vaccines have not resulted in clinical efficacy in virally suppressed as well as NA-naïve patients despite increasing cytokines or HBV-specific immune response. Because patients with chronic HBV infection have been exposed to high circulating HBsAg levels for years if not decades, new therapeutic vaccines deploy other HBV antigens, prime-boost approach, addition of immune checkpoint inhibitors, more potent adjuvants or combination of the above.[39] A phase 2b trial of Chimpanzee adenoviral and modified vaccinia Ankara viral vectors encoding multiple HBV antigens (ChAdOx1-HBV/MVA-HBV) used in a prime-boost strategy in combination with a programed death 1 (PD-1) inhibitor resulted in sustained HBsAg decline in those with low baseline HBsAg level (<200 IU/mL) but functional cure was not observed.[40] Another trial showed that a therapeutic vaccine BRII-179 comprising pre-S1/pre-S2/S antigens in combination with pegIFN-α for 24 weeks resulted in HBsAg loss in 25% of patients 12 weeks posttreatment compared to 14% in those who received placebo/pegIFN-α.[41] Longer follow-up is needed to confirm durable HBsAg loss versus transient undetectable HBsAg due to binding to anti-HBs.

3) HBV-specific B-cell response

The importance of B cells in controlling chronic HBV infection was recognized when B-cell depleting therapies were shown to be associated with the highest risk of HBV reactivation. Passive infusion of anti-HBs or stimulation of active anti-HBs production can neutralize circulating HBsAg and prevent new infection of hepatocytes but effects would be short-lived unless HBsAg production is inhibited, and safety is a concern unless complications secondary to immune complexes can be prevented.

One trial comparing a neutralizing monoclonal antibody VIR-3434 to VIR-2218 (siRNA) alone or in combination with or without addition of pegIFN-α, showed HBsAg loss at the end-of-treatment was achieved in patients who received combination of VIR-3434 and VIR-2218 with or without pegIFN-α and not those who received either alone; but only those who received combination therapy with pegIFN-α had sustained HBsAg loss.[42]

4) Removing immune blockade

Checkpoint inhibitors have revolutionized cancer treatment and may restore immune control of HBV. A phase 1b study of 22 patients receiving 12 weeks of nivolumab (PD-1 inhibitor), with or without GS-4774, a therapeutic T-cell vaccine, showed one patient (4.5%) had undetectable HBsAg lasting 12 months after therapy.[43] A phase 2b study of Envafolimab (ASC22), a humanized PD-L1 antibody in virally suppressed patients showed 4 of 19 patients had HBsAg loss at the end of 24 week treatment though all had baseline HBsAg <100 IU/mL.[44]

5) Combination with pegIFN-α

In attempts to increase functional cure rate, several studies have explored the addition of pegIFN-α to new therapies.

One trial evaluating combination of JNJ3989 (siRNA) and NA with or without JNJ-6379 (CAM) followed by pegIFN-α in HBeAg-positive patients with mild ALT elevation noted that 16% had HBsAg loss at follow-up week 24.[45] Another study showed that the combination of pegIFN-α, xalnesiran (siRNA) and NA achieved the highest rate of sustained HBsAg loss, 23% compared to 13% in those who received xalnesiran, NA and ruzotolimod (TLR7), and 3% to 7% in those who received xalnesiran and NA.[37] A third study explored sequential treatment of bepirovirsen (ASO) and NA followed by pegIFN-α found that HBsAg loss at the end of bepirovirsen, pegIFN-α, and at follow-up week 24 was 65%, 53%, and 24%, respectively in the 24-week bepirovirsen group, and 59%, 47%, and 41%, respectively in the 12-week bepirovirsen group, with minimal incremental HBsAg loss during pegIFN-α treatment and failure of pegIFN-α to prevent HBsAg relapse.[46] A fourth study compared VIR-3434 (monoclonal anti-HBs) alone or in combination with VIR-2218 (siRNA) without or with pegIFN-α, showed sustained HBsAg loss was observed only in the group that received pegIFN-α.[42]

To date, functional cure is mainly observed in combination therapies of direct-acting antivirals with immune modulatory therapies particularly pegIFN-α (Fig. 3), but

all trials involved small numbers of patients with responses mainly in those with low baseline HBsAg levels and uncertain long-term durability. Furthermore, only one trial included a pegIFN-α monotherapy arm with functional cure rate of 14% in that control arm raising concerns about the contribution of siRNA/ASO and other immune modulatory agents in the combination trials described above.

