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A review on current scenario and future perspectives of Hepatitis B – Clinical management strategies and treatment modalities

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ABSTRACT: Globally, chronic hepatitis B (CHB) is a most popular disease, which leads to mortality. A significant amount of financial and intellectual resources have been committed by scientists, physicians, pharmaceutical corporations, and health organisations to the search for a cure, raising vaccination rates, and decreasing the prevalence of CHB worldwide. Periodically, recommendations for disease prevention and treatment are released by national and international health-related organisations such as the World Health Organisation, the European Association for the Study of the Liver (EASL), the Asia Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Disease (AASLD), and the Centre for Disease Control. An overwhelming majority of the mentioned studies were published before 2018, according to our evaluation of the most recent guidelines released by the Taiwan Association for the Study of the Liver, AASLD, EASL, and APASL. We looked at research on Hepatitis B that was published in 2018 and later to find new findings and obstacles that will probably guide future attempts to eradicate Hepatitis B. There is still a great deal of space for improvement in our understanding of the hepatitis B viral life cycle and the subsequent medication development, despite the hopeful breakthrough. There is a dearth of information on high-risk groups who are more susceptible to the severe consequences of hepatitis B infection and reactivation.

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INTRODUCTION:

For at least the last 40,000 years, people have been infected with the hepatitis B virus (HBV), which is currently the 10th largest cause of mortality worldwide [1,2]. The only DNA-based hepatotropic virus that causes fibrosis, carcinogenesis, and other detrimental effects on infected cells is HBV [3]. According to estimates from the World Health Organisation (WHO), 257 million individuals had chronic hepatitis B (CHB) in 2015, and 887,000 of those cases resulted in death from hepatitis B complications [4]. Only 10 % of CHB sufferers

worldwide are aware that they have the virus. Our ability to create vaccines and nucleoside/nucleotide analogues (NAs) to lower the rate of new infections and achieve virologic suppression has improved due to our advanced understanding of the biology of hepatitis B, laboratory testing, and the immune response [5]. The vast majority of research that has been referenced in the most current guidelines from different societies were released before 2018 [6–10]. In order to identify the worldwide strategies and knowledge gaps that will soon define the scientific endeavour in this sector, our paper will evaluate the recent literature for new breakthroughs. The objective of the present review for clinical management and treatment of Hepatitis B.

MODERN TREATMENT STRATEGIES AND PREVENTION OF HEPATITIS B INFECTION:

Serological Markers for Hepatitis B Infection:

Chronic HBV infection has a wide range of intricate serologic patterns. HIV infection is linked to several antigens and antibodies, such as the hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs), the hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc), and the hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Evaluation of the quantity and presence of circulating HBV DNA can also be done by testing. Throughout the various stages of HBV infection, at least one serologic marker is present. Since there is no free HBcAg circulating in blood, serologic tests are commercially available for all indicators other than HbcAg [11].

There is abundant evidence that antiviral medication enhances intermediate prognosis, lowers death, lowers the incidence of hepatocellular carcinoma (HCC), and improves overall health outcomes. Therefore, the most recent report from the US Preventive Service Task Force suggests that adults and adolescents who are at a higher risk of HBV be screened for hepatitis B using HBsAg tests that have been approved by the US Food and Drug Administration, followed by a confirmatory test if the results are initially reactive [12]. An acute or chronic infection is indicated by a positive HBsAg test result. In addition to HbsAg, initial testing with anti-Hbs and/or anti-Hbc is recommended for screening particular populations [10]. Concurrent or post-HBsAg screening serologic panels facilitate diagnosis and help select the best course of treatment [12]. Serological indicators play a vital role in tracking the effectiveness of treatment and forecasting side effects. Based on tests with a lower detection limit (LLOD-0.05 IU/mL) with or without HBsAg seroconversion and undetectable blood HBV DNA after finishing a course of treatment, the main outcome for treatment is lasting HBsAg loss (functional cure) [13]. The findings of a multicenter trial evaluating the kinetics of HBsAg in 1795 HBV patients were reported by Zhang, *et al*. in 2018. Patients with HBeAg positive HBV had HBsAg titers that were considerably greater ($P < 0.0001$) than those with HBeAg negative HBV. They showed that whilst alanine aminotransaminase (ALT) and necro-inflammatory activity were directly connected with HBsAg titers in HBeAg negative HBV patients, HBsAg titers were inversely proportional to fibrosis in patients with positive HbeAg [14]. HBsAg clearance profile (CPs, characterised by elimination of binding at both loops 1 and 2 epitopes of the 'a' determinant) is one of the biomarkers for HBV functional cure [15]. It was found to be positively correlated with HBsAg loss (SL), seroconversion, and treatment response in genotype A CHB patients treated with tenofovir or adefovir for at least four years before, according to a 48th and 192nd week HBsAg CPs analysis [15]. If a functional cure is not achieved for the majority of CHB patients, long-term NA is probably required. Even with persistent viral suppression, liver-related problems can still arise from long-term medication. In order to achieve a functional cure, which is defined as off-therapy virological suppression, additional virological indicators were created to forecast the risk of liver-related problems in these patients, who frequently had undetectable serum HBV DNA [16]. Viral proteins are transcribed using the covalently closed circular DNA (cccDNA) protein as a template, which is then translated. The fundamental mechanism for infection reactivation following treatment discontinuation is the persistence of cccDNA within the nucleus of infected hepatocytes despite therapy and viral suppression [17]. Hepatitis B Core-Related Antigen (HBcrAg) is a composite of three related viral proteins (HBcAg, HBeAg, and a shortened 22 kDa precore protein) among the several viral proteins that are synthesized [18,19]. Antiviral therapy-induced decreases in HBV DNA levels and intrahepatic HBV cccDNA levels are better correlated with HbcrAg [20–23]. It is also useful in anticipating the development of HCC and HBV reactivation in immuno-compromised people [24–28]. Similar to HBcrAg, HBV RNA is a pregenomic RNA biomarker that is very new [16]. It contains a virion. When compared to HBV DNA blood

Table 1. Various types of study and main findings.

Study Type	Main Findings	References
Prospective trial	In patients receiving NA treatment, higher HBV RNA levels are predictive of response. There exists a robust linear association between HBV RNA, HBV DNA and HBsAg titer. In NA-treated patients, HBcrAg and HBV RNA may predict long-term off-therapy HBV virological control.	Gao, *et al*. [32], 2017
Randomized, controlled, double-blind clinical trial	Patients with HBeAg positive HBV had substantially higher ($P < 0.0001$) HBcrAg titers. HBsAg titers showed an inverse relationship with fibrosis and a direct correlation with necro-inflammatory activity.	Zhang, *et al.* [14], 2018
Prospective trial	The HBsAg clearance profile in individuals receiving long-term Adefovir or Tenofovir therapy is positively correlated with HBsAg loss, seroconversion, and responsiveness to treatment.	Walsh, *et al.* [15], 2019
Prospective trial	HBcrAg values are useful for tracking hepatic histological alterations and indicate the course of liver parenchymal fibrosis.	Chang, *et al.* [34], 2019
Prospective trial	Proven usefulness of monitoring HBcrAg and HBV RNA levels in patients receiving NA therapy but having undetectable HBV DNA.	Liao, *et al.* [35], 2019
Prior Studies	Antiviral therapy-induced decreases in HBV DNA levels and intrahepatic HBV cccDNA levels are better correlated with HBcrAg. Hepatocellular carcinoma development and HBV reactivation in immunocompromised people can be predicted by HBcrAg. Pregenomic RNA HBV RNA contains a virion with a profile like that of HBcrAg. Patients with CHB who are not on treatment have blood levels of HBV RNA that are 1-2 logs lower than those of HBV DNA.	Multiple Authors [16, 20-30]

