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Hepatitis B Virus–Related Hepatocellular Carcinoma: Carcinogenesis, Prevention, and Treatment

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Additional information is available at the end of the chapter

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the second leading cause of cancer death. Hepatitis B virus (HBV) infection is one of the major risk factors for the development of HCC in the world. Most of the burden of disease (85%) is observed in the HBV endemic regions. Chronic infection with HBV predisposes patients with or without cirrhosis to HCC. Patients with high HBV DNA levels are at an increased risk for HCC. Studies have shown that the suppression of HBV with anti-viral therapy (nucleos(t)ide analogs) (NAs) decreases the incidence of HCC but does not eliminate the risk entirely. Chronic viral suppression alone is not sufficient treatment to prevent HCC development. Therefore, along with NAs, treatment may need to include targeting the cccDNA and inhibiting the viral entry into the newly formed hepatocytes and T-cell vaccine which specifically targets HBV and enhancing innate immunity with Toll-like receptor agonist. With all of these working together, we may achieve the goal of HBV cure.

Keywords: HBV, HCC, nucleos(t)ide analogs, antiviral treatment, prevention of HCC, HBV cure, hepatocarcinogenesis

1. Hepatitis B virus (HBV)

1.1. The discovery of HBV

Following the “icteric epidemic” in the 1880s, viral hepatitis was recognized as infectious in nature [1]. The discovery of HBV did not occur until 1965 when Baruch Blumberg, an American physician and geneticist, found a unique antigen in the serum of Australian aborigines (Australia Antigen, AuAg) that reacted with the serum of hemophiliacs [2, 3]. This

antigen AuAg is now recognized as the hepatitis B surface antigen (HBsAg). Later, the link between viral hepatitis and this newly discovered antigen was firmly established when a technician in Blumberg's laboratory developed acute hepatitis [4]. Blumberg was awarded the Nobel Prize in Medicine in 1976 for his discovery of HBV.

Dane et al. identified the entire viral particle using electron microscopy in the 1970s [5]. Subsequently, in 1971, Blumberg and Millman developed a blood test to start screening blood donations for HBV [6]. In 1980, the FDA approved the first commercially available HBV vaccine once the genome of HBV was sequenced [7, 8]. While this first generation vaccine is no longer available in the United States, a recombinant HBV vaccine has been in use since 1986. A strong association between HBV and hepatocellular carcinoma (HCC) was described by Beasley et al. in their landmark study of 22,707 men in Taiwan [9]. Therefore, this vaccine has been designated by the World Health Organization as a bonafide "cancer vaccine".

1.2. HBV epidemiology

From a global view, a recent meta-analysis shows that the worldwide HBsAg prevalence is 3.61% [10]. There are over 248 million people currently living with chronic hepatitis B (CHB). Africa has the highest endemicity, with an HBsAg prevalence of 8.83%. However, the country with the largest number of people living with CHB is China with 95 million people, with an HBsAg prevalence of 5.49%. India and Nigeria have the second and third highest population of HBsAg (+) individuals, respectively, at 17 and 15 million people.

Chronic hepatitis B is a major risk factor for the development of hepatocellular carcinoma. A study in New York City found that Korean males had the highest rate of liver cancer-related mortality compared with all racial/ethnic groups. In fact, liver cancer was the second and third cause of cancer-related deaths in NYC Chinese and Korean men, respectively [11]. The Asian American Hepatitis B Program (AAHBP), a large community-based program in New York City, has found 13.3% HBsAg positivity among over 4000 newly screened individuals born in Asia [12].

2. HBV carcinogenesis

2.1. Risk of HCC from HBV infection

In a landmark paper in 1981, Beasley et al. established the association between HBV and HCC in 22,000 HBsAg (+) Taiwanese men. Compared to uninfected controls, their relative risk for HCC was found to be 63 [9]. Since then, co-infection with HCV [13], family history of HCC [14], alcohol intake [15], HBV genotype C greater than B [16, 17], and core promoter mutations [18, 19] have all been identified as risk factors for HCC development.

In highly endemic areas, HBV transmission is nearly all from mother to newborn and as many as 90% of infected babies develop chronic infections [20]. This differs from areas that have a low prevalence of HBV, where transmission is horizontal through sexual and parenteral routes in adulthood. More than 90% of these cases of acute HBV infection resolve spontaneously and

do not lead to chronic infections. Longer periods of chronic HBV infection contribute to a higher risk for HCC; therefore, endemic areas have a higher incidence of HCC.

