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ABOUT COVER

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REVIEW

Advances in treatment and prevention of hepatitis B

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Abstract

Chronic hepatitis B (CHB) continues to contribute to worldwide morbidity and mortality significantly. Scientists, clinicians, pharmaceutical companies, and health organizations have dedicated substantial Intellectual and monetary resources to finding a cure, increasing immunization rates, and reducing the global burden of CHB. National and international health-related organizations including the center for disease control, the national institute of health, the American Association for the study of liver disease (AASLD), The European association for the study of the Liver (EASL), The Asia Pacific association for the study of the Liver (APASL) and the world health organization release periodic recommendations for disease prevention and treatment. Our review of the most recent guidelines by EASL, AASLD, APASL, and Taiwan Association for the Study of the Liver revealed that an overwhelming majority of cited studies were published before 2018. We reviewed Hepatitis B-related literature published 2018 onwards to identify recent developments and current barriers that will likely direct future efforts towards eradicating hepatitis B. The breakthrough in our understanding of the hepatitis B virus life cycle and resulting drug development is encouraging with significant room for further progress. Data from high-risk populations, most vulnerable to the devastating effects of hepatitis B infection and reactivation remain sparse. Utilization of systems approach, optimization of experimental models, identification and validation of next-generation biomarkers, and precise modulation of the human immune response will be critical for future innovation. Within the foreseeable future, new treatments will likely complement conventional therapies rather than replace them. Most Importantly, pragmatic management of CHB related population health challenges must be prioritized to

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produce real-world results.

Key Words: Chronic hepatitis B; Hepatitis B virus; Hepatitis B prevention; Hepatitis B treatment; Hepatitis B vaccination; Hepatitis B reactivation

Core Tip: Given the hepatitis B viral life cycle's unique characteristics, a true cure is lacking. Most recent guidelines from multiple societies including the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, Asia Pacific Association for the Study of the Liver, and Taiwan Association for the Study of the Liver, primarily include data published before 2018. A significant amount of hepatitis B relevant literature has been published since 2018. Our manuscript aims to review the recent literature for new developments and to identify the global strategies and knowledge gaps that will soon shape the scientific endeavor in this field.

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INTRODUCTION

Hepatitis B virus (HBV) has infected humans for at least the past 40000 years[1] and is the 10th leading global cause of death[2]. HBV is the only DNA-based hepatotropic virus that exerts many adverse effects on the infected cells leading to necroinflammation, fibrosis, and carcinogenesis[3]. The world health organization (WHO), in 2015 has estimated 257 million people infected with chronic hepatitis B (CHB), while 887000 died from complications of hepatitis B[4]. Worldwide approximately only 10% of the patients with CHB are aware of the infection. A better understanding of hepatitis B biology, laboratory tests, and the immunological response has helped us develop vaccines and nucleoside/nucleotide analogs (NAs) to reduce new infection rates and achieve virologic suppression[5]. An overwhelming majority of studies cited in the most recent guidelines from various societies were published before 2018[6-10]. Our manuscript aims to review the recent literature for new developments and to identify the global strategies and knowledge gaps that will soon shape the scientific endeavor in this field.

METHODS

Literature search: We conducted online electronic searches (published human clinical trials in English) of the National Library of Medicine (Bethesda, MD, United States) MEDLINE database, Cochrane Library, and manual searches of selected specialty journals to identify any pertinent literature. We searched three MEDLINE databases (Ovid, PubMed, and EMBASE) using the following keywords hepatitis B, prevention of hepatitis B, hepatitis B and co-infection, management of hepatitis, hepatitis B and transplantation, hepatitis B mortality, hepatitis B vaccination, hepatitis B reactivation, systematic review for hepatitis B, meta-analysis and hepatitis B. The references of articles were reviewed for additional articles.

Inclusion criteria: Articles describing original research and high-quality review articles published within the last three years were selected. The search was focused on hepatitis B articles published in 2018 or later.

Exclusion criteria: Articles that did not contribute significantly to research and scientific knowledge after 2018 were excluded.

ADVANCES IN TREATMENT AND PREVENTION OF HEPATITIS B

Serological markers for hepatitis B infection

The serologic patterns of chronic HBV infection are varied and complex. Antigens and antibodies associated with HBV infection include hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs), hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc), and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Testing also can be performed to assess the presence and concentration of circulating HBV DNA. At least one serologic marker is present during each of the different phases of HBV infection. Serologic assays are commercially available for all markers except HBcAg, because no free HBcAg circulates in blood[11] (Table 1).

There is overwhelming evidence that antiviral therapy reduces mortality, and risk of hepatocellular carcinoma (HCC) and improves intermediate prognosis, and overall health outcomes. As such, the most recent document from the United States Preventive Service Task Force recommends screening for hepatitis B in adolescents and adults at increased risk of HBV, with HBsAg tests approved by the United States Food and Drug Administration, followed by a confirmatory test for initially reactive results[12]. A positive HBsAg result indicates chronic or acute infection. Screening recommendations for special populations include initial testing with anti-Hbs and or anti-Hbc in addition to HbsAg[10]. Serologic panels performed concurrently with or after HBsAg screening allow for diagnosis and to determine further management[12].

Serological markers are critical for monitoring treatment response and predicting complications. The primary endpoint for treatment is durable HBsAg loss (functional cure) based on assays with a lower detection limit (LLOD-0.05 IU/mL) with or without HBsAg seroconversion and undetectable serum HBV DNA after completing a course of treatment[13].

Zhang *et al*[14] published in 2018, results from a multicenter trial, assessing kinetics of HBsAg in 1795 HBV patients[14]. The HBsAg titers were significantly higher (P < 0.0001) in patients with HBeAg positive HBV than HBeAg negative HBV patients. They demonstrated that in patients with positive HBeAg, the HBsAg titers were inversely proportional to fibrosis, while alanine aminotransaminase (ALT) and necroinflammatory activity were directly correlated with HBsAg titers in HBeAg negative HBV patients[14].

Biomarkers for HBV functional cure include HBsAg clearance profile (CPs, defined by loss of binding at both loops 1 and 2 epitopes of the 'a' determinant)[15]. A 48th week and 192nd week HBsAg CPs analysis of genotype A CHB patients on either tenofovir or adefovir for at least four years prior revealed its positive association with HBsAg loss (SL), seroconversion, and response to treatment[15].

For most patients with CHB who do not achieve a functional cure, long-term NA is likely needed. Despite long-term therapy, liver-related complications can still occur even with sustained viral suppression. To this end, newer virological markers were developed to predict the risk of liver-related complications in these patients who often have undetectable serum HBV DNA, and the likelihood of achieving a functional cure, which is defined as off-therapy virological suppression[16].

The covalently closed circular DNA (cccDNA) protein is a template used for transcription and subsequent translation of viral proteins. The persistence of cccDNA within the nucleus of infected hepatocytes despite treatment and viral suppression is the underlying mechanism for infection reactivation after treatment cessation[17]. Of the various viral proteins synthesized, the hepatitis b core-related antigen (HBcrAg) is a combination of three related viral proteins (HBcAg, HBeAg, and a truncated 22kDa precore protein)[18,19]. HBcrAg has a superior correlation to the decline in HBV DNA levels with antiviral therapies, and with intrahepatic HBV cccDNA levels[20-23]. It is also helpful in predicting HBV reactivation in immunosuppressed individuals and the development of HCC[24-28]. Another relatively novel biomarker, HBV RNA is a pregenomic RNA containing virion similar to HBcrAg[16]. Treatment naive patients with CHB have lower serum levels (lower by 1-2 logs) of HBV RNA when compared to HBV DNA serum levels[29,30]. However, in patients receiving NA's, the HBV RNA levels are significantly higher than HBV DNA and hence it is a predictor of response. HBV RNA has a strong linear correlation with both HBV DNA and HBsAg titers[31, 32]. Both, HBcrAg and HBV RNA, can predict long-term off-therapy HBV virological control in patients treated with NA's[29,33]. A recent prospective trial by Chang *et al* [34] confirmed HBcrAg levels to reflect on-treatment hepatic fibrosis progression, and hence its role in monitoring hepatic histological changes[34]. Liao *et al*[35] demonstrated the utility of monitoring of HBV RNA and HBcrAg levels for NA-treated patients with undetectable HBV DNA and undetectable HBV RNA occurring before HBcrAg undetectability[35].

