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# Chronicles of HBV and the Road to HBV Cure

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**Abstract:** Chronic hepatitis B remains a major public health concern and a leading cause of morbidity and mortality worldwide, specifically through its causative role in chronic liver disease and hepatocellular carcinoma. Worldwide, it affects up to 292 million people. In this paper, we review the historic discovery of the hepatitis B virus and chronicle the significant advances in our understanding of the virus and its interactions with the human host to cause disease. We also overview advancements in therapies for hepatitis B virus and the current absence of curative therapies and highlight on-going therapeutic efforts in search of curative therapies to control transmission and eradicate hepatitis B virus.

**Keywords:** hepatitis B virus; chronic hepatitis B; hepatocellular carcinoma; antiviral; viral suppression; functional cure; cccDNA; HBV cure

## 1. Introduction

Hepatitis B virus (HBV) infection is one of the most common infectious diseases worldwide with prevalence varying geographically among regions and countries, from high (>8%), intermediate (2–7%), to low (<2%) prevalence [1,2]. HBV (Figure 1) belongs to a group of closely related DNA viruses termed hepadnaviruses, and there are eight HBV genotypes, A to H, each with distinct geographical distribution [2,3]. This family of viruses has a predilection for infecting hepatocytes. HBV is DNA virus but uniquely replicates through an RNA intermediate and can integrate into the host genome (Figure 2). Transmission of HBV occurs via three main routes: exposure to blood and body fluids, sexual contact, and perinatally from mother to baby [4]. In areas of high HBV endemicity, perinatal transmission predominates while horizontal transmission through sexual contact and exposure to blood and body fluids via injection drug use or occupation predominates in areas of low endemicity [4].