Approximately 25% of those chronically infected people with HBV will develop HCC [21]. In addition to the earlier report by Beasley et al. [9], Franceschi et al. also reported a 30-fold increased risk of HCC in chronic HBV carriers [22]. A systematic review estimated the incidence rates of HCC in subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 person-years in inactive carriers (HBsAg-positive but with normal levels of ALT), 0.6 person-years for those with chronic HBV infection without cirrhosis, and 3.7 person-years for those with compensated cirrhosis [23]. HBV can cause HCC in the absence of cirrhosis though 70–90% of HBV-related HCC occur in patients with cirrhosis [24].

The risk of HCC is increased in patients with higher levels of HBV replication. One large study followed 11,893 Taiwanese men for a mean of 8.5 years to evaluate the effect of HBV replication on the risk of HCC. The incidence rate of HCC was 1169 per 100,000 person-years among men who were positive for both HBsAg and HBeAg, 324 per 100,000 person-years for those who were only HBsAg-positive, and 39 per 100,000 person-years for those who were HBsAg-negative [25]. The relative risks of HCC among men who were positive for both HBsAg and HBeAg were increased 60-fold compared to 10-fold among those who were only HBsAg positive [25]. Another prospective study from Taiwan reported that in a cohort of 3653 HBsAg-positive participants, the incidence of cirrhosis and HCC increased in proportion to the HBV DNA level, from <300 copies/mL at 0.74% incidence to $\geq 1,000,000$ copies/mL at 13.50% incidence over 13 years of follow up [26]. Furthermore, inactive carriers of HBV (HBeAg negative, HBV DNA <10,000 copies/mL, normal liver enzyme levels, no cirrhosis) are still at a 5-fold greater risk for HCC than HBsAg-negative controls [27].

2.2. Entry of HBV DNA into host cells

Hepatitis B virus is an enveloped DNA virus belonging to the *Hepadnaviridae* family. HBV contains a partially double-stranded circular DNA genome (rcDNA) [28]. HBV recognizes highly sulfated heparin sulfate proteoglycans (HSPGs) on the surface of liver cells, allowing the virus to be highly hepatotropic [29]. When HBsAg binds a liver-specific receptor named sodium taurocholate cotransporting polypeptide (NTCP or SLC10A1) during an infection, the virus gains entry into its host cell [30].

Upon entering the human hepatocyte, rcDNA becomes a covalently closed circular DNA (cccDNA) in the nucleus. This cccDNA functions as a template for transcription of all four viral mRNAs, which then translate all seven HBV proteins [28]. The largest viral mRNA transcript encodes the viral polymerase and is a template for DNA [31]. Current HBV antiviral medications thwart this step of the viral replication [32].

2.3. HBV X protein

The HBV X protein (HBx) is a 154 amino acid polypeptide with a mass of 17 kDa. Its role in the development of HCC is critical. HBx regulates cellular transcription, protein degradation, and cellular proliferation and apoptosis. HBx acts on cellular promoters by protein-protein

interactions instead of binding directly to DNA. HBx can downregulate Wnt/ β -catenin expression and suppress cell growth by not only repressing cell proliferation but also triggering cell apoptosis [33]. HBx protein also interacts with the tumor suppressor adenomatous polyposis coli to activate Wnt/ β -catenin signaling, which upregulates the epithelial cell adhesion molecule in HCC cells to promote tumor initiation [34, 35]. Therefore, HBx activation of Wnt/ β -catenin may directly promote the transformation of hepatocytes into cancer initiating cells [36]. Overall, the seemingly contradictory roles of HBx in regulating apoptosis demonstrate the complexity of hepatocarcinogenesis.

There are numerous ways in which HBx may induce anti-apoptotic effects. The most salient is its ability to inhibit p-53-mediated apoptosis. HBx may increase the expression of telomerase reverse transcriptase and telomerase activity, thus prolonging the lifespan of hepatocytes and leading to malignant transformation [36]. In addition, carboxyl-terminal (C-terminal) truncated HBx protein loses its proapoptotic properties and may enhance the protein's ability to transform oncogenes [36].

2.4. Integration of HBV DNA into host DNA

HBx truncation occurs with HBV integration into host DNA. The 3'-end of HBx is the preferred region of HBV genome involved in integration. When HBV integrates, the 3'-end of HBx is often deleted. Therefore, HBV integration is an important step in HCC development [37]. The C-terminal region produced by HBx truncation also contributes to HCC development. The C-terminal region has been suggested to be required for ROS production and 8-oxoguanine formation, biomarkers of oxidative stress [38]. The 24 amino acids truncated at the C-terminal end play a role in increasing cell invasiveness and metastasis in HCC through activation of MMP10 by C-Jun signaling [39]. Lastly, C-terminal truncated HBx has been reported to directly regulate miRNA transcription and promote hepatocellular proliferation [40].

