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Liver (J Bajaj, Section Editor)

Updates on Chronic HBV: Current Challenges and Future Goals

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Abstract

Purpose of Review Chronic HBV (CHB) remains a global public health problem with over 257 million people chronically infected worldwide. Without appropriate management, 20% of individuals infected with CHB will die from complications of cirrhosis, liver failure, or hepatocellular carcinoma (HCC). Despite an effective vaccination to prevent infection, HBV has yet to be successfully eradicated globally. Current treatments can only control and suppress the virus but cannot cure. Updates in the management of chronic HBV will be reviewed, including latest treatments and treatment strategies as well as potential curative therapeutic agents in clinical trial.

Recent Findings A new nucleotide analogue drug, tenofovir alafenamide fumarate (TAF), has been added to the HBV therapeutic armamentarium. A more potent drug showing non-inferiority, TAF has shown to improve renal and bone laboratory safety parameters compared to TDF. In addition, new treatment recommendations have been made for both general and special populations including pregnancy and HBV reactivation. There is growing data supporting the importance of antiviral therapy in patients with advanced liver disease and liver decompensation which has resulted in improved outcomes. In addition, at least 30 potential therapeutics are in clinical trials in the pursuit of curative treatments for chronic HBV with the goal of "functional cure."

Summary CHB remains a global public health problem with complications including cirrhosis, liver failure, and HCC. Current antiviral therapy can cause reversal of liver disease, improve outcomes, and prevent complications such as reactivation but still requires long-term use. Curative treatments for HBV are greatly needed with promising curative drugs in early phase studies.

Introduction: current challenges and trends

Despite the development of an effective vaccine over 30 years ago, chronic hepatitis B (CHB) virus infection remains a global public health problem with over 257 million people chronically infected worldwide and 887,000 deaths annually [1, 2]. With potential life-threatening complications including the development of cirrhosis and liver cancer, approximately 20% of individuals infected with CHB will die from liver failure or hepatocellular carcinoma (HCC) without appropriate management [2]. Globally, CHB is responsible for over 50% of HCC with infected individuals having a 30-fold increase risk for HCC [3]. CHB prevalence has historically remained the highest in Asia and sub-Saharan African with 6.2% prevalence in the World Health Organization (WHO) Western Pacific Region and 6.1% in the WHO African Region [1]. Although 0.7% of the population of the WHO Region of the Americas is infected, with the influx of immigrants from HBV endemic regions, the prevalence of CHB is expected to increase in the USA to as high as 2.2 million [1, 4, 5]. The WHO has implemented a Global Strategy on Viral Hepatitis with a 2030 goal of eliminating HBV and HCV globally through targeted interventions that involve widespread vaccinations, screening/diagnosis, and linkage to care for those chronically infected [1].

The challenge in the management of CHB is the lack of "curative" treatments due to "the persistence" of its covalently closed circular DNA (cccDNA), an episomal mini-chromosome that infects the nucleus of the human hepatocyte and gives the virus ability to evade the host immune system. Effective antivirals are able to suppress replication and reduce risks of complications from CHB but are unable to eradicate the cccDNA. HBV is not a cytopathic virus, and damage to the host hepatocytes is caused by host immune response to virus-infected hepatocytes leading to liver cell injury. Ultimately, this increases the risk of cirrhosis and liver cancer from long-term chronic liver inflammation and the lack of immune-mediated viral clearance.

The additional challenge of CHB is that it is a dynamic disease. Individuals with chronic infection should be monitored regularly due to the ability of chronic infection to transition through different clinical phases that are characterized by variable levels of serum alanine aminotransferase (ALT), HBV DNA, and antigens. Therefore, serial testing of ALT and HBV DNA will be important in guiding treatment decisions. The authors of this review will discuss updates in the management of CHB including new treatments, updates in guidelines, and treatment strategies in addition to current clinical trials evaluating new curative treatments.

Current treatments

Current available antiviral therapy for CHB are nucleoside/nucleotide analogues (NAs) and pegylated interferon (PEG-IFN). The NAs which inhibit viral polymerase/reverse transcriptase are effective in suppressing viral replication and decreasing risk for the development of cirrhosis and HCC. Rarely do they result in eradication of the virus and usually involve lifelong therapy. PEG-IFN is the first treatment approved for CHB with mechanisms of action involving interference in the HBV lifecycle [6]. Compared to NAs, the advantage of PEG-IFN therapy is to induce long-term immunological control with a finite duration treatment with higher rates of HBeAg and HBsAg loss. There is no risk for selection of resistant variants. The disadvantages of PEG-IFN therapy are less effective suppression of viral replication and the requirement of subcutaneous injection with adverse events including flu-like symptoms, myelosuppression, worsening of underlying mood disorders, and exacerbation of underlying autoimmune conditions. It is also contraindicated in patients with pregnancy, decompensated cirrhosis, or severe exacerbations of hepatitis. Due to these reasons, PEG-IFN is not used widely in treatment.