Table 1 Studies addressing hepatitis B testing and diagnosis

Ref.	Study type	Findings
Gao *et al*[32], 2017	Prospective trial	Higher HBV RNA levels, in NA-treated patients are a predictor of response
		HBV RNA has a strong linear correlation with HBV DNA and HBsAg titer
		HBcrAg and HBV RNA can predict long-term off-therapy HBV virological control in NA-treated patients
Zhang *et al* [14], 2018	Randomized, controlled, double-blind clinical trial	HBcrAg titers were significantly higher ($P < 0.0001$) in patients with HBeAg positive HBV. HBsAg titers were directly proportional to necro-inflammatory activity, and inversely proportional to fibrosis
Walsh *et al* [15], 2019	Prospective trial	HBsAg clearance profile has positive association with HBsAg loss, seroconversion, and response to treatment in patients treated chronically with Adefovir or Tenofovir
Chang *et al* [34], 2019	Prospective trial	HBcrAg levels reflect liver parenchymal fibrosis progression, and have utility in monitoring hepatic histological changes
Liao *et al*[35], 2019	Prospective trial	Demonstrated utility of monitoring HBV RNA and HBcrAg levels for NA-treated patients with undetectable HBV DNA
Multiple authors	Prior Studies	HBcrAg has a superior correlation to the decline in HBV DNA levels with anti-viral therapies, and with intrahepatic HBV cccDNA levels[20-23]
		HBcrAg can predict HBV reactivation in immunosuppressed individuals and the development of Hepatocellular Carcinoma[24-28]
		HBV RNA is a pregenomic RNA containing virion that has a similar profile to HBcrAg[16]. Treatment naïve patients with CHB have lower (1-2 logs lower) serum levels of HBV RNA compared to HBV DNA [29,30]

HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; NA: Nucleos(t)ide analogs; HBV: Hepatitis B virus; HBcrAg: Hepatitis b core-related antigen; cccDNA: Covalently closed circular DNA; CHB: Chronic Hepatitis B.

Multiple challenges must be met before these biomarkers can be fully utilized in clinical practice. The specific methods and technical details of serum RNA detection vary widely between different studies and standardization of such is urgently needed [16]. To exclude interference from viral DNA, methods for measuring pgRNA usually require a selective DNA degradation step, which is complicated and time-consuming and also compromises the accuracy of detection[36]. Further research is needed to determine specific cutoff values of HBcrAg to determine clinical outcomes and determine the role of HBV RNA in occult hepatitis B infection, HbsAg seroclearance, HBV reactivation, and development of HCC[16]. Additionally, the biomarkers will need to be validated in different racial and ethnic populations. Studies correlating novel biomarkers with hepatic fibrosis and cccDNA require serial liver biopsies, resulting in reduced sample sizes. In a recent trial, Brakenhoff *et al*[37] showed that HBV RNA decline without concomitant viral antigen decrease is associated with a low probability of sustained response and hepatitis B surface antigen loss. This study highlighted the need for future trials that consider the kinetics of combined biomarkers to assess antiviral efficacy[37].

HEPATITIS B VACCINATION

Current recommendations advocate pre-exposure universal vaccination for newborns and non-immune individuals who are at a high risk of exposure or have a poor disease outcome [patients with hepatitis C virus infection, human immunodeficiency virus (HIV), men who have sex with men, intravenous drug users, health care workers, and household contacts of patients with a positive hepatitis surface antigen][38,39]. Until 2017, most available HBV vaccination schedules required three doses of the vaccine to be administered at specific intervals and had > 90% protective response[40].

On November 9, 2017, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant, was approved by the Food and Drug Administration for the prevention of HBV in persons aged ≥ 18 years[41]. The vaccine is administered in two doses, one month apart. On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP)* recommended HepB-CpG for use in persons aged ≥ 18 years[42].

Unfortunately, 5%-10% of patients lack an immunological response and remain unprotected despite vaccination[43]. A hepatitis B "non-responder" refers to a person

who does not develop Hepatitis B surface antibodies after completing two whole series of hepatitis B vaccine and for whom an acute or CHB infection has been ruled out[44]. Non-response is associated with different HLA-DR alleles and impaired Th cell response, among other factors such as route of injection, age, gender, body mass, and other factors[45]. For non-responders to the initial vaccination series, a second series of the original vaccination schedule is recommended[46]. Persons with Hepatitis B surface antibody (anti-HBs) < 10 mIU/mL following receipt of 2 doses of HepB-CpG should be revaccinated with a second complete HepB vaccine series followed by anti-HBs testing 1–2 mo after the final dose. Alternatively, revaccination may consist of administration of an additional single HepB vaccine dose followed by anti-HBs testing 1–2 mo later (and, if anti-HBs remains < 10 mIU/mL, completion of the second HepB vaccine series followed again by anti-HBs testing 1–2 mo after the final dose)[47]. Post-exposure prophylaxis should be considered for individuals following a needlestick injury or potentially infectious exposure to body fluids with blood or semen)[47].

Recent studies evaluating the efficacy of alternate revaccination regimens in non-responders are promising and could shape future recommendations. Raven *et al*[48] studied 480 immunocompetent, non-responders in a multicenter, open-labeled, randomized, controlled superiority trial comparing the effectiveness of revaccination with initial regimen (control arm: With HBVaxPro 10 µg or Energix B 20 µg) *vs* three alternate regimens (Twinrix 20 µg or Fendrix 20 µg, or HBVaxPro 40 µg). Revaccinating with Fendrix 20 µg (83%) or HBVaxPro 40 (98%) resulted in significantly higher proportions of responders compared to controls (67%). Authors argued that the indication for these vaccines should be expanded to enable revaccination of non-responders[48]. In 2018, Koc *et al*[49] attempted to enhance the immune response of the HBVaxPro©-10-µg vaccine by adding a cytokine-based adjuvant. This new adjuvant AI20, containing 20-µg recombinant human Interleukin (IL)-2 attached to 20-µg aluminum hydroxide, was added to HBVaxPro©-10-µg (HBAI20). In an open-label trial, HBAI20 elicited protective anti-HBs titers in 90% of previous non-responders[49].

Additionally, researchers have turned to "Systems vaccinology" to precisely understand vaccine mechanisms and potential determinants of immunological non-response[50,51]. Technological advances with DNA microarrays and high throughput DNA sequencing, mass spectrometry powered proteomics, bioinformatics, and computational methods enable data integration that serves as the basis of systems vaccinology[52].

Qiu *et al*[53] performed transcriptome and cytokine analysis of seven responders and seven non-responders pre-and post-vaccination with a three-dose boost regimen. Compared with responders, nine coding genes (*BPI*, *DEFA1B*, *DEFA4*, *CEACAM8*, *MMP8*, *FOLR3*, *LTF*, *TCN1* and, *TKTL1*) were significantly upregulated in non-responders, which could probably be the characteristic genes in hepatitis B vaccine non-responsiveness. This probability was further strengthened by gene ontology analysis results showing that most of these differentially expressed genes were related to immune response. Cytokine analysis demonstrated that IL-27 and CXCL12 concentrations in responders were significantly higher than non-responders. In multiplex cytokine assay, IL-27 and CXCL12 may probably act as the characteristic cytokine marker for responders[53]. Da Silva *et al*[54] demonstrated a reduced baseline CXCR3+CCR6- CXCR5+ memory T cells, contributing to impaired seroconversion with vaccination in patients with chronic kidney disease (CKD)[54]. The authors further suggested an augmented 40-µg HBV dose schedule for CKD (comparable to hemodialysis patients) rather than the 20-µg dose suggested by the center for disease control (CDC)[55-57].