3. Natural history

HBV carriers often are asymptomatic without significant liver injury because HBV replication in itself is not directly cytotoxic to hepatocytes [21, 41]. Hepatocellular injury occurs largely from host immune responses, both through major-histocompatibility-complex (MHC) class II-restricted, CD4+ helper T cells and MHC class I-restricted, CD8+ cytotoxic T lymphocytes [21, 42]. Four distinct phases comprise the natural history of HBV infection.

3.1. Acute “immune tolerant” phase

In the acute phase of infection with HBV, the “immune tolerant” phase is HBeAg (+) with high viral loads, normal serum alanine aminotransferase (ALT), and near normal liver histology [43]. When HBV is acquired in adulthood, this phase is very short [44]; however, perinatal and early childhood infection lead to a long “immune-tolerant” phase [45, 46]. The risk of progression to chronic carrier state differs greatly between those infected perinatally (90%) and as an adult (<1%) [44, 47, 48]. At the current time, antiviral treatment is not recommended

during the immune-tolerant phase but rather for the immune clearance phase. Interestingly, some recent reports have shown evidence of immune reactivity during the immune-tolerant stage [49–51]. As was presented by Zoulim and Mason, there is an argument to consider earlier treatment of CHB in order to prevent HCC [52].

3.2. “Immune clearance” phase

The “immune clearance” phase, developing during adolescence, is characterized by high viral load, HBeAg (+), and elevated ALT. Antiviral therapy is usually recommended during this phase. The salient feature of this phase is elevated ALT levels, which is a result of T-cell immune-mediated lysis of hepatocytes [53, 54]. The frequency of flares and duration of this phase are correlated with the risk of cirrhosis and HCC [55, 56]. High ALT level is a marker of vigorous host immune response, which is correlated with spontaneous HBeAg seroconversion. HBeAg seroconversion to anti-HBe is a pertinent outcome of this phase [57, 58].

3.3. “Inactive carrier” phase

Following HBeAg seroconversion, an “inactive HBsAg carrier” phase begins. It is marked by HBeAg (–), anti-HBe (+), normal ALT, and low or undetectable viral load [59]. Liver biopsy at this time would show mild hepatitis, minimal fibrosis, but cirrhosis may also be seen in patients who have experienced severe liver injury in the previous “immune clearance” phase [60]. Antiviral therapy is not indicated in this phase, but patients do need regular screening for HCC given the persistent risk while remaining positive for HBsAg and anti-HBc (IgG). Spontaneous seroclearance of HBsAg at a yearly incidence of 0.7–2.4% may happen after patients become HBeAg (–) [57, 61]. This phase may persist indefinitely.

3.4. “Reactivation/HBeAg-negative chronic hepatitis” phase

The last phase in the natural history of HBV infection is more recently recognized. The “reactivation of HBV replication/HBeAg-negative chronic hepatitis B” stage, also known as “e-CHB”, is marked by HBeAg (–), anti-HBe (+), detectable viral load, elevated ALT, and continued necroinflammation on histology [62]. Patients may enter the “e-CHB” phase after some years in the “inactive carrier” phase or directly progress from HBeAg (+) chronic hepatitis to HBeAg (–) chronic hepatitis [63]. Many mutations in the viral core promoter and pre-core regions inhibit the synthesis of HBeAg without affecting HBV replication. Nucleotide 1896 is one of the most studied mutations associated with e-CHB in the pre-core region [64].

4. Prevention of HCC

4.1. Results of vaccination

Taiwan, a country with a high prevalence of chronic HBV, instituted a nationwide HBV vaccination program in 1984 for all citizens ranging from neonates to adults. A landmark paper published in the *New England Journal of Medicine* in 1997 reports the effect of vaccination on

childhood HCC in Taiwan [65]. In 1984, the prevalence of seropositivity of HBsAg was 10.6% in six-year olds. Ten years after launching the vaccination campaign, this prevalence was reduced to <1% in six-year olds by 1994. The incidence of HCC in children ages 6–9 significantly declined from 0.52 per 100,000 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986.

Given the availability of national health records, Taiwan is a country with tremendous potential for public health and epidemiological investigations. A newer study from the same group published recently re-examines the effect of HBV vaccination by comparing the rate of HCC in different time periods [66]. Between 1983 and 2011, 1509 patients were diagnosed with HCC. 1343 were born before and 166 were born after the HBV vaccination program began. The relative risk for HCC in patients 6–9 years old, 10–14 years old, 15–19 years old, and 20–26 years old who were vaccinated vs. unvaccinated were 0.26, 0.34, 0.37, and 0.42, respectively. Out of the 166 cases of HCC that occurred after HBV vaccination began in Taiwan, the two strongest risk factors were transmission of HBV from highly infectious mothers and incomplete immunization.