Current US Food and Drug Administration (FDA)-approved NAs recommended as first-line therapy are tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and entecavir (ETV) (Table 1). TAF, approved by the FDA in November 2016, is a prodrug of TDF that has demonstrated antiviral efficacy similar to TDF but at a lesser dose. TAF, like TDF, is a NA that inhibits reverse transcriptase of pre-genomic RNA to HBV DNA. Two landmark studies compared TAF to TDF in randomized, double-blind, non-inferiority phase III trials. The trial of 873 HBeAg-positive patients randomized to TAF 25 mg daily and TDF 300 mg daily in a 2:1 ratio showed similar 48-week responses, with serum HBV DNA <29 IU/mL in 64% vs. 67%, ALT normalization in 72% vs. 67%, HBeAg loss in 14% vs. 12%, and HBsAg loss in 1% vs. 0.3% in the TAF and TDF groups, respectively [7]. For the 426 HBeAg-negative patients randomized to TAF 25 mg daily or TDF 300 mg daily in a 2:1 ratio, there was comparable 48-week normalization in 83% vs. 75% in the TAF and TDF groups, respectively. However, no patient in either group lost HBsAg [8].

TAF was also noted to cause significantly less decline in bone density and renal function at 48 weeks of treatment compared to TDF. In HBeAg-positive patients, the mean decline in the GFR rate was −0.6 mL/min in TAF patients compared to −5.4 mL/min decline in TDF patients (P<0.0001). In HBeAg-negative patients, the mean decline in the estimate GFR was −1.8 mL/min in TAF patients compared to a decline of −4.8 mL/min in TDF patients (P=0.004). For hip and spine bone mineral density measurements after 48 weeks, the adjusted percentage difference in spine bone mineral density for TAF vs. TDF was 1.88% (95% confidence interval, 1.44–2.31; P<0.0001) for HBeAg-positive patients and 1.64% (95% confidence interval, 1.01–2.27; P<0.0001) in HBeAg-negative patients.

Both studies met the primary endpoint of non-inferiority to TDF. Patients receiving TAF also experienced higher rates of normalization of ALT. TAF and TDF were generally well-tolerated by patients in both studies. Overall, TAF was shown to have greater plasma stability and more efficient delivery of drug to hepatocytes compared to TDF. Because it is given at a lower dose, TAF is able to improve renal and bone laboratory safety parameters compared to TDF.

Treatment indications

The decision to initiate therapy depends upon the presence or absence of cirrhosis or advanced fibrosis, HBeAg and HBeAb status, level of HBV DNA, and aminotransferase levels. Recent updated guidelines on HBV management from the American Association for the Study of Liver Diseases (AASLD) recommend treating patients with persistently elevated ALT ≥2 times the upper limit of normal (ULN) and an elevated HBV DNA >20,000 international units/mL in HBeAg-positive patients or HBV DNA ≥2000 international units/mL in HBeAg-negative patients [9]. They also recommended using an ULN of ALT 35 U/L for men and 25 U/L for women to guide management decisions. The ULN of ALT in healthy adults have been reported to be 29–33 U/L for males and 19–25 U/L for females [9–12].

Growing evidence supports the importance of timely initiation of antiviral therapy. When initiated early, NAs can arrest progression of liver disease. Histologically, this can result in significant improvement of necroinflammation and fibrosis. For those with established cirrhosis, this can even result in

Table 1. Preferred HBV treatments (not head to head comparisons)

Drug	Dose	HBV DNA suppression %	ALT normalization %	HBeAg loss % (eAg pos)
Peg-IFN-2a[a]	180 µg weekly	eAg pos: 30–42 (<2000–40,000 IU/mL) 8–14 (<80 IU/mL) eAg neg: 43 (<4000 IU/mL) 19 (<80 IU/mL)	eAg pos: 34–52 eAg neg[b]: 59	32–36
TAF[c]	25 mg daily	eAg pos: 73 (<29 IU/mL) eAg neg: 90 (<29 IU/mL)	eAg pos: – eAg neg[b]: 81	22
TDF[d]	300 mg daily	eAg pos:76 (<60 IU/mL) eAg neg: 93 (<60 IU/mL)	eAg pos: 67–68 eAg neg[b]: 76	–
ETV[e]	0.5 mg daily	eAg pos: 61 (<50–60 IU/mL) eAg neg: 90–91 (<50–60 IU/mL)	eAg pos: 68–81 eAg neg[b]: 78–88	22–25