Booster doses are not indicated in immunocompetent individuals if the primary vaccination series is complete, as long-term follow-up studies show that immune memory persists despite declining hepatitis B surface antibody (anti-HBs) levels[58].

In a recent prospective trial published in 2019, 101 adults vaccinated with recombinant hepatitis B vaccine 20-30 years prior, were challenged with a dose of HBsAg vaccine. 100% of patients developed an anamnestic response by day 30 with a significant increase in HBsAg-specific memory B and $CD4^+$ T cells expressing at least two activation markers. These results align with current knowledge and suggest sustained immune memory and long-term protection 20-30 years after a complete primary HBsAg vaccination course during adulthood[59].

Specific immunocompromised populations present an exception to this rule. One such population is patients undergoing bone marrow transplant. In this respect, the American Association for the study of liver disease (AASLD) guidelines are informed by the "Recommendation of the ACIP" document published in January 2018[47]. The document suggests that the humoral response to the hepatitis B vaccine is reduced in

children and adults who are immunocompromised (*e.g.*, hematopoietic stem cell transplant recipients, patients undergoing chemotherapy, and HIV-infected persons)[60,61]. Modified dosing regimens, including a doubling of the standard antigen dose or administration of additional doses, might increase response rates. However, data on response to these alternative vaccination schedules is limited[62].

Chawansuntati *et al*[63] showed a reduced tumor necrosis factor (TNF)-α and IL-2 Level from CD4+ T cells in HIV-infected patients receiving standard HBV vaccinations and suggested an increased dose or frequency to counter this problem[63].

In 2018, Palazzo *et al*[64] published the results of a prospective study assessing the safety and efficacy of revaccination in 122 multiple myeloma patients on maintenance dose Lenalidomide post autologous hematopoietic stem cell transplant. The efficacy of revaccination was determined by comparing pre-and post-vaccination antibody titers. Their data suggested absolute safety and 40% efficacy in those receiving the Hepatitis B vaccine (Twinrix, GlaxoSmithKline, London)[64].

Surprisingly, the development of HBV reactivation following hematopoietic stem cell transplant (HSCT) can occur despite successful revaccination and maintenance of serum anti-HBs at more than protective levels. Nishikawa *et al*[65] in 2020, published their results from a prospective trial studying vaccination to prevent HBV reactivation after hematopoietic stem cell transplantation[65]. The authors showed that of the 27 patients vaccinated 12 mo after HSCT and monitored for two years, six showed HBV reactivation, with a 2-year cumulative reactivation incidence of 22.2%. Factors associated with HBV reactivation included the discontinuation of immunosuppressants (P = 0.0379) and baseline titers of anti-HBs (P = 0.004)[65]. Nucleic acid-based vaccine for HBV prevention is a novel approach but yet to show effectiveness in generating a sustained immune response in clinical trials[66] (Table 2).

HEPATITIS B TREATMENT

Per the 2018 updates to the AASLD guidelines, patients with CHB (Persistence of HBsAg > six months) should be considered for treatment if the ALT > 2 ULN and patients are HBeAg positive with HBV DNA > 20000 or HBeAg Negative with HBV DNA > 2000. Approved therapies are limited to single-drug regimens, including Nucleoside/Nucleotide reverse transcriptase inhibitors and pegylated Interferon (PEG-IFN). Approved regimens are divided into preferred [PEG-IFN, Entecavir (ETV), tenofovir fumarate, and tenofovir alafenamide (TAF)] and Non-Preferred (Lamivudine, Adefovir, Telbuvidine)[10].

Multiple recently published studies support the recommendations in demonstrating the safety and efficacy of IFN and Tenofovir over the non-preferred drugs.

Chuang *et al*[67] demonstrated sustained HBeAg seroconversion rates of 67.1%, five years after completion of the NEPTUNE trial, with a PEG-IFN dose of 180 μg/wk for 48 wk suggesting that the licensed regimen (180 μg × 48 wk) is more efficacious for HBeAg-positive patients than a lower dose and/or shorter treatment duration[67]. A 96-week HBV viral suppression for patients treated with both TAF, a prodrug of tenofovir disoproxil fumarate (TDF), and TDF, were comparable at 73% *vs* 75% and 90% and 91%, for HBeAg positive and HBeAg negative patients respectively[68]. A prospective randomized controlled trial (RCT) by Yim *et al*[69] studying partial responders to ETV (defined by detectable HBV DNA > 60 IU/mL), continuing ETV *vs* switching to TDF, revealed a statistically significant 12-mo HBV virological response (P = 0.022) in the subgroup that was switched to TDF[69]. In another prospective trial, stable switching to TDF monotherapy yielded non-inferior results at 96 wk compared to Lamivudine + Adefovir combination therapy in patients with Lamivudine resistant CHB and non-detectable HBV DNA[70]. Marcellin *et al*[71] published a 10-year efficacy (HBV suppression in 100% of HBeAg-negative and 98% in HBeAg positive patients) and safety data (few renal or bone-related adverse events, with no resistance) with tenofovir fumarate treatment for CHB virus infection in 585 patients (203 completed the 10-year study)[71]. A large, multicenter RCT, published in January 2019, including 320 treatment Naïve HBeAg positive patients showed that after long term treatment (144 wk), both tenofovir fumarate and ETV suppressed HBV DNA similarly (ETV *vs* TDF; -6.6485 *vs* -6.692 log 10 IU/mL, P = 0.807) and had similar serologic, biochemical, and side-effect profiles[72]. Recent encouraging data from a 104-wk prospective study on treatment of naïve HBeAg positive patients treated with telbivudine-based therapy shows a reduction in liver stiffness (monitored by Fibroscan©), from 8.6 at baseline to 6.1 at week 24, and 5.3 at week 104[73].

Table 2 Studies addressing hepatitis B vaccination strategies

Ref.	Study type	Main findings
Koc *et al*[49], 2018	Prospective open label trial	HBAI20 (HBVaxPro©-10-μg vaccine combined with an adjuvant AI20, a recombinant human IL-2) exhibited protective anti-HBs titers in 90% of previous non-responders likely due to an enhanced immune response
Qiu *et al*[53], 2018	Prospective trial	Genome wide comparative analysis revealed significant transcriptome and cytokine changes in HBV vaccine non-responders
Da Silva *et al*[54], 2018	Randomized prospective trial	Impaired seroconversion for HBV vaccination in CKD patients was linked to reduced baseline CXCR3 + CCR6- CXCR5+ memory T cells levels
Van Damme *et al* [59], 2019	Prospective trial	Immune challenge, in previously vaccinated adults (HBsAg vaccine 2-3 decades prior) showed a 100% anamnestic response by day 30 with significant increase in HBsAg-specific memory B and $CD4^+$ T cells
Raven *et al*[48], 2020	Open-labeled, randomized, controlled superiority trial	In Immunocompetent non-responders, revaccination with Fendrix 20 μg or HBVaxPro 40 μg resulted in significantly higher response rates compared to HBVaxPro 10 μg, Energix B 20 μg, or Twinrix 20 μg
Chawansuntati *et al* [63], 2018	Prospective trial	HBV patients with HIV co-infection have reduced levels of TNF-α and IL-2 levels, and may require an increased HBV vaccine dose to counter this problem
Palazzo *et al*[64], 2018	Prospective trial	Revaccination with the Hepatitis B vaccine (Twinrix, GlaxoSmithKline, London), in HBV patients on maintenance Lenalidomide post autologous hematopoietic stem cell transplant was absolutely safe with 40% efficacy
Nishikawa *et al* [65], 2020	Prospective trial	For HBV vaccinated, HSCT recipients, 2-year and 3-year cumulative HBV reactivation rates were 22.2% and 28.9% respectively. Discontinuation of immunosuppressants (P = 0.0379) and baseline titers of anti-Hbs (P = 0.004) were related to HBV reactivation

IL-2: Interleukin 2; anti-HBs: Anti Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen; HIV: Human Immunodeficiency virus; HBV: Hepatitis B virus; TNF: Tumor necrosis factor; HSCT: Hematopoietic stem cell transplant; CKD: Chronic kidney disease.