At this point, 180 countries have introduced infant HBV vaccination, and the global HBV vaccination coverage rate for the third dose is about 78% [67]. HBV vaccines are usually administered in three doses, with the second dose given one month after the first dose and the third dose given six months after the first dose. The dose recommended for adults is 10–20 µg and for infants and children 5–10 µg. With regard to the immunogenicity of HBV vaccines, over 90% of infants, children, and adolescents have protective serum anti-HBs antibody concentrations (>10 mIU/mL) after the vaccine series has been completed. However, host factors such as age older than 30, obesity, immunosuppression, and smoking have been linked to inadequate immunogenicity to the HBV vaccine.

Vaccination is most important for infants, particularly those born to HBsAg (+) mothers. In addition, the WHO recommends high-risk groups should also be vaccinated as well, including [1] people who frequently require blood transfusions, such as dialysis patients and recipients of solid organ transplantations [2]; people interned in prisons [3]; IV drug users [4]; household and sexual contacts of people with chronic HBV infection [5]; people with multiple sexual partners, health-care workers, and others who are exposed to blood or blood products through work [6]; and travelers who have not completed their HBV vaccine series. Although post-vaccination testing for immunity is not generally recommended, it has been the practice at our institution to conduct post-vaccination test to confirm the presence of anti-HBs at the protective level (>10 IU). For those who fail to produce antibody, it is important to rule out the occult HBV infection not uncommonly seen among the family members of HBV patients.

4.2. Surveillance for HCC

It is generally recommended to perform HCC surveillance in those with CHB and especially if the patient has cirrhosis. CHB is an independent risk factor for the development of HCC, which can occur even without cirrhosis. The surveillance method includes imaging, whether triple-phase CT or MRI with contrast, should occur every 6 months. The evidence for

serological testing for alpha fetal protein (AFP) in surveillance for HCC is unclear; however, at our institution it is obtained at 6-month intervals with imaging.

A recent study shows the importance of HCC surveillance even in those with seroclearance of HBsAg [68]. In a retrospective analysis of 829 patients (mean age: 52.3 years; 575 males; 98 with cirrhosis) after HBsAg seroclearance, the estimated annual incidence of HCC was 2.85% and 0.29% in patients with and without cirrhosis, respectively. In non-cirrhotic patients, the annual rate of HCC was higher in males than females (0.40% vs. 0%, respectively). The study concludes that HCC surveillance should be considered for cirrhotic patients and non-cirrhotic male patients over age 50, even after HBsAg seroclearance, especially those infected with HBV genotype C.

4.3. Prevention of recurrent HCC post-resection, transplantation, and local tumor ablation

Antiviral therapy after tumor resection aims to improve prognosis by suppressing viral replication. Recent evidence indicates high serum HBV DNA levels, either preoperatively or postoperatively, is associated with a higher risk of HCC recurrence [69]. Furthermore, the incidence of HCC recurrence was significantly higher in patients who experienced acute postoperative exacerbations of hepatitis with high-serum concentrations of HBV DNA and sustained HBsAg expression postoperatively [70]. Antiviral therapy has been shown to induce the remission of active hepatitis, maintain liver function, and increase the likelihood of successful treatment for HCC recurrence even if recurrence developed after curative resection [71]. In addition, high levels of HBV DNA are significantly associated with shorter survival times, with the cause of death being HCC recurrence [71]. A recent meta-analysis shows that antiviral therapy with nucleos(t)ide analogs (NAs) reduces HCC-related mortality and HCC recurrence postoperatively, and improves overall survival in patients with HBV-related HCC [72].

There is a lack of evidence to guide the management of HBV after liver transplantation for HBV-related HCC; however, lifelong antivirals are used in most centers. In the case of transplantation for HBV cirrhosis, recurrent HBV may lead to graft loss and poor post-transplant survival. There is a direct relationship between the HBV VL at time of transplantation and the rate of HBV recurrence [73]. Since the study by Samuel et al. [74], hepatitis B immune globulin (HBIG) has been used as prophylaxis against HBV recurrence after liver transplantation for HBV cirrhosis.

We have reported favorable effects of antiviral therapy on the survival of HCC patients following local tumor ablation through interventional radiology [75]. We included 25 patients, who met criteria with a single HCC ≤ 7 cm and underwent tumor ablation with curative intent. Sixteen patients (diagnosed 1999 and after) received antiviral therapy and nine patients (diagnosed before 1999) did not. While there was no difference in their median tumor size and AFP, the survival was significantly different ($p < 0.001$). The median survival of the untreated was 16 months while that of the treated was 80 months. Fourteen of 16 treated patients are alive to date with two longest survivors alive for ≥ 151 months. Overall, there is evidence for lifelong antiviral therapy for patients with HCC treated with resection, transplantation, or local regional therapy.