Drug	HBeAg seroconversion % (eAg pos)	HBsAg loss %	Pregnancy category[f]	Side effects
Peg-IFN-2a[a]	29–36	eAg pos: 2-7; 11 (3 years post treatment) eAg neg: 4; 6 (3 years post treatment)	C	Flu-like symptoms, fatigue, mood disturbance, cytopenia, autoimmune disorders
TAF[c]	18	eAg pos: 1 eAg neg: <1	Insufficient human data	Lactic acidosis
TDF[d]	21	eAg pos: 8 eAg neg: 0	B	Nephropathy, Fanconi's syndrome, osteomalacia, lactic acidosis
ETV[e]	21–22	eAg pos: 4–5 eAg neg: 0–1	C	Lactic acidosis (in decompensated cirrhosis)

[a]At 6 months after 12-month completion of therapy
[b]Based on laboratory definition of normal and not AASLD definition of ULN≥ALT 35 U/L for men and ≥25 U/L for women
[c]After 2 years of treatment
[d]After 3 years of continuous therapy
[e]After 3 years of continuous therapy
[f]The FDA in 2015 implemented a new labeling system for pregnancy risk, replacing letter-based risk designation with more specific language on pregnancy and lactation

regression of fibrosis. Moreover, decompensated cirrhosis can improve or even resolve [13]. In one study evaluating 707 patients on treatment with antiviral therapy after decompensation, 423 treated persons had significantly better 5-year transplant-free survival than untreated persons (59.7% vs. 46%) [14]. In addition, 33.9% of treated persons were subsequently delisted. In another study, the impact of antiviral therapy on wait list registration for liver transplant was evaluated in the Scientific Registry of Transplant Recipients database from 2003 to 2015 [15•]. In the era of DAA and effective antiviral therapy for HBV, listing for decompensated cirrhosis from HCV and HBV decreased between 2011 and 2015 while listing for HCC in HBV patients remained stable.

It is important to note that despite improvement in survival outcomes in patients receiving long-term effective NA therapy, there still remains a risk for the development of HCC despite treatment with NAs. Although studies do show decrease in the risk of HCC for patients on antiviral therapy, the risk is still present. Patients should continue to undergo routine HCC surveillance imaging [16, 17].

Special populations

HBV reactivation

The phenomenon of HBV reactivation (HBVr) has been well documented in patients with resolved infection or inactive carrier state receiving cancer chemotherapy. HBVr is characterized by (1) rise in HBV DNA compared to baseline (or an absolute level of HBV DNA when a baseline is unavailable) and (2) reverse seroconversion (seroreversion) from HBsAg negative to HBsAg positive for HBsAg-negative and anti-HBc-positive patients. When reactivation occurs, a hepatitis flare can ensue demonstrated by ALT elevation [18–25].

The consequences of HBVr can be self-limiting or lead to fulminant liver failure and death. Reactivation can necessitate the early termination of chemotherapy or delay treatment. Studies have shown that HBVr from anticancer therapies occurred in 41–53% of HBsAg-positive/anti-HBc-positive patients and 8–18% of HBsAg-negative/anti-HBc-positive patients [24, 25]. Based on a systematic review, patients receiving anticancer therapy who were HBsAg positive/anti-HBc positive had liver failure rates around 13.9% (polled estimate, range 8.6–20.3%) [24]. For anti-rheumatic therapies, the risk of HBVr has been reported to be 12.3% in HBsAg-positive/anti-HBc-positive patients and 1.7% in HBsAg-negative/anti-HBc-positive patients [26, 27].

The mechanism behind HBVr is again attributed to the persistence of the virus in infected cells from the formation of cccDNA which is resistant to cellular breakdown and immune clearance. Despite serologic recovery from HBV (positive HBsAb), the cccDNA can still persist in the hepatocyte as a latent form of infection with various immunologic mechanisms to prevent viral replication from occurring. This likely involves both adaptive and innate immune activities. However, during immunosuppression, latent infection can reactivate leading to active hepatitis. HBVr can be easily prevented through antiviral treatment. Multiple meta-analyses have supported the importance of antiviral therapy use prophylactically to reduce reactivation risk, the development of hepatitis, reduction of mortality, and interruption of anticancer therapy [28–31].

Recent societal guidelines including AASLD, European Association for Study of the Liver (EASL), and the Center for Disease Control (CDC) advise that all persons prior to receiving immunosuppressive, cytotoxic, or immunomodulatory therapy be screened for HBV with HBsAg and anti-HBc (total or IgG) before the initiation of immunosuppressive therapy [5, 9, 32]. It is the authors' recommendation that all patients undergoing immunosuppressive therapy be screened for HBsAg, HBsAb, and anti-HBc. The decision to initiate prophylactic antiviral therapy should be risk stratified based on the patient's HBV serologic status, underlying disease, and the immunosuppressive therapy used.