Despite the efficacy and safety of current regimens in achieving viral suppression, reactivation is, unfortunately, the norm after treatment cessation due to the persistence of cccDNA[74]. Recent studies further highlight this serious shortcoming.

The Toronto STOP study evaluated 67 HBV patients who achieved HBeAg seroconversion and undetectable HBV DNA after treatment with a NA. Patients were then randomly selected to discontinue. Sustained virological remission was maintained in only 29% of patients who stopped the treatment *vs* 82% of patients who continued NA [75]. Buti *et al*[76] studied the safety and efficacy of discontinuing HBV treated (with TDF) patients after eight years of therapy. At 24 wk following discontinuation of NA, almost a third of patients had grade 3 hepatotoxicity (indicated by aspartate aminotransferase/ALT of > 5 - < 10 ULN, and total bilirubin of > 3 - < 10 ULN)[76].

In another follow-up study of a phase 2 trial at two centers, Immune-tolerant patients with CHB received TDF and/or Emtricitabine for four years and were followed for another four years after cessation. The authors recorded a 100% virological relapse at week 4 (HBV DNA > 2000) and a 50% clinical relapse (HBV DNA > 2000 and ALT > 2 ULN) at 15 ± 11 wk[77].

Given the limitations noted by these studies, researchers have resorted to utilizing combination regimens with IFN and NA in hopes of improving seroconversion rates while others have attempted to determine predictors of response to develop a more targeted approach.

Liem *et al*[78], while looking for the optimal candidates that could benefit from a combination of PEG-IFN with nucleos(t)ide, prospectively evaluated HBeAg positive HBV patients treated with ETV. Randomized addition of PEG-IFN to ETV therapy was associated with a higher 48-week response rate (response defined as HBeAg loss), with a significant P = 0.03, compared to ETV monotherapy[78]. The HERMES Study Group published their results from a prospective RCT in 2019 showing that the addition of PEG-IFN alfa-2a (for 48 wk) to ongoing NA therapy significantly decreased HBsAg levels (defined by greater than 50% decline) in HBeAg-negative patients with genotype D infection[79].

In a recent prospective trial CHB patients who seroconverted on ETV, were switched to weekly PEG-IFN alfa-2a. The authors recorded an 88% sustained response in patients with a baseline HBsAg < 1500 IU/mL, while 50% of patients with a baseline HBsAg < 500 developing HBsAg loss[80]. The same group also validated data from 647 patients with HBeAg positive CHB on PEG-IFN alfa-2a to develop a pre-treatment scoring system using baseline factors like age, sex, alanine aminotransferase ratio, HBsAg level, and HBV DNA level to predict response to therapy[81].

A recently published large meta-analysis with 24 studies and 6674 subjects confirmed the importance of longer treatment duration and addition of IFN for HBsAg lowering and highlighted the potential value of immune-based therapies[82].

Recent identification of novel targets within the hepatitis B viral life cycle has led to the development of multiple therapeutic agents with varying mechanisms[83]. These include either direct inhibition of viral replication by targeting fundamental steps such as entry, cccDNA formation/stability, viral transcription, capsid assembly, and secretion or manipulating the host immune system for augmentation of innate and/or adaptive immunity[17]. The viral life cycle, resulting viral products, and their role in the pathogenesis of CHB is a rather broad and complex topic in and of itself. We found a recent article by Tsukuda *et al*[84] titled 'Hepatitis B viral biology and life cycle' to be an excellent resource for further information on this topic[84].

The discovery of the sodium taurocholate co-transport polypeptide (NTCP) (gene: *SLC10A1*) receptor as a gateway for HBV entry into hepatocytes was made approximately a decade ago[85]. The discovery has been a significant source of optimism, and NTCP has served as a target for developing viral entry inhibitors, including myrcludex and cyclosporine[86,87]. Additionally, NTCP complemented stable cell lines, cell cultures, and infection model systems have allowed standardized research to understand better the HBV life cycle and development of therapeutic options[88-91]. By allowing the study of authentic infection in cell lines, these model systems have helped achieve a better understanding of the formation and degradation of cccDNA, a key target to achieve the ultimate goal of HBV cure[92,93]. National institute of health (NIH)-funded trials to target viral proteins required for viral entry into uninfected hepatocytes, viral replication targeting adaptive immunity (anti-programmed cell death 1/programmed death-ligand 1 antibodies, chimeric antigen receptor T cells), and silencing of cccDNA are underway[94]. A preclinical trial of cccDNA endonucleases (CRISPR/Cas9) showed a reduction in cccDNA, other viral gene expression parameters as well as replication *in vitro*[95]. Multiple recent trials have evaluated the safety and efficacy of Core Protein (Capsid) Assembly Modulators in patients suffering from CHB. In a phase 1 study of HBeAg-positive CHB patients without cirrhosis, NVR 3-778 was well tolerated and demonstrated antiviral activity. The agent reduced serum levels of HBV DNA and HBV RNA, to the greatest extent combined with PEG-IFN. The observed reductions in HBV RNA confirmed the novel mechanism of NVR 3-778 [96]. A phase I, randomized placebo-controlled trial published in Lancet in 2020, showed acceptable safety, pharmacokinetics, and antiviral effects on an investigational HBV core protein inhibitor ABI-H0731[97]. Another phase I trial, by Zhao *et al*[98], evaluated the safety, tolerability, and pharmacokinetics of GLS4 (a novel HBV capsid assembly inhibitor), with or without ritonavir (used to enhance plasma levels of GLS4) and was found to have acceptable tolerability and sustained higher than proposed effective plasma trough concentration, when used in combination[98]. A phase I double-blind, RCT of 30 healthy adults, by Vandenbossche *et al*[99], looked into the safety, tolerability, and pharmacokinetics of JNJ-56136379 (a novel HBV capsid assembly modulator), showed it to be well-tolerated, with a more than three times the 90% effective plasma concentration required to inhibit viral replication[99].

HBV regulatory protein X (HBX) was recently found to promote transcription from cccDNA through an interaction with a host protein DDB1[100]. Sekiba *et al*[101] applied a newly constructed split luciferase assay system to comprehensive compound screening to identify candidate compounds that targeted the HBX-DDB1 interaction and showed that nitazoxanide (NTZ), efficiently inhibits the HBX-DDB1 protein interaction. NTZ significantly suppressed viral transcription and viral protein production in human primary hepatocytes naturally infected with HBV[101]. Antisense oligonucleotides are small single-stranded nucleic acid sequences that bind selectively to their target RNAs and cause degradation[102]. GSK3389404 is a liver-targeted antisense oligonucleotide that inhibits the synthesis of HBsAg and all other HBV proteins. A recent randomized double-blind controlled phase 1 trial showed acceptable safety and pharmacokinetic profile, supporting further clinical investigation in patients with CHB[103].