5. Current treatment of hepatitis B

Since the advent of antiviral drugs, survival of patients with HBV has been remarkably improved. Current treatments for hepatitis B include nucleos(t)ide analogs (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) and an interferon [pegylated-interferon alpha-2a (peg-IFN α -2a)] (**Table 1**) [4, 76]. The ultimate goal in the treatment of chronic hepatitis B is to prevent the development of HCC.

Name	Trade name	Strengths	Weaknesses	Approved
Pegylated interferon-2a	Pegasys	Finite duration of treatment	Needle injection	1991
		Durable response post-treatment	High cost	2005
		No known resistance	65–70% fail to respond	
			Significant side effects	
Lamivudine	Epivir	Oral	Long-term treatment is necessary	1998
		Safe with negligible side effects	High incidence of resistance	
		Effective and safe in pregnancy		
		Least expensive		
Adefovir dipivoxil	Hepsera	Oral	Long-term treatment is necessary	2002
		Low resistance	Long-term treatment for renal toxicity	
			Less potent than other treatments	
Entecavir	Baraclude	Oral	Long-term treatment is necessary	2005
		Potent viral suppression	High cost	
		Safe with negligible side effects		
		Low resistance		
Telbivudine	Tyzeka	Oral	Long-term treatment is necessary	2006
		Potent viral suppression	High incidence of resistance	
		Effective and safe in pregnancy		
Tenofovir	Viread	Oral	Long-term treatment is necessary	2008
		Potent viral suppression		
		Safe with negligible side effects		
		No known resistance so far		
		Effective and safe in pregnancy		

Adapted from Halegoua-De Marzio and Hann [4].

Table 1. Current approved drugs for treatment of HBV.

5.1. Pegylated-interferon alpha-2a

Pegylated-interferon alpha-2a (peg-IFN α -2a) has replaced interferon alpha-2b due to better pharmacokinetic properties, weekly injection schedule, and similar efficacy. Its major mechanism of action is in immune modulation with a weak antiviral effect [77]. Peg-IFN α -2a has the highest rate of sustained response after 1 year of therapy, with a 27% rate of HBeAg

seroconversion and 25% rate of loss of HBV DNA after 48 weeks of treatment [78, 79]. After 18 months of follow up, 4–6% of patients showed serum positivity for anti-HBs and had loss of HBsAg [78, 79]. Even after the end of treatment, 12–65% of patients had seroclearance of HBsAg within 5 years of losing HBeAg [80, 81]. A study of 542 patients, who received the medication for 48 weeks, shows patients with the best response include genotype A with HBV DNA $<9 \log_{10}$ copies/mL or ALT $\geq 2 \times$ ULN, or genotype B and C with ALT $\geq 2 \times$ ULN and low HBV DNA ($<9 \log_{10}$ copies/mL) [84]. Remission long after discontinuing therapy was associated with an early virological response, defined as suppressing levels to below 10^5 copies/mL within the first 2 weeks of therapy or $>2 \log_{10}$ decrease in serum HBV DNA [82, 83].

Peg-IFN α -2a only makes up about 10% of all hepatitis B prescriptions in the United States due to its substantial side effect profile and need for administration by injection [85].

5.2. Lamivudine

Approved by the Food and Drug Administration (FDA), lamivudine is a nucleoside analog reverse transcriptase inhibitor. Due to availability of other oral antivirals that have higher genetic barriers to resistance, lamivudine is not commonly used today. The most common reasons for its use currently are during pregnancy in HBsAg (+) women to perinatal transmission and during chemotherapy and immunosuppression to prevent reactivation of HBV in HBsAg (+) patients.

With 12 months of treatment, lamivudine is associated with 16–18% rate of HBeAg seroconversion [86]. In HBeAg (+) patients, the rate of HBeAg seroconversion increases with the duration of treatment, from 17% at 1 year to 27% at 2 years to 47% at 4 years [87]. Therapy for 1 year also results in 60–70% HBV DNA suppression in HBeAg (–) patients with chronic hepatitis B [88].

Lamivudine has been shown to decrease the rate of fibrosis and the incidence of HCC [89]. A study of 651 Asian patients with advanced fibrosis was stopped prematurely at 32 months because a significantly lower proportion of the lamivudine-treated group reached the primary endpoint of development of hepatic decompensation, HCC, or death from liver disease compared to placebo (7.8% vs. 17.7%) [89]. Lamivudine-treated patients have been observed to have a significant reduction in the incidence of HCC [90]. Reversal of fibrosis was significantly more likely to be seen on histology after 52 weeks of treatment with lamivudine than placebo [87].

Despite these positive attributes, there is a decrease in lamivudine usage due to its resistance profile. A large-scale safety study showed resistance rates of 23% at one year and 67% at five years of therapy in HBeAg (+) patients [91]. In a small study at our institution, lower resistance rate of 3% at one year and 10% at two years was found when 150 mg dose of lamivudine was used [92]. Pretreatment HBV DNA level is the most important factor for lamivudine resistance. Tenofovir has been shown to have stronger antiviral effect than adefovir against lamivudine-resistant HBV [93]. Furthermore, tenofovir monotherapy has been shown to be superior to adefovir and lamivudine combination therapy in lamivudine-resistant HBV [94].