levels, treatment-naive CHB patients exhibit reduced HBV RNA serum levels (by 1-2 logs) [29,30]. On the other hand, HBV RNA is a predictor of response since it is substantially greater in patients receiving NAs than HBV DNA. HBV DNA and HBsAg titers have a robust linear association with HBV RNA [31,32]. Chang et al.'s recent prospective research [34] revealed that HBcrAg levels represent the course of hepatic fibrosis after therapy, supporting its use in tracking hepatic histological alterations. For NA-treated patients with undetectable HBV DNA and undetectable HBV RNA that occur prior to HBcrAg undetectability, Liao, *et al*, [35] showed the value of monitoring HBV RNA and HBcrAg levels. Before these biomarkers may be fully employed in clinical practice, a number of obstacles must be overcome. There is an urgent need for standardisation of serum RNA detection techniques and technical details as they range greatly throughout studies [16]. Measurement techniques for pgRNA often involve a selective DNA degradation phase to eliminate interference from viral DNA. This procedure is laborious, time-consuming, and reduces detection accuracy [36]. More investigation is required to identify precise HBcrAg cutoff values in order to assess clinical outcomes and understand the function of HBV RNA in latent HBV infection, seroclearance of HbsAg, HBV reactivation, and HCC development [16]. Furthermore, validation of the biomarkers in other racial and ethnic communities will be necessary. Sample sizes are lowered because studies linking new biomarkers to cccDNA and hepatic fibrosis need repeated liver biopsies. Hepatitis B surface antigen loss and a poor chance of a sustained response are linked to HBV RNA drop without concurrent viral antigen decrease, according to a recent study by Brakenhoff, *et al* [37]. Future studies that take into account the kinetics of combination biomarkers to evaluate antiviral activity are important [37].

Vaccination of Hepatitis B:

For newborns and non-immune people who are at high risk of exposure or have a poor disease outcome, such as patients with hepatitis C virus infection, HIV, men who have sex with men, intravenous drug users, healthcare workers, and household contacts of patients with a positive hepatitis surface antigen, current recommendations recommend pre-exposure universal vaccination [38,39]. The majority of HBV vaccination regimens that were available up to 2025 required the vaccine to be given in three doses at predetermined intervals and had a protective response of at least 90 %

[40]. The Food and Drug Administration authorised Heplisav-B (HepB-CpG) on November 9, 2017, as a single-antigen HepB vaccine with a unique immunostimulatory sequence adjuvant for the prevention of HBV in people who are at least 18 years old [41]. Two doses of the vaccine are given, separated by one month. The Advisory Committee on Immunisation Practices (ACIP) approved HepB-CpG for use in individuals ≥ 18 years old on February 21, 2018 [42]. Regretfully, even after vaccination, 5 to 10 % of patients do not have an immune response and are not protected [43]. An individual who does not produce hepatitis B surface antibodies after receiving the full course of the vaccination twice and for whom an acute or CHB infection has been ruled out is referred to as a "non-responder" to hepatitis B [44]. In addition to other variables including injection site, age, gender, body mass, and others, non-response is linked to distinct HLA-DR alleles and compromised T-helper cell response [45]. A second round of the original immunisation schedule is advised for individuals who did not react to the first round [46]. After receiving two doses of HepB-CpG, individuals with Hepatitis B surface antibody (anti-HBs) < 10 mIU/mL should have a second full series of HepB vaccinations, with anti-HBs testing conducted 1 to 2 months after the last dose. As an alternative, revaccination might involve administering one more dose of the HepB vaccine and testing for HBs 1 to 2 months later. If anti-HBs is still less than 10 mIU/mL, revaccination could also involve finishing the second HepB vaccine series and testing for HBs 1 to 2 months following the last dose [47]. For those who have had a needle stick injury or who may have encountered bodily fluids containing blood or semen, post-exposure prophylaxis should be taken into consideration [47]. Promising new research assessing the effectiveness of different revaccination schedules in non-responders may influence future guidelines. Raven, *et al,* [48] conducted a controlled superiority trial involving 480 immunocompetent non-responders across multiple centres. The trial compared the efficacy of revaccination using the initial regimen (control arm: HBVaxPro 10 µg or Energix B 20 µg) against three alternative regimens (Twinrix 20 µg, Fendrix 20 µg, or HBVaxPro 40 µg). Compared to controls (67 %), revaccinating with Fendrix 20 µg (83 %) or HBVaxPro 40 (98 %) resulted in a considerably larger percentage of responders. The authors contended that in order to allow non-responders to be vaccinated again, the indications for these vaccinations have to be widened [48]. In 2018, Koc, *et al* [49], made an effort to improve the HBVaxPro©-10-µg vaccine's immune response by using an adjuvant based on cytokines. HBVaxPro©-10-µg (HBAI20) was supplemented with this novel adjuvant, AI20, which comprises 20 µg of recombinant human Interleukin (IL)-2 linked to 20 µg of aluminium hydroxide. In 90 % of prior non-responders, HBAI20 produced protective anti-HBs titers in an open-label trial [49]. Furthermore, in order to accurately comprehend vaccination processes and probable causes of immunological non-response, researchers have resorted to "Systems vaccinology [50,51]. Systems vaccinology relies on data integration, which is made possible by technological advancements in mass spectrometry-powered proteomics, DNA microarrays, high throughput DNA sequencing, bioinformatics, and computational techniques [52]. Using a three-dose booster protocol, Qiu, *et al*. examined the transcriptome and cytokine profiles of seven responders and seven non-responders both before and after immunization [53]. There was a substantial upregulation of nine coding genes (BPI, DEFA1B, DEFA4, CEACAM8, MMP8, FOLR3, LTF, TCN1, and TKTL1) in non-responders as compared to responders. These genes may be indicative of hepatitis B vaccination non-responsiveness. The likelihood was reinforced by the findings of the gene ontology study, which indicated that the majority of these genes with differential expression were associated with immune response. The results of cytokine analysis showed that responders had considerably greater quantities of CXCL12 and IL-27 than non-responders did. IL-27 and CXCL12 may likely function as the distinctive cytokine markers for responders in multiplex cytokine assays.[53] A lower baseline level of CXCR3+ CCR6-CXCR5+ memory T cells was shown by Da Silva et al,[54] which may have contributed to individuals with chronic kidney disease (CKD) having worse sero-conversion after immunisation. Instead of the 20-µg dosage recommended by the Centres for Disease Control (CDC), the authors proposed an enhanced 40-µg HBV dosing schedule for individuals with chronic kidney disease (CKD) that is equivalent to haemodialysis patients [55–57]. After the first vaccine series is finished, booster doses are not recommended for immuno-competent patients since long-term follow-up studies demonstrate that immunological memory endures even in the face of decreasing hepatitis B surface antibody (anti-HBs) levels [58]. A dose of the HBsAg vaccine was administered to 101 persons who had received a

Table 2. Various types of study and main findings.