The human immune system controls and clears adulthood-acquired hepatitis B in over 95% of patients[94]. A large body of data links suppressed T and B cell responses to persistent hepatitis B and liver injury[104-106]. Moreover, data from trials involving B and T cell responses strongly suggest that augmentation of immunity can clear the infection[107]. Therefore, boosting the magnitude and quality of the virus-specific immune response is a rational strategy for therapy[108]. Various toll-like receptor (TLR) agonists have shown promising antiviral effects in small prospective trials. GS-9620, a TLR-7, when administered for 12 wk, though did not significantly affect serum HBsAg levels. However, it did increase T-cell and NK-cell responses[109-111]. Han *et*

al[112] demonstrated HBeAg positive CHB patients to have a lower baseline galactosylation level, and hence being suitable candidates for the use of HBsAg-hepatitis B immune globulin (HBIG) immune complex, administered as a therapeutic vaccine, to achieve HBeAg seroconversion. The marked-up regulation of IL-2 and galactosylation levels confirmed this to be an immune response[112].

The goal of therapeutic vaccination is to stimulate or boost the host immune response to restore immune control, leading to sustained suppression of HBV replication and ultimately HBsAg loss[13]. A recently published meta-analysis of 15 studies reviewed the evidence for therapeutic vaccines' efficacy and safety in CHB patients[113]. The authors concluded by saying that therapeutic vaccines do not appear to be efficacious for the treatment of CHB but were limited by few RCTs, suboptimal therapeutic vaccines, and patient selection.

An open-label phase III trial comparing a therapeutic vaccine (NASVAC, containing 100 μg of each HBs and HBc antigens, administered in 2 cycles of 5 doses) *vs* PEG-IFN alfa 2b (180 μg every week for 28 wk in naïve CHB patients showed significantly better controlled HBV DNA, 24 wk post-treatment ($P < 0.05$) and a lower rate of progression to cirrhosis in the NASVAC group[114]. HBsAg-based recombinant vaccines, administered every eight weeks for 48 wk, with a total of 7 doses, have been shown to reduce HBsAg levels ($P = 0.0005$) and achieve HBsAg seroconversion in 10.52% of the patients with low HBsAg titers[115]. A multicenter prospective phase 2 RCT by Boni *et al*[116] demonstrated improved HBV specific T cell responses, including IFN-γ, TNF-α, and IL-2, with a combined GS-4774 (yeast-based engineered vaccine) and tenofovir *vs* tenofovir alone[116].

The HBV Endeavor prospective trial by Wu *et al*[117] looked into switching HBV patients with confirmed viral suppression and HBsAg loss from nucleos(t)ide analogs to immunomodulators (IL-2) and therapeutic vaccines with IFN to enhance HBsAg loss to achieve HBV virological cure. HBsAg loss was documented to be 9.38%, 3.03%, and 3.7% in the IFN/vaccine/IL-2 group, IFN group, and the ETV group, respectively. The higher titers of CD16-NK cells and lower titers of regulatory T cells corresponded to higher response rates of HBsAg loss[117] (Table 3).

HEPATITIS B SPECIAL POPULATIONS

Mother to child transmission of hepatitis B

Antiviral therapy has been studied as an intervention to reduce perinatal HBV transmission amongst pregnant women with high HBV viral DNA levels[9,118,119]. All newborns born to HBV infected mothers should receive HBIG and HBV vaccine within 12 h of delivery followed by completion of 2 or 3 vaccine series[47]. AASLD suggests antiviral therapy starting at 28-32 wk to reduce perinatal HBV transmission when maternal HBV DNA is > 200000 IU/mL[9]. Tenofovir is recommended as the preferred agent due to lack of resistance and availability of safety data and the therapy is discontinued at some point between birth and three months postpartum[9].

Cressey *et al*[120] assessed for the first time tenofovir exposure during pregnancy and postpartum in HBV-infected HIV-uninfected women receiving TDF to prevent mother-to-child transmission of HBV. They concluded that the modest reduction in tenofovir exposures observed during pregnancy does not warrant a dose adjustment [120].

At least two recent studies have demonstrated the safety and efficacy of the addition of TDF to standard newborn immune prophylaxis in reducing maternal to child transmission (MTCT) in pregnant women, with very high viral loads[121,122]. Alternatively, in a multicenter, double-blind clinical trial performed in Thailand, authors demonstrated that in a setting in which the rate of mother-to-child HBV transmission was low with the administration of hepatitis B immune globulin and hepatitis B vaccine in infants born to HBeAg-positive mothers, the additional maternal use of TDF did not result in a significantly lower rate of transmission[123].

These studies reiterate the safety, efficacy, and practicality of Tenofovir in pregnant women at high risk for MTCT of hepatitis B. In their July 2020 guidelines on antiviral prophylaxis in pregnancy, WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with HBV DNA ≥ 5.3 log10 IU/mL (≥ 200000 IU/mL) receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose[124].

In immune-tolerant (HBeAg positive) CHB patients awaiting assisted reproduction, an RCT conducted by Wu *et al*[125] showed greater viral clearance (90% *vs* 67.2%, $P =$

Table 3 Studies addressing hepatitis B treatment

Ref.	Study type	Findings
Conventional treatment agents		
Chuang *et al*[67], 2018	Prospective study	PEG Interferon at a dose of 180 μg/wk for a duration of 48 wk resulted in better sustained HBeAg seroconversion rates, than in patients with a lower dose and/or shorter treatment duration
Agarwal *et al*[68], 2018	Randomized controlled trial	96-wk HBV suppression rates were comparable in patients treated with TAF and TDF, for HBeAg positive (73% *vs* 75%) and HBeAg negative (90% *vs* 91%) patients
Yim *et al*[69], 2018	Prospective randomized controlled trial	HBV patients who were partial responders to ETV, fared better (12-mo HBV response, $P = 0.022$), when switched to TDF versus continuing ETV
Lee *et al*[70], 2018	Prospective trial	In Lamivudine resistant HBV patients with non-detectable HBV DNA, while on Lamivudine + Adefovir combination therapy, switching to TDF monotherapy yielded non-inferior results at 96-wk
Marcellin *et al*[71], 2019	Prospective trial	A 10-yr TDF efficacy study showed HBV viral suppression in 100% of HBeAg-negative and 98% in HBeAg positive patients), with few renal or bone-related adverse events, and no resistance to TDF
Cai *et al*[72], 2019	Multicenter randomized controlled trial	HBV treatment naïve HBeAg positive patients treated with ETV or TDF, showed similar HBV DNA suppression (-6.6485 *vs* -6.692 log 10 IU/mL, $P = 0.807$) at 144 wk as well as similar serologic, biochemical, and side-effect profiles
Liang *et al*[73], 2018	Prospective trial	HBV treatment naïve HBeAg positive patients treated with Telbivudine-based therapy showed a reduction in liver stiffness, monitored by Fibroscan©), from 8.6 at baseline to 6.1 at week 24, and 5.3 at week 104
Liem *et al*[75], 2019	Randomized controlled trial	In HBV patients who received NA, and achieved HBeAg seroconversion with undetectable HBV DNA, maintenance of remission was seen in 82% of those who continued NA *vs* 29% of those who discontinued NA
Buti *et al*[76], 2019	Prospective trial	HBV patients treated with TDF, and then discontinued: At 24 wk following discontinuation of NA, almost a third of patients had grade 3 hepatotoxicity (indicated by AST/ALT of > 5 - < 10 ULN, and total bilirubin of > 3 - < 10 ULN)
Wong *et al*[77], 2018	Phase II prospective trial	HBV immune-tolerant patients who received TDF and/or Emtricitabine for 4 yr and were followed for another 4 yr after cessation, showed 100% virological relapse at week 4 (HBV DNA > 2000) and a 50% clinical relapse (HBV DNA > 2000 and ALT > 2 ULN) at 15 ± 11 wk
Liem *et al*[78], 2019	Randomized prospective trial	Randomized addition of PEG-IFN to ETV therapy, in HBeAg positive HBV patients was associated with a significantly higher 48-wk response rate (HBeAg loss), compared to ETV monotherapy ($P = 0.03$)
Lampertico *et al*[79], 2019	Prospective randomized controlled trial	Genotype D, HBeAg-negative HBV patients, on NA therapy showed a significant 50% decrease in HBsAg levels, with the addition of PEG-IFN alfa-2a for 48 wk
Chan *et al*[80], 2019	Prospective trial	In CHB patients, switched to weekly PEG-IFN alfa-2a after seroconversion on entecavir, those with lower HBsAg titers, showed a greater sustained response (88% at HBsAg < 1500 IU/ml and 50% at HBsAg < 500 IU/mL)
Chen *et al*[82], 2020	Meta-analysis	Confirmed the importance of longer treatment duration and addition of IFN for HBsAg lowering and highlighted the potential value of immune-based therapies
New direct antiviral agents		
Ramanan *et al*[95], 2015	Pre-clinical prospective study	Use of ccc DNA endonucleases (CRISPR/Cas9) resulted in a reduction in both ccc DNA and other parameters of viral gene expression and replication *in vitro*
Yuen *et al*[96], 2019	Phase 1 prospective trial	Non-cirrhotic HBeAg-positive CHB patients, tolerated NVR 3-778 (a capsid assembly protein modulator), and showed reduced serum levels of HBV DNA and HBV RNA, to the greatest extent in combination with PEG-IFN
Yuen *et al*[97], 2020	Phase I, randomized placebo-controlled trial	Demonstrated acceptable safety, pharmacokinetics, and antiviral effects on an investigational HBV core protein inhibitor ABI-H0731
Zhao *et al*[98], 2019	Phase I, randomized controlled trial	Demonstrated acceptable safety and pharmacokinetics of GLS4 (a novel HBV capsid assembly inhibitor), with or without ritonavir (used to enhance plasma levels of GLS4)
Vandenbossche *et al*[99], 2019	Phase I double-blind, randomized	Demonstrated acceptable safety and pharmacokinetics of JNJ-56136379 (a