5.3. Adefovir dipivoxil

Approved in 2002 by the FDA, adefovir dipivoxil is a nucleotide analog reverse transcriptase inhibitor. Treatment with adefovir for one year in HBeAg (+) patients leads to a 12% HBeAg seroconversion and 53% histological improvement [89, 95, 96]. Furthermore, HBeAg seroconversion is sustained in 91% of patients [97]. Development of resistance is associated with persistent viremia after 48 weeks of therapy. Rates of adefovir resistance at 1, 2, 4, and 5 years of therapy have been reported at 0%, 3%, 18%, and 29%, respectively [98]. Nevertheless, adefovir use is declining with the arrival of newer medications.

5.4. Entecavir

Approved by the FDA in 2005 for the treatment of CHB, entecavir is a nucleoside analog that inhibits HBV polymerase. It is administered as an oral dose of 0.5 mg/day, resulting in superior reduction of HBV DNA levels compared to lamivudine ($6.98 \log_{10}$ copies/mL vs. $5.4 \log_{10}$ copies/mL) [99]. In a phase three clinical trial entecavir to lamivudine, those who received 52 weeks of entecavir achieved better virological response with HBV DNA < 400 copies/mL (67% entecavir vs. 36% lamivudine), normalization of ALT (78% vs. 70%), and histological improvement (72% vs. 62%) [99]. While entecavir is superior to lamivudine in HBeAg (-) patients, it does require indefinite treatment to maintain viral suppression and prevent relapse [100, 101]. After 6 years of therapy, 96% of HBeAg (+) CHB patients had histological improvement and 88% showed improved fibrosis scores even in cirrhosis [102]. Continuous entecavir treatment for up to 5 years in HBeAg (+) patients has been able to maintain HBV DNA suppression <300 copies/mL in 94% of patients [103].

In comparison to adefovir, entecavir has been shown to achieve viral suppression more rapidly within 14 days of initiating therapy [98]. Entecavir also has a higher rate of HBV clearance (58% vs. 19%) and ALT normalization (76% vs. 63%) when compared with adefovir after 48 weeks of treatment. No significant difference was observed in the rate of HBeAg loss or HBeAg seroconversion [104].

The incidence of HCC has been shown to decrease in entecavir-treated patients compared to non-treated. The five-year cumulative HCC incidence was 3.7% and 13.7% for entecavir-treated and control groups, respectively [105]. HBsAg loss has been associated with entecavir treatment [106, 107]. Compared to lamivudine treatment in HBeAg (+) patients, 96 weeks of entecavir treatment resulted in HBsAg loss in 5% of patients and 3% of lamivudine-treated patients [108]. Unlike HBeAg (+) patients, HBeAg (-) patients show no significant HBsAg loss on entecavir [109].

The biggest advantage of entecavir is its high genetic barrier and low resistance profile. The cumulative incidence of resistance after 6 years of entecavir in nucleoside-naïve patients is low at 1.2%. However, in lamivudine-refractory patients, the rate of resistance to entecavir is 57% at 6 years [110].

5.5. Telbivudine

Telbivudine is an L-nucleoside that is structurally related to lamivudine; it was approved by the FDA in 2006. It specifically inhibits HBV viral DNA synthesis, and it has been shown to be superior to lamivudine in both HBeAg (+) and HBeAg (–) patients with CHB. The seroconversion of HBeAg with telbivudine was found to be 22% and 30% at 1 and 2 years, respectively, in patients who are HBeAg (+) [111, 112]. In these patients, suppression of HBV DNA < 300 copies/mL was 60% and 56% at 1 and 2 years, respectively [105, 106]. Furthermore, recent evidence shows telbivudine has renoprotective effects, both in preventing adefovir-induced nephrotoxicity and improving renal function in liver transplant patients [113–116].

However, resistance to telbivudine has been reported at 21.6% and 8.6% after 2 years of therapy in HBeAg (+) and HBeAg (–) patients [117]. Predictive factors for response to telbivudine include ALT > 2×ULN at baseline or HBV DNA < 9 log₁₀ copies/mL in HBeAg (+) patients [118, 119]. Telbivudine treatment has good therapeutic result in patients with low baseline HBV DNA and negative HBV DNA at week 24 [118].

Telbivudine is a pregnancy category B medication. A study of 186 pregnant Asian women with HBV DNA > 6,000,000 copies/mL, half received telbivudine from second trimester of pregnancy until 4 weeks postpartum and all infants received hepatitis B immune globulin (HBIG) within 24 h of birth, telbivudine treatment showed better outcomes compared with the control group with more women achieving undetectable HBV DNA (30% vs. 0%) [120]. Importantly, no infants born to women in the treatment group were HBsAg (+) compared to 8.7% in the control group.