STRATEGIES TOWARDS HBV CURE

Achievement of functional HBV cure will require complete suppression of HBV DNA replication, inhibition of HBsAg production from both cccDNA and integrated HBV DNA, and restoration/boosting of innate and adaptive immune responses against HBV, but the most efficient way to accomplish each step remains unclear (Fig. 4). For example, does each step require 1 or >1 class of drugs and

HBsAg loss in clinical trials of HBV cure therapies

	End of treatment	FU week 8–24	Comments
CAM	N	N	
CAM+siRNA	N	N	
CAM+pegIFN-α	N	N	
CAM+siRNA+pegIFN-α	Y	**Y**	JNJ-6379+JNJ-3989
siRNA	Y (rare)	**Y (1 study)**	Xalnesiran
siRNA+pegIFN-α	Y	**Y**	Xalnesiran, VIR-2218, imdusiran
siRNA+TLR7	Y	**Y**	Xalnesiran+ruzotolimod
siRNA+vaccinal Ab	Y	N	
siRNA+vaccinal Ab+pegIFN-α	Y	**Y**	VIR-2218+VIR-3434
ASO*	Y	**Y**	Bepirovirsen
ASO+pegIFN-α	Y	**Y**	Bepirovirsen
Therapeutic vaccine	N	N	
Therapeutic vaccine+checkpoint inhibitor	?	**Y**	1 participant
Therapeutic vaccine+pegIFN-α	Y	**Y**	BRII-179 (pre-S1, pre-S2, S)
Checkpoint inhibitor	Y	**Y**	Envafolimab, low baseline HBsAg
NAP+pegIFN-α	Y	**Y**	Small study, to be confirmed

Fig. 3. Success in achieving off-treatment hepatitis B surface antigen (HBsAg) loss in clinical trials of hepatitis B virus (HBV) cure therapies. Highest rates of sustained HBsAg loss have been achieved with combination therapies of 3 to 4 drugs that include nucleos(t)ide analogue (NA) and pegIFN-α, plus additional direct-acting antiviral and/or immune modulatory therapy. All but one trial* included NA. Some trials used concurrent therapies while others used sequential therapies. FU, follow-up; CAM, capsid assembly modulator; siRNA, small interfering RNA; pegIFN-α, pegylated interferon-α; TLR7, Toll-like receptor 7; Ab, antibody; ASO, antisense oligonucleotide; NAP, nucleic acid polymer.

Parameters	Considerations
Efficacy HBV DNA replication HBsAg production HBV-specific immune response	Is 1 drug class sufficient for each step? Which drug class is most efficacious? Which combinations have additive or synergistic effects? Should immune modulatory therapy be used concurrently with or following direct-acting antivirals?
Safety	Is there risk of drug resistance, hepatitis flares, systemic adverse events?
Personalization	Which patients need immune modulatory therapy and how to select the optimal approach? Will the most effective combination be the same for patients in immune tolerant vs immune active phase of chronic HBV infection, in children vs adults, in patients with vs without cirrhosis, and in those with vs without HIV or HDV coinfection?
Practicality	Route of administration: oral vs parenteral 1 vs >1 drug Duration of treatment Availability and cost

Fig. 4. Challenges in developing hepatitis B virus (HBV) cure therapies. HBV cure therapies need to be efficacious, safe, simple, and provide incremental value compared to currently available treatment. HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; HIV, human immunodeficiency virus.

do all patients require immune modulatory therapy. NAs will remain a backbone in suppressing HBV DNA replication though they may potentially be replaced by second-generation CAMs. Post-transcription inhibitors, siRNA and ASO, will be pivotal in inhibiting HBsAg and other HBV protein production but appeared to be insufficient in achieving HBsAg loss. Identifying which patients can restore immune control without the need for immune modulatory therapy after HBV DNA replication and HBsAg production are suppressed will be important. For the remaining patients, being able to select immune modulatory therapies tailored to the individual patient's HBV-immune responsiveness rather than an empiric approach will be ideal. Recent studies suggest pegIFN-α may have a critical role in some patients but the minimal duration of pegIFN-α required, the correct timing to start pegIFN-α–de novo versus sequential, in all patients, only those with HBsAg suppressed to low levels or only those with specific HBV genotypes or host characteristics remain to be determined.

It is gratifying to see that >20% functional cure rates have been reported in several recent combination therapy trials, but these promising results need to be confirmed in larger trials and durability of HBsAg loss ascertained with longer duration of follow-up. Of note, these combination regimens should be considered proof-of-concept as they involve 3 to 4 drugs, with 2 to 3 being administered parenterally and potential adverse effects, and costs that are expected to be much higher (>100-fold) than generic NA.

A major challenge with new therapies currently in clinical trials is that they are not aimed at eliminating cccDNA or integrated HBV DNA. To do so will require gene silencing or epigenetic modification with risk of off-target effects or elimination of all infected hepatocytes with risk of severe hepatitis and hepatic failure. The former approach is being tested and *in vitro* and pre-clinical studies in cell lines and mouse models suggest it is feasible but their safety and efficacy in humans with chronic HBV infection have not been tested.

CONCLUDING PERSPECTIVES

Substantial progress has been made toward HBV cure. In parallel with development of new therapies, universal vaccination particularly birth dose vaccination, improved diagnosis and linkage to care, and treatment of those meeting guideline criteria using current therapies should be facilitated to achieve the goal of HBV elimination.

CONFLICTS OF INTEREST

A.S.F.L. has received research grants from Target Pharma and has served as an advisor/consultant for Abbott, GlaxoSmithKline, Grifols, Pfizer, Precision Sciences, Roche, TARGET, and Virion. Except for that, no potential conflict of interest relevant to this article was reported.

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