Study Type	Main findings	References
Prospective open label trial	90 % of prior non-responders to HBAI20 (HBVaxPro©-10-µg vaccination with adjuvant AI20, recombinant human IL-2) showed protective anti-HBs titers, most likely as a result of an improved immune response.	Koc, *et al,* [49] 2018
Prospective trial	Significant transcriptome and cytokine alterations were found in HBV vaccination non-responders by genome-wide comparative study.	Qiu, *et al,* [53] 2018
Randomized prospective trial	Lower baseline HBV vaccine seroconversion was associated with chronic kidney disease (CKD) patients. Levels of CXCR3 + CCR6-CXCR5+ memory T cells.	Da Silva, *et al,* [54] 2018
Prospective trial	When people who had received the HBsAg vaccination two to three decades earlier were given an immune challenge, they demonstrated a 100 % anamnestic response by day thirty and a notable increase in CD4+ T cells and HBsAg-specific memory B cells.	Van Damme, *et al,* [59] 2019
Open-labeled, randomized, controlled superiority trial	Revaccination with Fendrix 20 µg or HBVaxPro 40 µg produced noticeably greater response rates in immunocompetent non-responders than with HBVaxPro 10 µg, Energix B 20 µg, or Twinrix 20 µg.	Raven, *et al,* [48] 2020
Prospective trial	HIV co-infected HBV patients had lower TNF-α and IL-2 levels; to address this issue, an additional dosage of the HBV vaccination may be necessary.	Chawansuntati, *et al,* [63] 2018
Prospective trial	When administered to HBV patients on maintenance Lenalidomide following autologous haematopoietic stem cell transplantation, the Hepatitis B vaccine (Twinrix, GlaxoSmithKline, London) shown to be 100 % safe and 40 % effective.	Palazzo, *et al,* [64] 2018
Prospective trial	The 2-year and 3-year cumulative HBV reactivation rates for HSCT recipients who had received an HBV vaccination were 22.2 and 28.9 %, respectively. Reactivation of HBV was associated with baseline anti-Hbs titers (P = 0.004) and immunosuppressant discontinuation (P = 0.0379).	Nishikawa, *et al,* [65] 2020

recombinant hepatitis B vaccination 20 to 30 years earlier as part of a recent prospective experiment that was reported in 2019. By day 30, anamnestic response had occurred in 100 % of patients, as evidenced by a significant increase in CD4+ T cells expressing at least two activation markers and HBsAg-specific memory B cells. These findings are consistent with existing knowledge and point to long-term immunity retention and protection 20 to 30 years following a full course of primary HBsAg vaccination in adulthood [59]. This regulation does not apply to certain populations of people who are immuno-compromised. Patients receiving bone marrow transplants are one such group. In this regard, the "Recommendation of the ACIP" paper, which was released in January 2018 [47], serves as guidance for the American Association for the study of liver disease (AASLD) recommendations. According to the paper, children and adults who are immuno-compromised (such as those receiving haematopoietic stem cell transplants, patients undergoing chemotherapy, and HIV positive individuals) have a decreased humoral response to the hepatitis B vaccine [60,61]. Response rates may be raised by altered dosage regimens, such as administering extra doses or twice the recommended antigen dose. However, data on how these different immunisation regimens are received are scarce [62]. In HIV-positive individuals getting routine HBV vaccines, Chawansuntati, *et al* [63]. observed decreased levels of tumour necrosis factor (TNF)-α and IL-2 from CD4+ T cells. They recommended increasing the dose or frequency of vaccinations to address this issue [63]. The findings of a prospective research evaluating the safety and effectiveness of revaccination in 122 patients with multiple myeloma receiving maintenance dosage Lenalidomide following autologous haematopoietic stem cell transplant were reported in 2018 by Palazzo, *et al* [64]. The comparison of pre and post-vaccination antibody titers was used to assess the effectiveness of revaccination. According to their statistics, recipients of the Hepatitis B vaccination (Twinrix, GlaxoSmithKline, London) showed 100 % safety and 40 % efficacy [64]. Remarkably, even after a successful revaccination and maintenance of serum anti-HBs at more than protective levels, HBV reactivation can still emerge after

haematopoietic stem cell transplant (HSCT). The findings of a prospective experiment investigating immunisation to prevent HBV reactivation following haematopoietic stem cell transplantation were reported by Nishikawa, *et al*. in 2020 [65]. Six patients out of the 27 who received vaccinations 12 months after haemodialysis and were followed up for two years demonstrated HBV reactivation, with a total reactivation frequency of 22.2 % over the course of the two years. The stopping of immunosuppressants (P = 0.0379) and baseline anti-HB titers (P = 0.004) were factors linked to HBV reactivation [65]. Although a new technique, the nucleic acid-based vaccination for HBV prevention has not yet demonstrated efficacy in producing a long-lasting immune response in clinical studies [66].

Treatment options of Hepatitis B:

Patients with CHB (Persistence of HBsAg > six months) who have an ALT > 2 ULN and who are HBeAg positive with HBV DNA > 20000 or HBeAg negative with HBV DNA > 2000 may be evaluated for therapy, according to the 2018 revisions to the AASLD recommendations. Only single-drug regimens, such as pegylated interferon (PEG-IFN) and nucleoside/nucleotide reverse transcriptase inhibitors are approved therapy. Preferred regimens (PEG-IFN, Entecavir (ETV), tenofovir fumarate, and tenofovir alafenamide (TAF)) and Non-Preferred regimens (Lamivudine, Adefovir, and Telbuvidine) are the two categories of approved regimens [10]. The recommendations are supported by many recently published studies that show IFN and Tenofovir are safer and more effective than the non-preferred medications. When Chuang, *et al*, [67] used a PEG-IFN dose of 180 µg/wk for 48 weeks; they were able to show sustained HBeAg seroconversion rates of 67.1 % five years after the NEPTUNE trial ended. This suggests that the licensed regimen (180 µg × 48 weeks) is more effective for HBeAg-positive patients than a lower dose and/or shorter treatment duration. Tenofovir disoproxil fumarate (TDF) prodrug TAF and TDF together produced a similar 96 weeks HBV viral suppression in 73 % of patients compared to 75 % in HBeAg positive patients and 90 and 91 % in HBeAg negative patients, respectively [68]. According to Yim et al.'s prospective randomised controlled trial (RCT), there was a statistically significant 12-month HBV virological response (P = 0.022) in the subgroup that switched to TDF among partial responders to ETV (defined as detectable HBV DNA > 60 IU/mL) [69]. The study looked at continuing ETV vs switching to TDF. In a different prospective study, individuals with non-detectable HBV DNA and CHB resistance to lamivudine showed non-inferior outcomes at 96 weeks when stable transitioning to TDF monotherapy was implemented instead of Lamivudine + Adefovir combination therapy [70]. Tenofovir fumarate treatment for CHB virus infection in 585 patients (203 of whom finished the 10-year study) was found to be 10-year efficacious (HBV suppression in 100 % of HBeAg-negative and 98 % in HBeAg positive patients) and safe (few adverse events related to the kidneys or bones, with no resistance) by Marcellin, *et al*.[71] After a long term treatment (144 weeks), 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, according to a large multicenter RCT that was published in January 2019 and included 320 treatment-naive HBeAg positive patients [72]. The treatment of naive HBeAg positive individuals with telbivudine-based medication has resulted in encouraging findings recently. The trial lasted 104 weeks and measured liver stiffness (monitored by Fibroscan©), which decreased from 8.6 at baseline to 6.1 at weeks 24 and 5.3 at weeks 104 [73]. Though current regimens are effective and safe in suppressing viruses, reactivation is the usual outcome after treatment ends because cccDNA persists [74]. This grave flaw is further highlighted by recent research. After receiving a NA; 67 HBV patients who had achieved HBeAg seroconversion and undetectable HBV DNA were assessed as part of the Toronto STOP trial. After that, patients were chosen at random to stop. Compared to 8 2% of patients who continued NA, only 29 % of patients who quit the medication were able to maintain a sustained virological remission [75]. The safety and effectiveness of stopping treatment for HBV in individuals receiving TDF after eight years of medication was examined by Buti, *et al* [76]. Almost one-third of the patients experienced grade 3 hepatotoxicity 24 weeks after stopping NA, as measured by total bilirubin of > 3 - < 10 ULN and aspartate aminotransferase/ALT of > 5 - < 10 ULN [76]. Immune-tolerant CHB patients were treated with TDF and/or Emtricitabine for four years and then monitored for an additional four years following discontinuation of treatment in a follow-up study of a phase 2 experiment conducted at two centres. The authors noted that there