Treatment recommendations

1. For HBsAg-positive patients, start anti-HBV prophylaxis prior to receiving immunosuppressive or cytotoxic therapy as there is high risk for HBV reactivation [19, 24, 33].
2. For HBsAg-negative/anti-HBc-positive patients, there is low risk for HBV reactivation compared to HBsAg-positive patients:

(a) Depending on the type of immunosuppressive treatment they will receive, one could initiate *antiviral therapy prophylactically* or closely monitor with *on-demand therapy* at first sign of HBVr [9].

(b) Anti-HBc-positive patients receiving biological therapies from rheumatic conditions or inflammatory bowel disease can be monitored without needing anti-HBV prophylaxis [34–38]. However, anti-HBc-positive patients receiving CD-20 agents (rituximab) such as for lymphoma or that undergo stem cell transplant should be started on prophylactic therapy [9, 33].

(c) If the decision is to monitor the patient without prophylaxis, HBV DNA and ALT should be checked every 1–3 months and up to 12 months after cessation of anti-HBV therapy with initiation of on-demand antivirals.

3. First-line therapy with TDF and ETV is advised due to their high potency and high resistance barrier. Antiviral therapy should be initiated prior to initiation of immunosuppressive therapy.

(a) Continue prophylactic antiviral therapy for additional 6–12 months after discontinuation of immunosuppressive therapy.

(b) Prophylactic antiviral therapy should be extended to 12 months from the time of last treatment dose for CD-20 therapy. Reactivation beyond 12 months has been reported [39–41].

HBV reactivation for HCV patients receiving DAA therapy

The FDA in 2016 issued a warning regarding the risk of HBVr in patients receiving DAA therapy. At least 29 cases of HBVr after HCV clearance have been reported, which included two fatal cases, and one leading to liver transplantation [42]. Because HBVr can occur soon after the start of DAA therapy, the FDA has advised screening all individuals who are to receive DAA for any evidence of prior HBV exposure.

The global prevalence of HBV-HCV coinfection among those infected with CHB is estimated to be between 3.5 and 7.0 million [43]. Attention to HBV-

HCV coinfected individuals remains important as there is higher risk of progression to cirrhosis and the development of HCC compared to mono-infected patients. The exact mechanism of HBVr in HBV-HCV coinfection is unclear; however, in dual infection, HCV often tends to dominate while HBV DNA tend to be low or undetectable. There may be an indirect immune-mediated mechanism of control of HCV over HBV through an innate immune response [44]. Because clinical trials for DAA therapy did not include HBsAg individuals with HCV coinfection, HBVr has only been reported after direct-acting antiviral agents (DAAs) became available for clinical use. Reports describing the presentation of HBVr in the setting of DAA therapy have ranged from asymptomatic individuals with only rise in HBV DNA to elevation of HBV DNA and ALT with or without liver failure [45, 46•, 47].

The only prospective study, and largest to date, is one from Taiwan which evaluated HBVr during DAA therapy in 111 patients with HBV/HCV coinfection, receiving sofosbuvir/ledipasvir for 12 weeks [46•]. Interestingly, 61% had genotype 1, 39% genotype 2 infection; 62% women, 16% with compensated cirrhosis, along with HBV infection. All but one were positive for the HBsAg; one patient who was HBsAg positive at screening was found to be HBsAg negative at baseline. Two groups of patients were evaluated: (1) patients with undetectable HBV DNA and (2) patients with HBV DNA >20 IU/mL at baseline. Of the 37 patients who had HBV DNA below 20 IU/mL, 31 (84%) had at least 1 episode of quantifiable HBV DNA through posttreatment week 12. Of the 74 patients who had baseline HBV DNA levels of 20 IU/mL or more, 39 (53%) had increases of HBV DNA greater than 1 $\log_{10}$ IU/mL through posttreatment week 12. Of the 5 patients who had increased levels of HBV DNA with a level of ALT >2 times the ULN through posttreatment week 12, three of these patients started HBV treatment. One patient with HBVr since week 8 and concomitant ALT elevation >2 times ULN at posttreatment week 48 started treatment at posttreatment week 53.

All of these reports have predominantly described asymptomatic increases of HBV DNA and or ALT without liver failure. The results of this Taiwanese study also show that most patients (63%, 70/111) demonstrated an increase in HBV DNA but only 5 (5%) had concomitant increase in ALT through posttreatment week 12. None had liver injury or a fatal outcome. Based on our current limited data, clinically significant HBVr in the setting of DAA therapy remains difficult to predict.

Guidance statement for treatment of patients with HBV/HCV coinfection per AASLD/IDSA [47]

1. All HBsAg-positive patients should be tested for HCV infection.
2. HBV treatment is determined by HBV DNA and ALT levels as per the AASLD HBV guidelines for mono-infected patients.
3. HBsAg-positive patients are at risk of HBV DNA and ALT flares with HCV DAA therapy:

(a) For HBsAg-positive patients whose HBV DNA level meets AASLD criteria for treatment, antiviral therapy for HBV should be initiated.