5.6. Tenofovir

Tenofovir is the most recent nucleotide analog to be approved by the FDA in 2008. It is similar in structure to adefovir but more potent. Compared with adefovir in HBeAg (+) patients, 48 weeks of tenofovir led to more normalization of ALT (68% vs. 54%), stronger viral suppression defined as < 400 copies/mL (76% vs. 13%), histological improvement (67% vs. 12%), and HBsAg loss (3.2% vs. 0%) [121]. After 7 years of therapy, 99.3% of patients maintained viral suppression, 80% of patients achieved normalization of ALT, and no resistance was detected. In patients who are HBeAg (+), 54.5% achieved HBeAg (–) and 11.8% HBsAg (–). In HBeAg (–) patients, only 0.3% achieved HBsAg loss. There were 10 patients (1.7%) who had elevated serum creatinine ≥ 0.5 mg/dL above baseline while on tenofovir, and no significant changes in bone density was observed. HCC incidence has been recently reported to be decreased in tenofovir-treated HBV patients [122].

5.7. Hepatitis B during pregnancy

Newborns to mothers with CHB should receive hepatitis B immune globulin and the first dose of hepatitis B vaccine within 12 h of birth to prevent vertical transmission of HBV. Two subsequent doses of hepatitis B vaccine are administered within 6–12 months of age. Nevertheless, 7–32% of infants born to carrier mothers with high viral loads still become HBsAg (+) despite passive-active immunoprophylaxis [123, 124]. A Chinese study shows vertical

transmission despite immunoprophylaxis failures occurred in HBeAg (+) mothers with HBV DNA levels $>6 \log_{10}$ copies/mL ($>200,000$ IU/mL) [125]. Therefore, it is very important to consider antiviral therapy in pregnant women with high levels of viremia, especially for mothers with infants who had previously failed immunoprophylaxis.

Both lamivudine and telbivudine have been used during the latter stages of pregnancy. They have comparable efficacy and safety in mothers and their newborns during 12 month post-partum observations, where the rate of vertical transmission was seen to be reduced when HBeAg (+) mothers with high viral loads received either lamivudine or telbivudine during the third trimester of pregnancy [121, 123, 126]. Currently, the use of oral antiviral agents during the first and second trimesters of pregnancy is not recommended.

Maternal HBV reactivation during pregnancy is uncommon but if encountered, antiviral therapy should be considered, especially if the reactivation is severe [126, 127]. Breastfeeding is not contraindicated for mothers who are on antiviral treatment as these medications are minimally excreted in breast milk and unlikely to cause significant toxicity [128].

5.8. Hepatitis B reactivation during chemotherapy or immunosuppressive therapy

With immunosuppressive therapy such as rituximab, chemotherapy, or corticosteroids, HBV reactivation can occur in HBsAg (+) carriers. Immunosuppression allows HBV replication and infection of hepatocytes, and reactivation usually occurs after discontinuation or withdrawal of immunosuppression as the immune system is reconstituted [129]. Reactivation leads to acute hepatitis, characterized by high levels of ALT and serum HBV DNA.

Lamivudine has been shown to be effective for prophylaxis of HBV reactivation during chemotherapy in a meta-analysis of 14 clinical trials [129]. It has been most effective when used for patients with low (<2000 IU/mL, $<10^4$ copies/ml) or undetectable HBV DNA level and/or receiving a short course of immunosuppression for less than 6 months. Furthermore, for patients who are compliant with the medication, low resistance has been observed with a dose of 150 mg daily [92]. On the other hand, if the patient is undergoing a long course of chemotherapy or has a high viral load, nucleos(t)ide analogs such as tenofovir or entecavir are recommended due to their lower rate of resistance.

Asian patients should be screened for HBsAg prior to the initiation of chemotherapy or immunosuppressive therapy due to the high prevalence of CHB in Asia. These patients may be silent HBsAg (+) carriers who are unaware of their HBV status [130]. Patients who are HBsAg (-) but anti-HBc (+) should be tested for serum HBV DNA [80]. All HBsAg (+) patients who require immunosuppression or undergo bone marrow transplantation should be treated with antiviral prophylaxis [131]. Furthermore, any anti-HBc (+) patients, whether anti-HBs (+) or anti-HBs (-), who require such therapies should be considered as candidates for antiviral treatment [132]. Guidelines proposed by different societies for preventing HBV reactivation during immunosuppression were reviewed and summarized (Table 2) [132–136].