was a 50 % clinical recurrence at week 15 ± 11 (HBV DNA > 2000 and ALT > 2 ULN) and a 100 % virological relapse at week 4 (HBV DNA > 2000) [77]. Researchers have turned to using combination regimens with IFN and NA in an attempt to increase seroconversion rates, but others have tried to identify response predictors in order to create a more focused strategy in light of the limitations shown by these trials. Liem, *et al.* prospectively assessed HBeAg positive HBV patients receiving ETV in an effort to identify the best candidates who would benefit from a combination of PEG-IFN and nucleoside [78]. When compared to ETV monotherapy, the randomised addition of PEG-IFN to ETV treatment was linked to a substantial P = 0.03 48-week response rate (response defined as HBeAg loss) [78]. The addition of PEG-IFN alfa-2a (for 48 weeks) to continuing NA medication dramatically lowered HBsAg levels (defined by greater than 50 % fall) in HBeAg-negative patients with genotype D infection, according to data reported by the HERMES Study Group in 2019 [79]. CHB patients who seroconverted on ETV were recently included in a prospective study and transferred to weekly PEG-IFN alfa-2a. In patients with a baseline HBsAg < 1500 IU/mL, the authors observed an 88 % sustained response, whereas 50 % of patients with a baseline HBsAg < 500 had HBsAg loss [80]. The same group also developed a pre-treatment scoring system utilising baseline parameters such as age, sex, alanine aminotransferase ratio, HBsAg level, and HBV DNA level to predict response to therapy [81]. The system was developed using data from 647 patients with HBeAg positive CHB on PEG-IFN alfa-2a. In addition to highlighting the potential benefit of immune-based therapy, a recently published extensive meta-analysis comprising 24 trials and 6674 individuals corroborated the significance of extended treatment duration and the inclusion of IFN for HBsAg lowering [82]. Many treatment drugs with different mechanisms have been developed as a result of the recent discovery of novel targets within the life cycle of the hepatitis B virus [83]. Innate and/or adaptive immunity can be enhanced by modulating the host immune system, or direct reduction of viral replication can be achieved by focussing on basic stages including entrance, cccDNA formation/stability, viral transcription, capsid assembly, and secretion [17]. In and of it, the viral life cycle, the viral products that arise from it and their function in the pathophysiology of CHB constitute a rather vast and intricate subject. For further information on this subject, we discovered the new paper Hepatitis B viral biology and life cycle by Tsukuda, *et al* [84]. is a great resource. About ten years ago, it was discovered that the sodium taurocholate co-transport polypeptide (NTCP) (gene: SLC10A1) receptor serves as a doorway for HBV entrance into hepatocytes [85]. A great deal of hope has been generated by the finding, and NTCP has been used as a target for the development of viral entry inhibitors, such as cyclosporine and myrcludex [86,87]. Stable cell lines, cell cultures, and infection model systems that are enhanced by NTCP have also made it possible to conduct standardised research to better understand the HBV life cycle and identify treatment options [88–91]. These model systems have made it possible to examine real infection in cell lines, which has improved our understanding of the synthesis and breakdown of cccDNA, a crucial target for achieving the ultimate objective of curing HBV [92, 93]. Trials to target the viral proteins needed for the virus to enter uninfected hepatocytes, to target adaptive immunity (anti-programmed cell death 1/programmed death-ligand 1 antibodies, chimeric antigen receptor T cells), and to silencing cccDNA are being funded by the National Institute of Health (NIH) are currently in progress [94]. Replication in vitro, other viral gene expression metrics and cccDNA were all reduced in a preclinical experiment using cccDNA endonucleases (CRISPR/Cas9) [95]. The effectiveness and safety of Core Protein (Capsid) Assembly Modulators in CHB patients have been assessed in a number of recent investigations. In a phase 1 trial, NVR 3-778 showed antiviral effectiveness and was well tolerated by HBeAg-positive CHB patients without cirrhosis. The drug most significantly decreased blood levels of HBV DNA and HBV RNA when coupled with PEG-IFN. The new mechanism of NVR 3-778 was validated by the observed decreases in HBV RNA [96]. ABI-H0731, an experimental HBV core protein inhibitor, demonstrated acceptable safety, pharmacokinetics, and antiviral efficacy in a phase I, randomised, placebo-controlled study that was reported in the Lancet in 2020 [97]. The safety, tolerability, and pharmacokinetics of GLS4, a novel HBV capsid assembly inhibitor, were assessed in a different phase I trial conducted by Zhao, *et al* [98]. GLS4 was found to have acceptable tolerability and to sustain higher than suggested effective plasma trough concentration when used in combination with ritonavir, which is used to enhance GLS4 plasma levels.