(b) For patients whose baseline HBV DNA level does not meet criteria for treatment, one can consider below approaches:

i. Initiate prophylactic antiviral therapy for those with low or undetectable HBV DNA levels. Prophylaxis should be continued until 12 weeks after completion of DAA therapy.

ii. Monitor HBV DNA levels every 4–8 weeks during treatment, immediately after DAA therapy, and for 3 months post-treatment. Initiate HBV antiviral therapy only if HBV DNA rises >10-fold above baseline or to >1000 IU/mL in those with previously undetectable HBV DNA level.

4. HBsAg-negative/anti-HBc-positive patients with HCV are at very low risk of reactivation with DAA therapy:

(a) ALT levels should be monitored at baseline, at the end of treatment, and during follow-up.

(b) Check HBV DNA and HBsAg for those whose ALT levels increase or fail to normalize during treatment or posttreatment despite declining or undetectable HCV RNA levels.

5. Patient should be followed up after stopping HBV antiviral therapy given concerns for flare after withdrawal of treatment.

Prevention of perinatal transmission

In countries with high prevalence of CHB, perinatal transmission accounts for the majority of HBV cases with high risk of transmission particularly in women with high viral loads [48, 49]. Without the use of active and passive immunization, the risk of mother-to-child transmission of HBV in HBsAg-positive mothers is as high as 90%. With the introduction of universal HBV vaccination and hepatitis B immune globulin (HBIG) for all newborns of HBsAg-positive mothers, the risk of transmission has significantly reduced. However, despite proper vaccination at birth, the rate of HBV transmission from mothers with high viremia to their infant has been reported between 9 and 39% [50–52]. The goal of HBV treatment during pregnancy is to minimize the risk of HBV transmission from vaccination failure.

Current guidelines recommend screening pregnant women for CHB during the first trimester of pregnancy [9]. Pregnant patients with HBV DNA levels >200,000 IU/mL should be offered antiviral prophylaxis at the end of the second trimester to early third trimester between weeks 28 and 30 and continued until 4–12 weeks after delivery [9].

Management options for HBV during pregnancy

NAs are the mainstay of HBV prophylaxis in the expectant mother. Several NAs have been shown to be beneficial and appear to be equally efficacious in preventing vertical transmission of HBV [53–56]. In a recent meta-analysis of five randomized control trials (RCTs) consisting of 444 pregnant women, administration of lamivudine (LAM) during pregnancy together with HBIG/HBV vaccination in infants led to an 11.7% reduction in HBsAg seropositivity and a 21.2% reduction in infant HBV DNA positivity compared to HBIG/HBV vaccination alone [57••]. Similarly, telbivudine (LdT) and HBIG/HBV vaccination led to lower infection rates in infants compared to HBIG/HBV vaccination alone.

Most studies of tenofovir-based derivatives have shown reduced risk of perinatal HBV transmission in patients on antiviral therapy [49, 55, 58]. However, in a recent RCT of 331 pregnant women with CHB [59••], TDF in combination with HBIG/HBV vaccination led to 0% transmission rate in infants, compared to a 2% transmission rate in the group receiving HBIG/HBV vaccination alone. The overall low transmission rates and the lack of difference between the two groups raise interest regarding a number of factors, including the stringent timing for administration of HBIG/HBV vaccination (within 4 h after birth), and the increased number of infant HBV vaccinations (five vaccinations at 0, 1, 2, 4, and 6 months, compared to the historical three vaccinations at 0, 1, and 6 months) [59••]. Indeed, this study challenges the current standard in regard to the optimal time window for HBV immunoprophylaxis in infants. Moreover, the increased frequency of HBV vaccinations provides an interesting concept that warrants further investigation [59••]. In a recent prospective study of 48 pregnant women who missed the optimal time window for antiviral prophylaxis, administration of TDF plus HBIG was found to induce a more rapid and sustained decline in HBV DNA compared to TDF alone [60•].

Safety of antiviral therapy in pregnancy

ETV is contraindicated in pregnancy due to significant carcinogenic potential in animal studies [9]. LAM, LdT, and TDF all appear safe during pregnancy with no increase in the risk of congenital malformation, prematurity, or maternal complications based either on human or animal data [57••]. Although long-term outcomes related to perinatal administration of these drugs in humans are unknown, TDF and LdT did not show any adverse pregnancy outcomes in animal studies or human studies. While LAM was found to be teratogenic in animal studies [56], human studies have supported its safety in pregnancy. There is insufficient safety data on TAF in pregnancy at this time.