	controlled trial	novel HBV capsid assembly modulator) with more than three times the 90% effective plasma concentration required to inhibit viral replication
Han *et al*[103], 2019	Phase I double-blind, randomized controlled trial	Demonstrated acceptable safety and pharmacokinetics of GSK3389404 (a liver-targeted antisense oligonucleotide that inhibits the synthesis of hepatitis B surface antigen and all other hepatitis B virus proteins)
New immune based therapies		
Boni *et al*[109], 2018	Phase I prospective trial	Administration of a 12-wk course of GS-9620 (TLR7 agonist) was safe but did not significantly affect serum HBsAg levels. However, it did increase T-cell and NK-cell responses
Janssen *et al*[110], 2018	Phase II prospective trial	Administration of a 12-wk course of GS-9620 (TLR7 agonist) was safe, demonstrated dose dependent increase in interferon-simulated gene m RNA expression, without IFN-α expression or reduction in HBsAg levels
Agarwal *et al*[111], 2018	Randomized controlled prospective trial	Addition of Vesatolimod (TLR7 agonist) to Tenofovir in treatment naïve viremic Hepatitis B patients was found to be safe. This intervention led to dose dependent pharmacodynamic induction of ISGs, without significant improvement in HBsAg decline
Han *et al*[112], 2019	Prospective trial	During YIC treatment, 26 patients with lower IgG galactosylation level at baseline showed (cellular immune response mediated), sustained increase of serum galactosylated IgG and responded to YIC treatment by HBeAg seroconversion
Al Mahtab *et al*[114], 2018	Open-label phase III trial	Treatment naïve CHB patients showed significantly better controlled HBV DNA, 24 wk post-treatment ($P < 0.05$) and a lower rate of progression to cirrhosis in the NASVAC group (therapeutic vaccine, containing 100 μg of each HBs and HBc antigens, administered in 2 cycles of 5 doses), versus PEG-IFN alfa 2b (weekly 180 μg)
Lai *et al*[115], 2018	Randomized controlled prospective trial	In low-level HBsAg CHB patients, serial HBsAg-based vaccinations were safe, resulting in significant HBsAg decline. HLA gene expression and genotypes played a role in vaccine responsiveness
Boni *et al*[116], 2019	Multicenter phase II prospective randomized controlled trial	Demonstrated improved HBV specific T cell responses, including IFN-γ, TNF-α, and IL-2, with a combined GS-4774 (yeast-based engineered vaccine) and tenofovir versus tenofovir alone
Wu *et al*[117], 2019	Prospective controlled trial(The HBV Endeavor prospective trial)	HBV patients with confirmed viral suppression and HBsAg loss while on ETV, when switched to immunomodulators (IL-2) and therapeutic vaccines with IFN, showed HBsAg loss in 9.38%, 3.03%, and 3.7% in the IFN/vaccine/IL-2 group, IFN group, and the ETV group, respectively. Higher titer of CD16-NK cells and lower titers of regulatory T cells corresponded to higher response rates of HBsAg loss
Kalkeri *et al*[142], 2020	Prospective trial	A repurposed compound SRI-32007 demonstrated anti-HBV activity *via* inhibition of HBV core promoter activity, and might be used in studying therapeutics to manage HBV
Hepatitis B in pregnancy		
Cressey *et al*[120], 2018	Phase III randomized prospective trial	Demonstrated a geometric mean tenofovir AUC (0-24) to be 20% (95%CI: 19%-21%) lower during pregnancy than postpartum, in HBV patients with HIV, should not warrant a dose adjustment (to compensate for the modest reduction in HBV transmission)
Lin *et al*[121], 2018	Randomized double-blind prospective trial	Initiation of TDF at 24th week of gestation and then 4 weeks after delivery reduced the MTCT from 13.5% (control group) to 0% cervical transmission, in pregnant HBsAg and HBeAg positive patients with high viral loads HBV DNA titer ≥ 2×10^6 IU/mL
Wang *et al*[122], 2019	Prospective trial	Initiation of TDF at 24th week of gestation revealed a 0.7% MTCT in the ITT group, and 0% in the *per* protocol group, in pregnant HBsAg and HBeAg positive patients with high viral loads HBV DNA titer > 6 $\log_{10}$ IU/mL
Jourdain *et al*[123], 2018	Multicenter, double-blind clinical trial	Initiation of TDF at 28th week of gestation till 2 mo postpartum mildly reduced the MTCT from 2% (control group) to 0% cervical transmission, in pregnant HBsAg and HBeAg positive patients with an ALT of < 60. The authors showed that addition of TDF only mildly reduced the MTCT to infants at age 6 mo
Wu *et al*[125], 2019	Randomized control trial	Immune-tolerant CHB patients awaiting assisted reproduction showed greater viral clearance (90% *vs* 67.2%, $P = 0.002$ at week 12, and 96.6% compared to 85.2 % at week 48 respectively) when on a combination of TDF and telbivudine, compared to TDF alone. No difference was noted in the HBeAg seroconversion rates for the two groups (8.3% *vs* 3.3%; $P = 0.233$)
Hepatitis B reactivation		