Vandenbossche, *et al*. Phase I double-blind RCT, which included 30 healthy adults, examined the pharmacokinetics, safety, and tolerability of JNJ-56136379. This novel HBV capsid assembly modulator was found to be well-tolerated, with an effective plasma concentration more than three times that needed to inhibit viral replication [99]. It has recently been discovered that the HBV regulatory protein X (HBX) interacts with the host protein DDB1 to enhance transcription from cccDNA [100]. In order to find potential drugs that targeted the HBX-DDB1 interaction, Sekiba, *et al* [101]. used a recently developed split luciferase assay technique. They then demonstrated that nitazoxanide (NTZ) effectively inhibits the HBX-DDB1 protein association. NTZ dramatically reduced the synthesis of viral proteins and viral transcription in human primary hepatocytes that were spontaneously infected with HBV.[101] Small single-stranded nucleic acid sequences known as antisense oligonucleotides preferentially attach to their target RNAs, causing degradation [102]. An antisense oligonucleotide that targets the liver, GSK3389404, prevents the creation of HBsAg and all other HBV proteins. The safety and pharmacokinetic profile of a recent randomised double-blind controlled phase 1 study were found to be satisfactory, hence endorsing more clinical research in individuals with CHB [103]. Over 95 % of people with adult-acquired hepatitis B are cured of it by their immune systems [94]. A substantial amount of evidence connects liver damage and chronic hepatitis B to inhibited T and B cell responses [104–106]. Additionally, evidence from studies involving T and B cell responses clearly imply that the infection can be eradicated by enhancing immunity [107]. Consequently, increasing the strength and calibre of the immune response specific to the virus makes sense as a therapeutic approach [108]. In limited prospective studies, a variety of toll-like receptor (TLR) agonists have demonstrated encouraging antiviral benefits. GS-9620, a TLR-7, did not considerably alter serum HBsAg levels over a 12-week administration. However, it did enhance NK- and T-cell responses [109–111]. According to Han, et al.'s research,[112] HBeAg positive CHB patients have a lower baseline level of galactosylation, making them good candidates for the therapeutic vaccination known as HBsAg-hepatitis B immune globulin (HBIG) immune complex, which is used to induce HBeAg seroconversion. This was verified as an immunological response by the significantly elevated levels of galactosylation and IL-2 [112]. The aim of therapeutic vaccination is to enhance the immunological response of the host in order to regain immune control. This will eventually result in the elimination of HBsAg and a persistent suppression of HBV replication. The data supporting the safety and effectiveness of therapeutic vaccinations in CHB patients was examined in a recently published meta-analysis of 15 studies [113]. In summary, the authors noted that patient selection, inadequate therapeutic vaccinations, and a lack of RCTs may have hampered the effectiveness of therapeutic vaccines in treating CHB. An open-label phase III trial compared PEG-IFN alfa 2b (180 µg weekly for 28 weeks) with the therapeutic vaccine NASVAC (100 µg of each HBs and HBc antigens, administered in 2 cycles of 5 doses) in naive CHB patients. The results showed that the NASVAC group had significantly better controlled HBV DNA 24 weeks post-treatment ($P < 0.05$) and a lower rate of progression to cirrhosis [114]. When given every eight weeks for 48 weeks, a total of seven doses of HBsAg-based recombinant vaccines have been demonstrated to lower HBsAg levels ($P = 0.0005$) and induce HBsAg seroconversion in 10.52 % of patients with low HBsAg titers [115]. A combination GS-4774 (a yeast-based modified vaccine) and tenofovir compared to tenofovir alone showed better HBV-specific T cell responses, including IFN-γ, TNF-α, and IL-2, according to a multicenter prospective phase 2 RCT by Boni et al.[116] Wu et al's HBV Endeavour prospective study [117] examined the possibility of transferring nucleoside analog-treated HBV patients with verified viral suppression and HBsAg loss to immunomodulators (IL-2) and therapeutic vaccinations containing IFN in order to improve HBsAg loss and accomplish HBV virological cure. The study reports on the HBsAg reduction in the IFN/vaccine/IL-2 group, the IFN group, and the ETV group, which were 9.38, 3.03, and 3.7 %, respectively. The response rates of HBsAg loss were correlated with greater titers of CD16-NK cells and lower titers of regulatory T cells [117].

HEPATITIS B SPECIAL CASES:

Transmission of hepatitis B from mother to child:

Pregnant women with elevated levels of HBV viral DNA have been investigated for perinatal HBV transmission; antiviral medication has been investigated as a potential intervention [9,118,119].

Table 3. Various Types of Study and Main Findings.

Study Type	Main findings	References
Conventional treatment agents		
Prospective study	PEG Interferon administered at a dosage of 180 µg/wk for 48 weeks produced higher sustained rates of HBeAg seroconversion compared to individuals receiving a lower dose and/or shorter treatment time.	Chuang, *et al,*[67] 2018
Randomized controlled trial	In patients treated with TAF and TDF, the 96-week HBV suppression rates were similar for HBeAg positive (73% vs. 75%) and HBeAg negative (90% vs 91%) individuals.	Agarwal, *et al,*[68] 2018
Prospective randomized controlled trial	Patients with HBV who responded partially to ETV had better (12-months HBV response, P = 0.022) when they were shifted to TDF as opposed to maintaining ETV.	Yim, *et al,*[69] 2018
Prospective trial	When Lamivudine + Adefovir combination treatment was used in Lamivudine-resistant HBV patients with undetectable HBV DNA, switching to TDF monotherapy produced non-inferior outcomes at 96 weeks.	Lee, *et al,*[70] 2018
Prospective trial	A 10-year TDF effectiveness trial revealed no resistance to TDF, minimal side effects linked to the kidneys or bones, and HBV viral suppression in 100% of HBeAg-negative and 98% of HBeAg positive patients.	Marcellin, *et al,*[71] 2019
Multicenter randomized controlled trial	HBV treatment naïve HBeAg positive individuals treated with TDF or ETV revealed similar serologic, biochemical, and side-effect profiles at 144 weeks, as well as similar HBV DNA suppression (-6.6485 vs. -6.692 log 10 IU/mL, P = 0.807).	Cai, *et al,*[72] 2019
Prospective trial	Fibroscan© monitoring revealed that liver stiffness decreased in HBV treatment-naïve HBeAg positive patients receiving Telbivudine-based therapy, from 8.6 at baseline to 6.1 at week 24 and 5.3 at week 104.	Liang, *et al,*[73] 2018
Randomized controlled trial	82 % of HBV patients who continued NA versus 29% of those who stopped NA saw maintenance of remission after achieving HBeAg seroconversion with undetectable HBV DNA.	Liem, *et al,*[75] 2019
Prospective trial	Patients with HBV who had TDF treatment but stopped it later: Almost one-third of the patients experienced grade 3 hepatotoxicity 24 weeks after stopping NA (defined as AST/ALT of > 5 - < 10 ULN and total bilirubin of > 3 - < 10 ULN).	Buti, *et al,*[76] 2019
Phase II prospective trial	Patients with high-level HBV immunity who were treated with TDF and/or Emtricitabine for four years and then monitored for a further four years after stopping the medication had a fifty percent clinical relapse at fifteen weeks along with a hundred percent virological relapse at week four (HBV DNA > 2000).	Wong, *et al,*[77] 2018
Randomized prospective trial	When PEG-IFN was added randomly to ETV therapy for HBV patients who tested positive for HBeAg, the 48-week response rate (HBeAg loss) was considerably greater than when ETV monotherapy was used (P = 0.03).	Liem, *et al,*[78] 2019
Prospective randomized controlled trial	Patients with genotype D, HBeAg-negative HBV, receiving NA treatment had a noteworthy 50% reduction in HBsAg levels when PEG-IFN alfa-2a was added for 48 weeks.	Lampertico *et al,*[79] 2019
Prospective trial	Patients with CHB who were shifted from entecavir to weekly PEG-IFN alfa-2a following seroconversion had a longer-lasting response (88% at HBsAg < 1500 IU/ml and 50% at HBsAg < 500 IU/mL).	Chan, *et al,*[80] 2019
Meta-analysis	Demonstrated the potential benefit of immune-based treatments and reaffirmed the significance of extended treatment durations and the inclusion of IFN for HBsAg reduction.	Chen, *et al,*[82] 2020
New direct antiviral agents		