It is important to recognize that none of these drugs are licensed for use in pregnancy; hence, the risks and benefits of antiviral therapy should be discussed prior to administration in the pregnant patient. Nonetheless, TDF is generally preferred over LdT and LAM due to lower resistance rates and the lack of teratogenicity in animal studies [9, 32, 56]. Among women on antiviral therapy, there was a prevalence of 2.8 birth defects per 100 live births measured in 19,005 live births [61]. This prevalence was not significantly different compared to data reported in the CDC's birth defects surveillance system (MACDP) or the Texas Birth Defects Registry (TBDR) [61].

Future therapeutics

The ultimate treatment endpoint in the CHB patient is the achievement of cure. What appears to be the most realistic and feasible goal is attaining "functional" cure, characterized by undetectable HBV DNA and loss of HBsAg, with or without antibody formation of anti-HBs. As mentioned previously, patients with functional cure still have persistent cccDNA and viral sequences within the host chromosomes. There are currently over 30 investigational agents in the pipeline targeting (1) specific viral gene products (direct-acting antiviral agents [DAAs]) and (2) host immune-modulatory response (indirect-acting antiviral agents

[IDAAs]). The most promising therapeutic strategies will likely involve a combination antiviral approach involving both direct acting and indirect acting agents (Table 2).

Targeting the virus: direct-acting antiviral agents

HBV attachment/entry inhibitors

The goal of HBV entry inhibitors is to prevent post-exposure infection such as in neonates of infected mothers or in recipients of HBV-infected livers. The recent discovery of sodium/taurocholate co-transporting polypeptide (NTCP), a bile acid transporter that is crucial to entry of HBV into the host hepatocyte, has garnered excitement about the potential therapeutic application of entry inhibitors [62]. Myrcludex B is a synthetic lipopeptide that binds to the NTCP receptor and thus prevents binding and entry of the virus through competitive inhibition [63, 64]. A recent phase 1b/IIa trial conducted on 24 HBV/HDV chronically infected patients randomized to myrcludex B, PegIFNa-2a, or combination therapy for 24 weeks showed decreased HDV RNA in all cohorts and decreased HBV DNA in patients on combination therapy [65]. An NTCP antagonist, irbesartan which is an angiotensin receptor blocker currently used in treating hypertension, has been shown to inhibit HBV uptake while preventing cccDNA in an in vitro cell line [66]. Additional clinical data are needed to further define the role of entry inhibitors in HBV therapy.

Viral transcript targets (RNA interference/siRNAs)

RNA interference (RNAi) is a mechanism in which double-stranded RNA degrades mRNA or blocks translation, thus inhibiting gene expression [67, 68]. Several small interfering RNAs (siRNAs) that block HBV protein transcription have been developed, and some of them, including ARC-520, ARB-1467, and ALN-HBV, have been tested in clinical trials [67, 69]. In a phase II trial, ARC-520 provided sustained knockdown of HBV DNA and viral antigens [70]. However, concerns for toxicities related to its delivery agent halted further clinical development of ARC-520 [70]. ARB-1467 was studied in 24 subjects and found to reduce HBsAg levels after administration of single and multiple doses [71]. ALN-HBV is currently in phase I/II clinical trials [72].

Gene editing strategies: cccDNA formation inhibitors/inactivators

Complete eradication of HBV requires mechanisms aimed at disrupting the formation of cccDNA, inhibiting its transcription, or eliminating it entirely from the host [73]. Early studies involving hepatocytes in cell culture showed that disubstituted sulfonamides, including CCC-0975 and CCC-0346, can disrupt the formation of cccDNA from rcDNA [74]. PEG-IFN, well established as therapy for HBV infection, inhibits cccDNA transcription through post-translational modifications [75]; and other compounds that confer post-translational modification show promise for cccDNA inhibition [76]. Recently, mechanisms that target and cleave cccDNA, including zinc finger nucleases (ZFNs), transcription activator-like endonucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)-associated system 9 (Cas9) proteins, are