Huang *et al*[127], 2013	Randomized double blind prospective trial	Prophylaxis with ETV significantly reduced HBV reverse seroconversion when compared with placebo in resolved hepatitis B patients receiving Rituximab for lymphoma (4.3% *vs* 25.9% at 18 mo; $P = 0.019$)
Kusumoto *et al*[130], 2019	Prospective trial	Resolved HBV patients with NHL, who received obinutuzumab or rituximab, and followed for HBV reactivation, revealed a strong correlation ($P < 0.0001$) of HBV reactivation with detectable baseline HBV DNA. Also, Prophylactic NA reduced risk of HBV reactivation ($P = 0.0018$)
Liu *et al*[131], 2019	Double bling randomized control trial	Resolved HBV patients with lymphoma who received chemotherapy, had similar reactivation rates with or without ETV prophylaxis (0% *vs* 3.2%; $P = 0.246$). Authors suggested that prophylactic use of entecavir was not a cost-effective strategy, especially for those with a baseline positive anti-HBs
Hammond *et al*[132], 2018	Retrospective study	The incidence of HBV reactivation, in patients on Ibrutinib, was 9.5% (2 out of the 21 patients with known past HBV infection)
Wang *et al*[135], 2018	Prospective trial	HBV DNA negative patients with HCC who underwent TACE were at risk of HBV reactivation. HBV reactivation rates were significantly lower in those receiving ETV compared with controls (5.9% vs 23.4%; $P < 0.05$)
Zhang *et al*[136], 2019	Meta-analysis	HBV DNA negative patients with HCC who underwent TACE were at risk of HBV reactivation ($P < 0.01$) and hepatitis ($P < 0.01$). Use of prophylactic anti-viral therapy significantly reduced the risk of HBV reactivation ($P < 0.01$) and hepatitis ($P = 0.02$)
Jun *et al*[137], 2018	Multi-center retrospective study	12.7% of HBV DNA negative patients with HCC who underwent RT had HBV reactivation. Use of prophylactic anti-viral therapy significantly reduced the risk of HBV reactivation ($P < 0.001$), when compared to the control group. Combined RT and TACE had significant risk for HBV reactivation ($P = 0.008$)
Liu *et al*[138], 2020	Retrospective study	CHB patients with SARS-CoV-2 infection had a 15% risk of HBV reactivation

CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HBeAg: Hepatitis B e-antigen; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; NA: Nucleos(t)ide analog; TLR7: Toll like receptor 7; YIC: Hepatitis B surface antigen-hepatitis B immunoglobulin immune complex; AST: Aspartate aminotransferase; ALT: Alanine aminotransaminase; PEG-IFN: Pegylated interferon; cccDNA: Covalently closed circular DNA; CRISPR: Clustered regularly, interspaced short palindromic repeats; Cas9: CRISPR associated protein 9; NK: Natural killer; IFN: Interferon; TNF: Tumor necrosis factor; IL-2: Interleukin 2; CD: Cluster of differentiation; HBIG: Hepatitis B immune globulin; AUC: Area under the ROC curve; ROC: Receiver operating characteristic; CI: Confidence interval; ITT: Intention to treat; MTCT: Maternal to child transmission; NHL: Non-Hodgkin's lymphoma; TACE: Trans-arterial chemoembolization; RT: Radio-therapy; HCC: Hepatocellular carcinoma; GGT: Gamma-glutamyl transferase; ISGs: Interferon stimulated gene transcripts; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

0.002 at week 12, and 96.6% compared to 85.2% at week 48 respectively) in patients on a combination of TDF and telbivudine, compared to TDF alone. However, there was no difference in the HBeAg seroconversion rates for the two groups (8.3% *vs* 3.3% $P = 0.233$)[125] (Table 3).

Anticancer therapy

Previous studies showed that HBV reactivation from anticancer therapies occurred in 41% to 53% of HBsAg-positive, anti-HBc–positive patients, and 8% to 18% of HBsAg-negative, anti-HBc–positive patients[126,127]. Those receiving B cell depleting therapies such as Rituximab are considered to be at a higher risk of reacti-vation[128,129]. The AASLD recommends screening patients requiring chemotherapy with both HBsAg and anti-HBc and prophylaxis with NAs before treatment initiation with B cell depleting therapies such as rituximab[10]. The role of baseline anti-HBs testing in this cohort is still not clear. Additionally, the data on hepatitis B reactivation during treatment with some of the newer immunochemotherapy agents such as obinutuzumab and Ibrutinib is sparse.

In a recent study, 326 patients with prior HBV receiving Obinutuzumab or Rituximab for B-Cell Non-Hodgkin's lymphoma (NHL) either received prophylactic NAs or underwent HBV DNA guided preemptive NA therapy. Multivariate regression analysis identified that seronegativity for anti-HBs and detectable HBV DNA levels at baseline (not the drug choice) were associated with increased risk of HBV reactivation[130]. While the reactivation rate was lower for patients receiving prophylactic antivirals, none of the patients in either group developed HBV-related hepatitis[130]. Results suggest that while prophylactic therapy can prevent reactivation and may be suitable for selected high-risk patients, HBV DNA-guided preemptive therapy can successfully prevent HBV hepatitis during anti-CD20 immunochemotherapy in B-cell NHL. Liu *et al*[131] conducted an RCT on lymphoma

patients on chemotherapy with past HBV infection (HBsAg negative, Anti HBV core total antibody positive, and negative HBV DNA), and the study concluded that the prophylactic use of ETV was not a cost-effective strategy, especially for those with a positive anti-HBs. The HBV reactivation was 3.2% compared to 0% (P = 0.246), in controls *vs* those of prophylactic ETV[131]. In a recent retrospective review, the authors identified two patients suffering from chronic lymphocytic leukemia who experienced hepatitis B reactivation after treatment with Ibrutinib. The incidence of hepatitis b reactivation, in patients on Ibrutinib, at the Dana-Farber/Harvard Cancer Institute was 9.5% (2 out of the 21 patients with known past HBV infection)[132].

These studies highlight the risk of hepatitis B reactivation with novel agents such as obinutuzumab and ibrutinib, the utility of baseline anti-HBs testing for risk stratification, and argue in favor of close surveillance with preemptive treatment being a safe and cost-effective strategy in these patients.

CHB patients receiving transarterial chemoembolization (TACE) for HCC are at a modestly increased risk for hepatitis B reactivation[133,134]. There is a lack of systemic data assessing antivirals' role in this subgroup of patients, and the most recent AASLD guidelines do not address this issue directly as such data from high-quality prospective trials and meta-analysis are needed to advance our knowledge of this field. In a recent prospective trial including 98 CHB patients with HCC requiring TACE, prophylactic antivirals were associated with a significant reduction in the incidence of hepatitis b reactivation (5.9% *vs* 23.4% $P < 0.05$)[135]. Zhang *et al*[136] recently performed a meta-analysis to investigate the reactivation of HBV following TACE in primary HCC patients (HBV-DNA negative) and evaluate TACE's effects combined with antiviral therapy. TACE significantly increased the risk of HBV reactivation (OR: 3.70; 95%CI: 1.45-9.42; $P < 0.01$) and subsequent hepatitis (OR: 4.30; 95%CI: 2.28-8.13; $P < 0.01$) in HCC patients. Preventive antiviral therapy reduced the rate of HBV reactivation (OR: 0.08; 95%CI: 0.02-0.32; $P < 0.01$) and hepatitis (OR: 0.22; 95%CI: 0.06-0.80; $P = 0.02$) in those undergoing TACE[136]. A recent multicenter retrospective study evaluated 133 patients receiving radiotherapy +/- TACE for the treatment of HCC, and the effect of antiviral therapy on HBV reactivation in quiescent HBsAg positive patients after radiotherapy for HCC was found to be 33.3% in the non-antiviral group, compared to 7.5% in the antiviral group, with a $P < 0.001$[137].