Society	Population (HBV DNA)	Prophylaxis	Prophylaxis type
AASLD [132]	Baseline HBV DNA <2000 IU/ml	Antiviral prophylaxis recommended	LAM or telbivudine (if IS < 12 months) or ETV > adefovir (if IS > 12 months)
	Baseline HBV DNA >2000 IU/ml	Antiviral prophylaxis recommended	LAM or telbivudine (if IS < 12 months) or ETV > adefovir (if IS > 12 months)
EASL [133]	Baseline HBV DNA <2000 IU/ml	Antiviral prophylaxis recommended	LAM
	Baseline HBV DNA >2000 IU/ml	Antiviral prophylaxis recommended	Antiviral w/ high barrier to resistance
AGA [134]	High risk (>10% HBVr incidence)	Antiviral prophylaxis recommended	Antiviral w/ high barrier to resistance
	Moderate risk (1–10% HBVr incidence)	Antiviral prophylaxis suggested or monitor	Antiviral w/ high barrier to resistance
	Low risk (<1% HBVr incidence)	None	N/A
APASL [135]	All HBsAg (+) patients	Antiviral prophylaxis recommended	ETV/TDF > LAM

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; AGA, American Gastroenterological Association; APASL, the Asian Pacific Association for the Study of the Liver; LAM, lamivudine; ETV, entecavir; TDF, tenofovir. Adapted from Wu and Hann [136].

Table 2. HBsAg (+) antiviral prophylactic guidelines for immunosuppression (IS) by society.

6. Seeking a cure for HBV

Firstly, defining the concept of HBV cure is important. The ultimate goal is eradication of cccDNA, also known as complete cure. However, functional cure (clearance of HBsAg, cessation of liver disease, even with persistent liver cccDNA) is achievable with current antivirals. Nonetheless, without eradication of HBV cccDNA, there remains a risk for HCC development even after years of successful antiviral treatment, especially in those with cirrhosis. Recent development of novel *in vitro* models has enriched the study of HBV pathogenesis and new antiviral strategies including immunotherapies.

Many new agents are in the pipeline. These include direct-acting antivirals (DAAs) and host-targeting agents (HTAs), which focus on targeting cccDNA in a number of different ways [28]. DAAs against HBV currently in development include novel polymerase inhibitors, capsid inhibitors, rcDNA-cccDNA conversion inhibitors, DNA cleavage enzymes, and small interfering RNA (siRNA)-based agents (**Table 3**) [137]. In addition, HTAs target sodium taurocholate co-transporting polypeptide (NTCP), host involvement in HBV secretion and budding, and immune responses (innate and adaptive) [28]. Novel agents to eradicate HBV would be a very important cancer cure given the role of hepatitis B virus in carcinogenesis.

Family/drug name	Mechanism	Status	Company
Nucleoside/nucleotide analogs			
Clevudine	Inhibits viral DNA polymerase	Approved in S. Korea and Philippines	Bukwang/Eisai
MIV-210 (lagociclovirvalactate)	Inhibits viral DNA polymerase	Phase II	Medivir/Daewoong
Besifovir (LB80380)	Inhibits viral DNA polymerase	Phase IIb	LG Life Sciences
Tenofovir alafenamide (GS-7340)	Inhibits viral DNA polymerase	Phase Ib	Gilead
CMX157	Inhibits viral DNA polymerase	Phase I	Chimerix
AGX-1009	Inhibits viral DNA polymerase	Phase I, China	Agenix
Non-nucleoside antivirals			
Myrcludex-B	Entry inhibitor	Phase Ia, Germany	Myr-GmbH
Bay 41-4109	Inhibits viral nucleocapsid	Phase I, Germany	AiCuris
GLS 4	Inhibits viral nucleocapsid	Phase I, China	Sunshine Lake
Phenylpropenamides	Inhibits viral encapsidation	Preclinical	
REP 9 AC	HBsAg release inhibitor	Phase Ib	REPLICor, Inc.
Nitazoxanide (alinia)	Small molecule	Preclinical	Romark Labs
dd-RNAi compound	Gene silencing	Preclinical	Benitec/Biomics
ARC-520	RNAi gene silencer	Phase I	Arrowhead Research
Immune-based			
Zadaxin (thymosin-alpha 1)	Immunomodulator	Orphan drug approval in United States for liver cancer	SciClone
NOV-205 (BAM 205)	Immunomodulator	Approved in Russia	Novelos
GS-9620	TLR7-agonist	Phase I	Gilead
GI-13020	HBV antigen	Preclinical	Global Immune
DV-601	Therapeutic HBV vaccine	Phase Ib	Dynavax
Adapted from Wang and Chen [137].			

Table 3. Emerging drugs against HBV.

Conflict of interest

BN declares no conflict of interest, and HWH receives clinical research grants from Bristol-Myers Squibb and Gilead Sciences.

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