Pre-clinical prospective study	When ccc DNA endonucleases (CRISPR/Cas9) were used, ccc DNA as well as other aspects of viral gene expression and replication in vitro decreased.	Ramanan, *et al,* [95] 2015
Phase 1 prospective trial	Patients with non-cirrhotic HBeAg-positive CHB were able to handle NVR 3-778, a capsid assembly protein modulator, and their serum levels of HBV DNA and HBV RNA were decreased, most notably when PEG-IFN was taken in conjunction with it.	Yuen, *et al,*[96] 2019
Phase I, randomized placebo-controlled trial	shown respectable pharmacokinetics, antiviral activity, and safety on the experimental HBV core protein inhibitor ABI-H0731.	Yuen, *et al,*[97] 2020
Phase I, randomized controlled trial	Shown that GLS4, a new HBV capsid assembly inhibitor, has good safety and pharmacokinetics whether taken with or without ritonavir, which is utilised to raise GLS4 plasma levels.	Zhao, *et al,*[98] 2019
Phase I double-blind, randomized controlled trial	JNJ-56136379, a new HBV capsid assembly modulator, has shown acceptable safety and pharmacokinetics. It has also demonstrated more than three times the 90% effective plasma dose needed to block viral reproduction.	Vandenbossche, *et al,* [99] 2019
Phase I double-blind, randomized controlled trial	GSK3389404, a liver-targeted antisense oligonucleotide that prevents the production of the hepatitis B surface antigen and all other hepatitis B viral proteins, has shown to have acceptable safety and pharmacokinetics.	Han, *et al,*[103] 2019
New immune based therapies		
Phase I prospective trial	Serum HBsAg levels were not considerably impacted by the 12-week course of GS-9620 (TLR7 agonist), but its administration was safe. Nonetheless, it did boost responses from NK and T cells.	Boni, *et al,*[109] 2018
Phase II prospective trial	A 12-week regimen of GS-9620 (a TLR7 agonist) was administered; it was safe and showed a dose-dependent increase in the production of interferon-simulated gene m RNA, without any reduction in HBsAg levels or IFN-α expression.	Janssen *et al,*[110] 2018
Randomized controlled prospective trial	In individuals with naïve viral hepatitis B, the addition of Vesatolimod (a TLR7 agonist) to Tenofovir was found to be safe. Without a discernible improvement in the fall of HBsAg, this intervention resulted in the dose-dependent pharmacodynamic induction of ISGs.	Agarwal, *et al,* [111] 2018
Prospective trial	26 individuals who had baseline IgG galactosylation levels below demonstrated a sustained rise in serum galactosylated IgG caused by the cellular immune response and responded to YIC therapy by HBeAg seroconversion.	Han, *et al,* [112] 2019
Open-label phase III trial	Patients with CHB who had not received treatment demonstrated significantly better controlled HBV DNA 24 weeks post-treatment ($P < 0.05$), and the NASVAC group (a therapeutic vaccine containing 100 µg of each HBs and HBc antigens, administered in 2 cycles of 5 doses) had a lower progression rate to cirrhosis than the PEG-IFN alfa 2b (weekly 180 µg) group.	Al Mahtab, *et al,*[114] 2018
Randomized controlled prospective trial	Serial HBsAg-based immunisations were safe and led to a considerable drop in HBsAg in low-level HBsAg CHB patients. The response to vaccination was influenced by genotypes and HLA gene expression.	Lai, *et al,*[115] 2018
Multicenter phase II prospective randomized controlled trial	Shown enhanced HBV-specific T cell responses, including as IFN-γ, TNF-α, and IL-2, when tenofovir and GS-4774 (a yeast-based modified vaccine) were taken together as opposed to only tenofovir alone.	Boni *et al,*[116] 2019

Prospective controlled trial(The HBV Endeavor prospective trial)	As HBV patients converted to immunomodulators (IL-2) and therapeutic vaccines with IFN, they demonstrated HBsAg loss in 9.38 %, 3.03 %, and 3.7 % in the IFN/vaccine/IL-2 group, IFN group, and the ETV group, respectively. These patients had proven viral suppression and HBsAg loss while on ETV. Higher HBsAg loss response rates were correlated with lower regulatory T cell titers and higher CD16-NK cell titers.	Wu *et al,*[117] 2019
Prospective trial	SRI-32007, a repurposed chemical, showed anti-HBV effectiveness by inhibiting HBV core promoter activity; it may be utilised to research treatments to treat HBV.	Kalkeri, *et al,*[142] 2020
Hepatitis B in pregnancy		
Phase III randomized prospective trial	Shown that in HBV patients with HIV, the geometric mean tenofovir AUC (0–24) was 20% (95%CI: 19%–21%) lower during pregnancy than postpartum. This suggests that there shouldn't be a dosage change necessary to make up for the little decrease in HBV transmission.	Cressey, *et al,* [120] 2018
Randomized double-blind prospective trial	In pregnant HBsAg and HBeAg positive patients with high virus loads, starting TDF at the 24th week of gestation and continuing it for 4 weeks after birth decreased the MTCT from 13.5% (control group) to 0% cervical transmission. DNA titer for HBV > 2 × 106 IU/mL	Lin, *et al,*[121] 2018
Prospective trial	When TDF was started at the 24th week of pregnancy, pregnant patients who tested positive for HBsAg and HBeAg and had high viral loads had an MTCT of 0.7% in the ITT group and 0% in the protocol group. TITERS of HBV DNA > 6 log10 IU/mL	Wang, *et al,*[122] 2019
Multicenter, double-blind clinical trial	TDF started at the 28th week of gestation and continued for two months after delivery, which somewhat decreased the MTCT in pregnant HBsAg and HBeAg positive patients with an ALT of less than sixty, from 2% (control group) to 0% cervical transmission. The authors demonstrated that the MTCT for babies at 6 months of age was only slightly lowered by the addition of TDF.	Jourdain, *et al,* [123] 2018
Randomized control trial	When using telbivudine in addition to TDF, immune-tolerant CHB patients who are waiting for assisted reproduction demonstrated higher viral clearance (90% vs 67.2%, P = 0.002 at week 12 and 96.6% compared to 85.2% at week 48, respectively). The HBeAg seroconversion rates for the two groups (8.3% vs 3.3%; P = 0.233) did not differ from one another.	Wu, *et al,*[125] 2019
Hepatitis B reactivation		
Randomized double blind prospective trial	In patients with cured hepatitis B who were receiving Rituximab for lymphoma, prophylaxis with ETV substantially decreased HBV reverse seroconversion as compared to placebo (4.3% vs. 25.9% at 18 month ; P = 0.019).	Huang, *et al,*[127] 2013
Prospective trial	After receiving obinutuzumab or rituximab for their HBV infection, resolved NHL patients showed a significant (P < 0.0001) association between HBV reactivation and detectable baseline HBV DNA. Prophylactic NA also decreased the chance of HBV reactivation (P = 0.0018).	Kusumoto, *et al,*[130] 2019
Double bling randomized control trial	Similar reactivation rates occurred with or without ETV prophylaxis in resolved HBV patients with cancer who underwent chemotherapy (0% vs. 3.2%; P = 0.246). The authors proposed that entecavir usage as a preventive measure was not a financially viable approach, particularly for those having a baseline positive anti-HBs test.	Liu, *et al,*[131] 2019
Retrospective study	In individuals using ibrutinib, the rate of HBV reactivation was 9.5% (2 out of 21 patients with known history of HBV infection).	Hammond, *et al,*[132] 2018
Prospective trial	Patients with HCC who had TACE but had negative HBV DNA were susceptible to HBV reactivation. When comparing ETV recipients to controls, HBV reactivation rates were considerably lower (5.9% vs. 23.4 %; P < 0.05).	Wang, *et al,*[135] 2018

Meta-analysis	Patients with HBV DNA negative and HCC who received TACE had a higher chance of hepatitis (P < 0.01) and HBV reactivation (P < 0.01). Prophylactic antiviral medication use dramatically decreased the probability of hepatitis (P = 0.02) and HBV reactivation (P < 0.01).	Zhang, *et al,*[136] 2019
Multi-center retrospective study	HBV reactivation occurred in 12.7 % of HBV DNA negative individuals with HCC who received RT. When compared to the control group, the use of preventive anti-viral medication significantly reduced the probability of HBV reactivation (P < 0.001). HBV reactivation was much more likely with combined RT and TACE (P = 0.008).	Jun, *et al,*[137] 2018
Retrospective study	There was a 15 % chance of HBV reactivation in CHB patients with SARS-CoV-2 infection.	Liu, *et al,*[138] 2020