CORONAVIRUS DISEASE 2019

Another interesting HBV reactivation phenomenon was described by Liu *et al*[138] in patients who are not necessarily immune-compromised but just infected with coronavirus disease 2019 (COVD-19). Liver dysfunction is apparent in COVID-19 patients with/without chronic HBV. COVID-19 patients co-infected with chronic HBV were found to be at risk of hepatitis B reactivation, making it necessary to monitor the liver function of COVID-19 patients concurrently with HBV-DNA levels during the whole disease course[138].

FUTURE DIRECTIONS

In November 2019, the NIH hepatitis B cure strategic plan working group released a visionary statement to end the hepatitis B endemic by improved screening, strategies for vaccinations, developing better hepatitis B treatment, and follow-up care. This guidance serves as a foundation for future concerted international efforts and would further help develop novel biomarkers to diagnose disease progression, in addition to novel therapeutics[139]. Due to the need for lifelong treatment, adverse effects, poor tolerability, and persistent risk of complications, including HCC, render the current treatments dissatisfactory.

The discovery of NTCP as an HBV receptor on human hepatocytes was the first of many critical discoveries that have revolutionized HBV research. Over the past decade, the discovery has translated into a significantly improved understanding of HBV pathogenesis and led to the development of novel animal models, cell lines, biomarkers, and therapeutic agents. Our armamentarium of potential HBV drugs has undergone a rapid expansion. Direct antivirals currently being studied include HBV entry inhibitors, capsid assembly modulators, cccDNA destabilizers and endonucleases, HBX inhibitors, Inhibitors of gene expression, HBsAg release inhibitors[13]. These agents are likely going to complement existing treatments rather than replacing them. Given the safety profile of NAs, novel agents will likely be compared and

combined with NAs in upcoming trials. The initial cure for HBV will most likely require a combination of agents that modulate viral and host factors at various levels. Given the efficacy of T cells for viral control in acute hepatitis, they have been studied extensively. Novel agents act either through innate and intrinsic cell responses (Toll like receptor agonists, RIG-1) or by targeting adaptive immune responses (checkpoint inhibitors, therapeutic vaccines, genetically engineered T cells/antibodies).

Loss of T cell response to HBV or T cell exhaustion is multifactorial in nature and a major hurdle to the development of immunomodulatory therapeutic agents. These concepts have been incorporated into therapeutic strategies that involve potent adjuvants, monoclonal antibodies, or pattern recognition receptor agonists that alter the liver environment. On the other hand, our understanding of HBV-specific B cells is limited to antibody production, and further studies are required to understand better their cytokine profiles and their role as antigen-presenting cells[108].

Another major limitation to preclinical testing of novel agents is the lack of optimal animal models. Because of the strict species specificity of HBV infection, animal models for studying the host response to the virus and disease pathogenesis have been limited and suboptimal[140]. Chimpanzees are the only nonhuman immune-competent animals that are naturally susceptible to HBV infection. However, given the discontinuation of chimpanzees' use due to bioethical considerations, the only other option is Tupaia (a tree shrew), woodchuck, or mice, all of which have significant drawbacks[141]. Future efforts to develop antiviral agents against viral genome reservoir or cccDNA or promote the patient's antivirus response must include the development of infection models that are durable, stable, and more reflective of the natural HBV life cycle within the human host.

To this end, drug repurposing may offer reduced effort, time, and cost related to new drugs' the testing and marketing of new drugs. Drug repurposing involves the investigation of existing drugs with demonstrated safety profiles for new therapeutic purposes. Thousands of compounds can be screened for the desired effect using high throughput screening. A recent study demonstrated anti-HBV activity of a repurposed compound SRI-32007 through inhibition of HBV core promoter activity[142]. Drug repurposing may allow for more systematic and substantially less expensive methods to discover new treatments for diseases compared to traditional drug development.

To promote and facilitate the planning and execution of new trials in the field of CHB with the ambition of developing a 'cure', the European Association for the Study of the Liver and the AASLD jointly organized an HBV Treatment Endpoint Conference [13]. The conference provided a strategy for conducting efficient phase II/III trials while maintaining excellent safety profiles. It was agreed upon that the primary endpoint of phase III trials should be HBsAg loss and undetectable HBV DNA 6 mo after completion of treatment. HBsAg loss in ≥ 30% of patients after 1 year of therapy is the desired rate of response in these phase III trials.

A comprehensive collaboration within the scientific community is required to standardize definitions, methods, and endpoints to achieve a complete understanding of viral biology and develop novel therapies in a time and cost-effective manner. That will be, however, just the beginning of the global battle against HBV. The WHO has identified significant barriers that hinder efforts to prevent and treat CHB in the most vulnerable populations. Structural barriers include inadequate leadership, commitment, coverage of prevention programs, data, and a lack of public health approach to hepatitis. Personal barriers include lack of education/insight, widespread stigma, and discrimination, lack of affordability, and healthcare access. With these challenges in mind, the WHO has developed a core strategy to eliminate viral hepatitis as a public health threat by 2030, to reduce new infections by 90% and mortality by 65%[94].

The cornerstone of this global strategy is going to be a pragmatic and efficient vaccination program. Hepatitis B vaccine is one of the most effective vaccines, with seroconversion rates above 90% when administered properly. Additional studies are needed to identify the host genetic factors and immune mechanisms that lead to a non-response in immunocompetent patients. The vaccination response of the immunocompromised host needs to be better studied, and practical strategies including immune priming need to be developed to achieve higher seroconversion rates. Vaccines biology can potentially help define, at baseline, predictive signatures for subjects generating protective responses following HBV vaccination leading to more personalized vaccination[143]. These findings need further testing to validate the concept of baseline predictors and the feasibility and utility of targeted modulation of the immune baseline before vaccinations[143]. Elimination of HBV infection as a public health threat requires a reduction in the prevalence of HBsAg to below 0.1% in children five years of age. It can be achieved through universal immunization of newborns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV

[124]. Significant challenges include low availability of HBIG due to the lack of resources required for storage and transportation and prohibitive cost. Despite the efficacy of vaccination in reducing MTCT, the birth dose vaccine coverage, especially in the African region, remains low[124]. Lack of infrastructure leads to reduced ability to test for HBV DNA and limits antiviral availability in high-risk populations. The immunocompromised patients also remain at a high risk of reactivation despite an initial vaccination response and positive antibody titers. Researchers have relied on Genome-wide association studies genome-wide association studies (GWAS) to identify the risk loci that predispose to the persistence of HBV infection, non-response to hepatitis B vaccine, and liver disease progression in chronic HBV infections[144]. Additional GWAS and fine-mapping studies, implemented with more refined case-control designs, larger samples, and in other ethnic populations, would further improve our understanding of HBV pathophysiology[144].

CONCLUSION

The breakthrough in our understanding of the HBV life cycle has resulted in a plethora of novel direct acting antivirals and immune based therapies being investigated. In the foreseeable future however, novel agents are likely to complement PEG-IFN and NAs than replace them. Recent studies utilizing combination regimens (PEG-IFN plus NA) and a longer duration of treatments with PEG-IFN have shown improved outcomes. Additionally, trials assessing alternate vaccination regimens for primary non-responders, and perinatal NAs for prevention of MTCT in high-risk individuals have shown promise and may alter future guidelines. Studies on novel biomarkers are fraught with technical difficulties, lack of standardization, and small sample size. Despite remarkable efficacy, the hepatitis B vaccine remains poorly utilized in many regions of the world due to a lack of infrastructure and implementation. Data from high-risk populations, most vulnerable to the devastating effects of hepatitis B infection and reactivation remain sparse. Utilization of systems approach, optimization of experimental models, identification and validation of next-generation biomarkers, and precise modulation of the human immune response will be critical for future innovation. Last but not the least, pragmatic management of MTCT and population health-related challenges must be prioritized to produce real-world results.

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