Table 2. Potential therapies for HBV in developmental pipeline

Drug class	Drug	Developer	Status
Direct-acting antiviral agents			
Entry inhibitors	Myrcludex B	Hepatera/MYR GmbH	Phase II
	Irbesartan	Sanofi Research	FDA-approved for hypertension
Viral mRNA inhibitors	ARC-520/–521	Arrowhead pharmaceuticals	Terminated
	ARB-1467	Arbutus Biopharma	Phase II
	ALN-HBV	Alnylam	Phase I/II
	RO7020322 (RG7834)	Roche	Phase I
	Ionis HBVRx (GSK3228836)	Ionis Pharma/GSK	Phase I
	IONIS-HBVLRx (GSK33389404)	Ionis Pharma/GSK	Phase I
	AB-452	Arbutus Biopharma	Preclinical
	ARB-1740	Arbutus Biopharma	Preclinical
Gene editing	REP2139 and REP2165	Replicor	Phase II
	AB-423	Arbutus Biopharma	Phase I
	AB-506	Arbutus Biopharma	IND enabling
	EBT106	Excision BioTherapeutics	Preclinical
	Di-substituted sulfonamides (ccc0975 and ccc0346)		Preclinical
	TALEN		Preclinical
	Zinc finger nuclease		Preclinical
Nucleocapsid assembly inhibitors/core inhibitors	GLS-4	HEC Pharm	Phase II
	JNJ56136379	Johnson and Johnson; Janssen	Phase I
	ABI-H0731	Assembly Biosciences	Phase I
	AB-423	Arbutus Biopharma	Phase I
	BAY41-4109	AiCuris	Phase I
	NVR 3-778	Noviral Pharmaceuticals/Janssen	Phase I
	ABI-H2158	Assembly Biosciences	IND enabling
	AB-506	Arbutus Biopharma	IND enabling
HBsAg release inhibitor	REP 2139	Replicor	Phase II
	REP 2165	Replicor	Phase II

Table 2. (Continued)

Drug class	Drug	Developer	Status
	BM601		Preclinical
Indirect antivirals (host immune system activators/modulators)			
Toll-like receptor agonists	GS-9620	Gilead Sciences	Phase II
	RO6864018 (RG7795)	Roche	Phase II
	GS-9688	Gilead Sciences	Phase II
Small molecules/checkpoint inhibitors	SB9200	Spring Bank Pharmaceuticals	Phase II
	PD-1/PDL-2 mAb	Merck Sharp and Dohme; Bristol-Myers Squibb	Preclinical
	CTLA-4 mAb		Preclinical
Therapeutic vaccines	ABX-203	Abivax	Phase II/III
	GS-4774	GlobeImmune	Phase II
	AIC649	AiCuris	Phase I
	FB-02.2	Altimmune	Phase I
	TF-1050	Transgene	Phase I
	INO-1800	Inovio	Phase I

being tested [77]. In particular, the CRISPR/Cas9 system holds promise as a potentially curative strategy for CHB infection [78], with several studies reporting robust targeting and cleavage of HBV DNA by CRISPR/Cas9 in vitro in cultured hepatocytes and in vivo in mice. However, several challenges, including specificity of viral targets and analysis of off-target effects, need to be overcome before CRISPR/Cas9 targeting of HBV reaches prime time [78].

Nucleocapsid assembly inhibition/core inhibitors

Core inhibitors, including third-generation 4-H heteroaryldihydropyrimidines (HAPs) such as BAY 41–4109 and GLS4, affect cccDNA occupancy in the nucleus by inhibiting RNA encapsidation and capsid disassembly [79]. Previous studies in mice showed that BAY 41–4109 potently reduced HBV DNA replication; however, there was a rapid rebound in HBV DNA replication at the end of treatment period [80]. GLS4 inhibited replication of adefovir-resistant HBV strains [81] and is currently in phase II clinical studies [82].

HBsAg release inhibitors

Highly stable nucleic acid polymers (NAP) are oligonucleotides containing a sulfur atom that serves as broad-spectrum viral attachment/entry inhibitors. Some of these compounds, including REP-2055, REP-2139, and REP-2165, have been shown to block the release of HBsAg from infected hepatocytes [83]. In a trial of 40 patients who received TDF for 26 weeks and then randomized to TDF plus PEG-IFN with or without NAP (REP-2139 or its derivative REP-2165) for an additional 48 weeks, most patients in the NAP group cleared HBsAg and close to 50% developed anti-HBs [84]. HBsAg release inhibitors show promise as therapy for HBV.

Targeting the host immune system: indirect-acting antiviral agents

Individuals with CHB exhibit weak anti-HBV T cell response; thus, restoration of immune response may play a role in sustained viral suppression. Several immune response modulators for HBV are currently being investigated. Some of these agents, including toll-like receptor (TLR) agonists and immune checkpoint inhibitors, boost innate immune responses, while others, including therapeutic vaccines and engineered T cells, aim to restore adaptive immunity.

Toll-like receptor agonists

The TLR family regulates innate and adaptive immune response by recognizing foreign pathogens, thus triggering cytokine activation and development of adaptive immunity. Preclinical studies showed that GS-9620 reduced serum and hepatic levels of HBV DNA, HBsAg, and HBeAg [85, 86]; however, this agent did not significantly affect HBV or HBsAg levels in phase IIb clinical trials [86, 87]. Combination of GS-9620 with other anti-viral agents may prove beneficial [88].