Within 12 h of birth, all neonates born to moms infected with HBV should get the HBV vaccine and HBIG, and then they should finish the second or third round of vaccinations [47]. When maternal HBV DNA is greater than 200000 IU/mL, American Association for the Study of Liver Diseases (AASLD) recommends antiviral medication beginning at 28 to 32 weeks to decrease perinatal HBV transmission [9]. Due to its lack of resistance and the availability of safety data, tenofovir is advised as the preferable agent. The medication is stopped between the time of delivery and three months after giving birth [9]. Tenofovir exposure throughout pregnancy and the postpartum period in HBV-positive but HIV-negative women using TDF to prevent HBV transmission from mother to child was evaluated for the first time by Cressey, *et al*. They came to the conclusion that a dosage change was not necessary in light of the little decrease in tenofovir exposures seen during pregnancy [120]. In order to reduce mother to child transmission (MTCT) in pregnant women with extremely high virus loads, at least two recent trials have shown the safety and effectiveness of adding TDF to routine neonatal immunological prophylaxis [121,122]. On the other hand, in a multicenter, double-blind clinical trial conducted in Thailand, researchers showed that administering hepatitis B immune globulin and hepatitis B vaccine to infants born to mothers who tested positive for HBeAg did not significantly reduce the rate of mother-to-child HBV transmission [123]. The safety, effectiveness, and usefulness of tenofovir in pregnant women at high risk for hepatitis B MTCT are reaffirmed by these investigations. In their July 2020 guidelines on antiviral prophylaxis in pregnancy, the World Health Organisation advises that, in order to prevent mother-to-child transmission of HBV, pregnant women who test positive for HBV infection (HBsAg positive) and have HBV DNA 5.3 log10 IU/mL (200000 IU/mL) should receive tenofovir prophylaxis starting on the 28th week of pregnancy and continuing until at least delivery. All babies receive a three-dose hepatitis B vaccination in addition to this, including a dose at the appropriate time of delivery [124]. Among immune-tolerant (HBeAg positive) CHB patients awaiting assisted reproduction, Wu, et al.'s RCT[125] revealed that patients receiving a combination of TDF and telbivudine had higher viral clearance (90 % vs 67.2 %, P = 0.002 at week 12 and 96.6 % compared to 85.2 % at week 48, respectively) than those receiving TDF alone. The HBeAg seroconversion rates for the two groups did not vary (8.3 % vs. 3.3 % P = 0.233) [125].

Anticancer therapy:

According to earlier research, 41 to 53 % of HBsAg-positive, anti-HBc-positive patients and 8 to 18 % of HBsAg-negative, anti-HBc-positive patients had HBV reactivation as a result of anticancer therapies [126,127]. Reactivation is thought to be more likely in patients following B cell depleting treatments like Rituximab [128,129]. Before beginning treatment with B cell depleting medicines like rituximab, the AASLD advises screening patients who require chemotherapy with both HBsAg and anti-HBc and prophylaxis with NAs [10]. It is yet unclear what function baseline anti-HBs testing serve in this group. Furthermore, there is a dearth of information about hepatitis B reactivation in patients receiving some of the more recent immunochemotherapy medications, such obinutuzumab and Ibrutinib. In a recent trial, prophylactic NAs or HBV DNA guided preemptive NA treatment were administered to 326 patients with past HBV who were receiving obinutuzumab or Rituximab for B-cell non-Hodgkin's lymphoma (NHL). Seronegativity for anti-HBs and detectable HBV DNA levels at baseline (rather than the medication choice) were linked to an increased likelihood of HBV reactivation, according to multivariate regression analysis [130]. Although patients taking preventive

antivirals had a decreased reactivation rate, neither group's patients had HBV-related hepatitis [130]. The results indicate that HBV DNA-guided preemptive therapy can successfully avoid HBV hepatitis during anti-CD20 immunochemotherapy in B-cell NHL, whereas preventive therapy can prevent reactivation and may be appropriate for some high-risk patients. The prophylactic use of ETV was determined to be a non-cost-effective strategy, particularly for those with a positive anti-HBs test. This was determined by Liu, *et al*'s RCT [131] on lymphoma patients undergoing chemotherapy who had a history of HBV infection (HBsAg negative, Anti HBV core total antibody positive, and negative HBV DNA). In comparison to individuals receiving preventive ETV, the HBV reactivation in controls was 3.2 % as opposed to 0% (P = 0.246) [131]. The authors of a recent retrospective study found that two patients with chronic lymphocytic leukaemia had hepatitis B reactivation following Ibrutinib therapy. At the Dana-Farber/Harvard Cancer Institute, the rate of hepatitis B reactivation in patients receiving ibrutinib was 9.5 % (2 out of 21 patients with known prior HBV infection) [132]. These studies emphasise the potential for hepatitis B reactivation in patients treated with novel agents like ibrutinib and obinutuzumab, the value of baseline anti-HBs testing for risk assessment, and the necessity of close monitoring in conjunction with preemptive treatment as a secure and economical approach. Hepatitis B reactivation is a slightly higher risk for CHB patients undergoing transarterial chemoembolization (TACE) for HCC [133,134]. Since systemic data from high-quality prospective trials and meta-analyses are required to further our understanding of this sector, the most current AASLD guidelines do not explicitly address this problem due to the absence of systemic data assessing antivirals' involvement in this category of patients. Prophylactic antivirals were linked with a substantial decrease in the frequency of hepatitis B reactivation (5.9 % vs 23.4 % P < 0.05) in a recent prospective study including 98 CHB patients with HCC needing TACE.[135] Recently, Zhang, *et al*,[136] conducted a meta-analysis to assess the impact of TACE in conjunction with antiviral medication and look into the reactivation of HBV in primary HCC patients (HBV-DNA negative). TACE markedly elevated the likelihood of HBV reactivation (OR: 3.70; 95%CI: 1.45-9.42; P < 0.01) and consequent hepatitis (OR: 4.30; 95 % CI: 2.28-8.13; P < 0.01) in patients with horizontal colon cancer. In patients receiving TACE, preventive antiviral medication decreased the risk of hepatitis (OR: 0.22; 95 % CI: 0.06-0.80; P = 0.02) and HBV reactivation (OR: 0.08; 95 % CI: 0.02-0.32; P < 0.01) [136]. An evaluation of 133 patients receiving radiotherapy +/- TACE for HCC was conducted recently in a multicenter retrospective study. The results showed that the effect of antiviral therapy on HBV reactivation in quiescent HBsAg positive patients after radiotherapy for HCC was 33.3 % in the non-antiviral group and 7.5 % in the antiviral group, with a P < 0.001 [137].

Coronavirus Disease 2019 (COVID - 19):

Liu, et al. reported an intriguing HBV reactivation event in individuals who have just contracted COVID-19 but are not necessarily immuno-compromised. It is evident that COVID-19 patients with or without chronic HBV have liver impairment. It was discovered that COVID-19 patients who were also co-infected with chronic HBV were at risk of experiencing hepatitis B reactivation. As a result, it was imperative to monitor both the patients' liver function and HBV-DNA levels during the whole course of the disease [138].