Immune check point inhibitors

Several chronic viral infections and malignancies produce immune exhaustion, a condition in which overwhelming antigen production leads to a tired immune response and results in increased expression of programmed death-1

receptor (PD-1) [89, 90]. PD-1 interacts with its ligands to inhibit T cell and lymphocyte function, resulting in evasion of immune response by cancer cells. In the last few years, PD-1 checkpoint inhibitors have changed the treatment frontier for several malignancies, including renal cell carcinoma, non-small cell lung carcinoma, and melanoma [91]. Monoclonal antibodies that block PD-1 are currently being investigated for their utility in HBV infection [92].

Engineered T cells

Individuals with HBV have defective T cell receptor (TCR) recognition of HBV; thus, engineering T cells may result in recovery of HBV-directed immune response [93]. T cells have been engineered to express TCRs specific to viruses in culture systems and in animals [94], and transient expression of engineered HBV-specific T cells resulted in targeting of HBV-infected hepatocytes [95]. In a recent study, autologous T cells were engineered to recognize HBV or HCV peptide–HLA complexes in chimeric mice [96]. Engineered T cells hold promise for immune recovery and elimination of HBV-infected hepatocytes.

Therapeutic vaccines

In patients with CHB, the goal of therapeutic vaccines is to stimulate HBV-specific T cell immunity. GS-4774 is a yeast-based therapeutic vaccine containing HBV core protein and X proteins that was recently studied in a phase IIb clinical trial in which 178 CHB patients who had achieved viral suppression with NA therapy were randomized to NA alone vs. NA plus GS-4774. No significant differences in mean HBsAg reduction from baseline to week 24 or 48 were seen [97]. In another phase II study of 195 CHB patients randomized to TDF alone vs. TDF plus GS-4774, modest decreases in HBsAg were seen in patients on combination therapy but with no seroconversion [98]. A phase IIb/III study of ABX203, a vaccine containing HBsAg and HBcAg recombinant proteins, in HBeAg-negative patients after cessation of ETV and TDF therapy [99] suggested that type of antiviral therapy associated with early virological relapse [100•].

NA treatment cessation

A potential new strategic approach in CHB therapy is to perform a structured discontinuation of NA treatment in patients who have been on treatment for a few years. Emerging data show that after cessation of treatment, 20–30% of patients will demonstrate immune system recovery from "exhaustion" related to chronic infection and may be able to mount increased immune response activity towards the virus once replications recur [101–104, 105••].

A recent trial conducted in Taiwan, and the largest to date, evaluated 691 out of 1075 HBeAg-negative patients (mean age of 52.3 years, 86% male, 44.6% cirrhosis) who remained HBsAg positive after NA treatment for a median of 156 weeks and had treatment stopped as per the Asian-Pacific Association for the Study of the Liver stopping rule [105••]. During a median off-therapy follow-up period of 155 weeks, HBsAg seroclearance occurred in 42 patients, representing a 6-year cumulative incidence of 13% and an estimated annual

incidence of 1.78%. Shorter time to undetectable HBV DNA (<12 weeks), greater HBsAg reduction during therapy (>1 $\log_{10}$), lower end-of-treatment HBsAg level (<100 IU/mL), patients with sustained response, and relapsers not retreated were factors for off-therapy HBsAg seroclearance. The incidence of HBsAg seroclearance after stopping NA therapy was much higher than that during therapy, and highest in patients without virologic and clinical relapse after therapy cessation. In addition, patients with clinical relapse who remained untreated had a 7.34 times higher rate of HBsAg clearance than those who received retreatment. This study supports growing evidence that transient untreated clinical relapse after interruption of NA may sufficiently boost the ability of immune cells to kill HBV-infected cells which can lead to functional cure.

Conclusion

CHB remains a global public health problem with risk for cirrhosis, liver failure, and HCC. Despite an effective vaccination to prevent infection, the cure for CHB remains elusive. Recent developments in CHB include the importance of appropriate screening and treatment of patients at risk for reactivation either undergoing DAA therapy for HCV or receiving immunosuppressive or anti-cancer therapy. Moreover, treating HBsAg pregnant mothers when indicated is crucial in reducing risk of HBV transmission to the infant from vaccination failure. The new addition to the antiviral armamentarium, TAF, demonstrates more potency and less renal and bone toxicity. In addition, robust data have affirmed the importance of antiviral therapy and its timely initiation. When initiated early, NAs can improve outcomes by arresting progression of liver disease. With over 30 investigational agents in the pipeline that hope to achieve "functional cure," promising therapeutic approaches will likely involve combination strategies with direct-acting antivirals that target the virus and indirect antiviral therapies that target the host immune system.

Author Contributions

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Critical revision (HL/BB)
Approved final draft (HL)

Compliance with Ethical Standards

Conflict of Interest
Hannah Lee declares that she has no conflict of interest. Bubu Banini declares that she has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

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- •• Of major importance

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