FUTURE PERSPECTIVES:

A visionary declaration to eliminate the hepatitis B endemic through better screening, vaccine techniques, enhanced hepatitis B treatment, and follow-up care was issued in November 2019 by the NIH hepatitis B cure strategic plan working group. This guideline would further aid in the development of innovative therapies as well as novel biomarkers to diagnose disease progression, and it serves as a platform for future coordinated worldwide efforts.[139] The existing therapies are not suitable because of the requirement for lifetime medication, poor tolerability, unpleasant effects, and a continuing risk of complications, including HCC. The first of several important findings that have completely changed the field of HBV research was the identification of NTCP as an HBV receptor on human hepatocytes. The finding has produced novel animal models, cell lines, biomarkers, and treatment drugs during the last ten years, as well as a markedly enhanced knowledge of HBV pathogenesis. Our arsenal of possible HBV medications has grown significantly. HBV entrance inhibitors, capsid assembly modulators, cccDNA destabilisers and endonucleases, HBX inhibitors, expression-inhibitors, and HBsAg release inhibitors are among the direct antivirals that are now being researched [13]. It is more likely that these agents will

enhance current therapies than to replace them. Future studies will probably compare and mix new agents with NAs due to the safety profile of NAs. It is highly likely that a combination of drugs that alter host and viral parameters in different ways will be needed for the first HBV cure. T cells are effective in controlling the virus in acute hepatitis, which is why they have been thoroughly researched. Novel medicines can target adaptive immune responses (checkpoint inhibitors, therapeutic vaccinations and genetically modified T cells/antibodies) or innate and intrinsic cell responses (Toll-like receptor agonists, RIG-1). Multifactorial T cell fatigue or loss of T cell responsiveness to HBV is a significant obstacle to the development of immunomodulatory treatment medicines. These ideas have been used to treatment plans that change the hepatic environment through the use of pattern recognition receptor agonists, strong adjuvants, or monoclonal antibodies. However, our knowledge of HBV-specific B cells is restricted to their ability to produce antibodies; more research is needed to fully comprehend their cytokine profiles and their function as antigen-presenting cells.[108] The absence of ideal animal models is a significant barrier to preclinical testing of new medicines. Animal models for researching the host response to the virus and disease progression have been scarce and subpar due to the high species specificity of HBV infection.[140] The only nonhuman immune-competent mammal that is inherently prone to HBV infection is the chimpanzee. The only alternatives left are Tupaia (a tree shrew), woodchucks, or mice, all of which have serious disadvantages, given the ban on using chimpanzees owing to bioethical concerns [141]. The creation of infection models that are resilient, stable, and more representative of the normal HBV life cycle inside the human host is essential for future research aimed at creating antiviral drugs against the viral genome reservoir or cccDNA or at enhancing the patient's immune system. In light of this, medication repurposing could result in less work, time, and money spent on the development, testing, and promotion of novel pharmaceuticals. Examining already-approved medications with proven safety profiles for novel therapeutic uses is known as drug repurposing. High throughput screening allows thousands of chemicals to be evaluated for the intended impact. A repurposed chemical called SRI-32007 was shown in a recent research to have anti-HBV efficacy by inhibiting the activity of the HBV core promoter.[142] Compared to standard drug development, drug repurposing may enable more methodical and significantly less expensive approaches to the discovery of novel medicines for illnesses. The European Association for the Study of the Liver and the AASLD collaborated to organise the HBV Treatment Endpoint Conference in order to encourage and facilitate the development and implementation of future studies in the field of CHB with the goal of creating a cure.[13] A method for carrying out effective phase II/III studies while upholding superior safety profiles was presented at the conference. It was decided that HBsAg reduction and undetectable HBV DNA six months after treatment completion should be the main outcomes of phase III studies. The target response rate in these phase III studies is HBsAg loss in ≥ 30% of patients after a year of medication. For the scientific community to fully comprehend viral biology and quickly and affordably create new treatments there must be a thorough collaboration to standardise terminology, procedures, and outcomes. But it will only be the start of the fight against HBV on a worldwide scale. Important obstacles that impede efforts to prevent and cure CHB in the most vulnerable groups have been recognised by the WHO. Inadequate commitment, leadership, data, coverage of preventive initiatives, and a deficiency in public health strategies to address hepatitis are examples of structural obstacles. Individual obstacles include a lack of knowledge or understanding, pervasive prejudice and stigma, access to healthcare, and affordability. In light of these obstacles, the World Health Organisation has created a fundamental plan to eradicate viral hepatitis as a public health hazard by 2030, slashing new infections by 90 % and death by 65 % [94].This worldwide approach will be built around a practical and effective immunisation campaign. When given correctly, the hepatitis B vaccine has seroconversion rates exceeding 90 %, making it one of the most successful vaccinations. Further research is required to determine the immunological processes and host genetic variables that result in an ineffective response in individuals who are immunocompetent. To increase seroconversion rates, it is necessary to better understand the immunocompromised host's vaccination response and create workable solutions like immune priming. In order to provide more individualised vaccination, vaccine biology may be able to identify, at baseline, predictive characteristics for individuals eliciting protective responses after HBV immunization [143]. To support the idea of baseline predictors and the viability and

usefulness of targeted immunological baseline modification prior to vaccines, these findings require more testing [143]. In order to eradicate HBV infection as a health risk to the public, HBsAg prevalence in children under five years old must be decreased to less than 0.1%. It can be accomplished by immunising all babies against hepatitis B and by implementing other measures to stop the transfer of HBV from mother to child [124]. Among the major obstacles are the prohibitively high cost and poor availability of HBIG as a result of insufficient resources for transportation and storage. Even while vaccinations are effective in lowering MTCT, birth dose immunisation rates are still low, particularly in Africa [124]. In high-risk communities, inadequate infrastructure restricts the availability of antivirals and makes it more difficult to test for HBV DNA. Even with a positive antibody titer and an initial vaccine response, the immuno-compromised individuals continue to be at high risk of reactivation. To determine the risk loci that predispose to the persistence of HBV infection, non-response to the hepatitis B vaccination, and the advancement of liver disease in chronic HBV infections, researchers have relied on genome-wide association studies (GWAS) [144]. Our understanding of HBV pathophysiology would be further enhanced by more GWAS and fine-mapping investigations conducted in different ethnic communities, with bigger samples and more precise case-control designs [144].

CONCLUSION:

Numerous innovative direct acting antivirals and immune-based treatments are being researched because of the breakthrough in our understanding of the HBV life cycle. However, it is more probable that new agents will supplement PEG-IFN and NAs rather than completely replace them in the near future. Improved results have been shown in recent trials using combination regimens (PEG-IFN + NA) and longer PEG-IFN treatment durations. Furthermore, studies evaluating different vaccination schedules for primary non-responders and prenatal NAs for MTCT prevention in high-risk persons have demonstrated potential and might change recommendations in the future. Novel biomarker studies are hampered by limited sample sizes, lack of standardization, and technological issues. The hepatitis B vaccination is still underutilized in many parts of the world despite its outstanding effectiveness because of inadequate infrastructure and execution. There is a dearth of information on high-risk groups who are more susceptible to the severe consequences of hepatitis B infection and reactivation. Future innovation will depend heavily on the use of systems approach, experimental model optimization, next-generation biomarker discovery and validation, and precise human immune response manipulation. Finally, but just as importantly, in order to provide practical outcomes, managing MTCT and population health-related issues pragmatically must be given top priority.

ABBREVIATIONS:

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; 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; 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.

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