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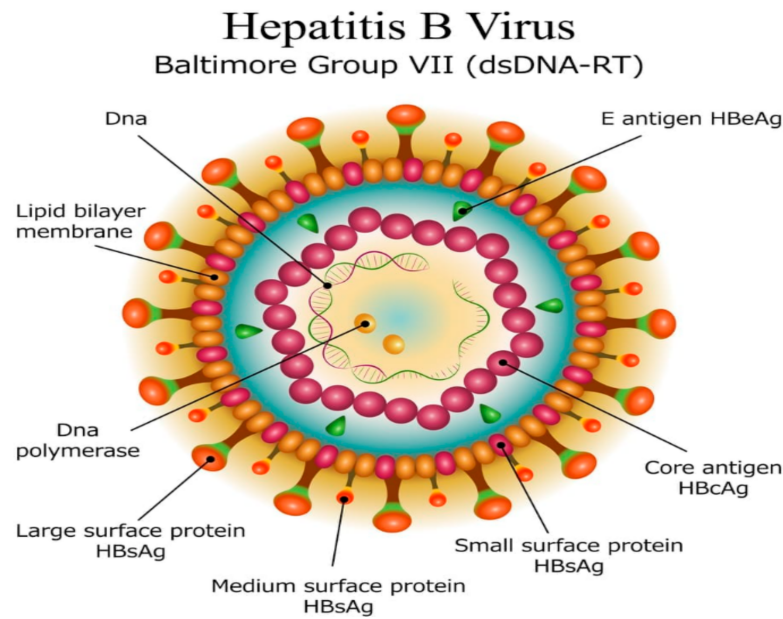
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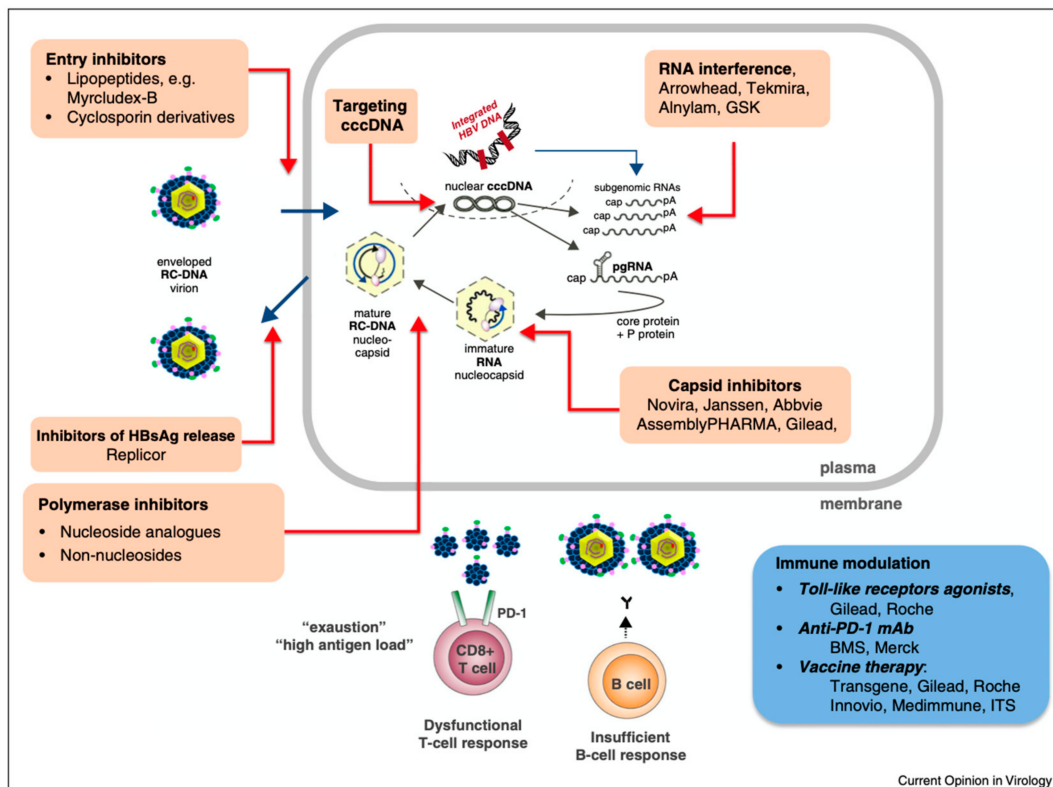
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**Figure 1.** A schematic of the hepatitis B virion. Source: Hepatitis B foundation. Accessed at <https://www.hepb.org/assets/Uploads/Officialwith-Hepatitis-B-WhatNext-If-you-have-been-diagnosed-with-hepatitis-B-you-are-not-alone.-In-fact-nearly-1-in-3-people-worldwide-will-be-infected-with-the-hepatitis-B-virus-in-their-lifetime.-1.pdf>. Accessed on 13 October 2022.



**Figure 2.** A schematic of the HBV replication cycle highlighting anti-HBV therapeutic efforts. All steps of the viral replication cycle and the immune responses to HBV are currently being researched as potential novel therapeutic targets [5].

## 2. Chronicles of Hepatitis B Virus

Baruch Blumberg and his colleagues first discovered HBV in 1965 in the United States (U.S.) [6]. Thereafter, in 1976, for his discovery of HBV, Dr. Blumberg was awarded the Nobel Prize in medicine [7]. This discovery began with the esoteric detection of the novel ‘Australia antigen’ protein (Au), now known as the hepatitis B surface antigen (HBsAg), by Blumberg et al. during their studies of polymorphisms in precipitins that developed in the serum of leukemia and thalassemia patients who received multiple blood transfusions [6]. In 1966, Blumberg et al. then made the association between Au and acute viral hepatitis, and from thereon, their complex work provided the investigational blueprint used to elucidate the HBV virion and its pathogenetic mechanisms. Correspondingly, their research has streamlined developments of preventative vaccination and therapeutic interventions against this common problem, HBV [7,8]. Such advances include the 1969 implementation of universal screening of donor blood excluding Au-positive donors that led to a significant reduction in the incidence of posttransfusion hepatitis down to an astounding 6% [7]. Dane et al. illustrated the virion, initially termed the “Dane particle”, using electron microscopy [9]. In 1982, the U.S. Food and Drug Administration approved the patent for the production of the first HBV vaccine (Heptavax B), developed by Millman and Blumberg using a novel approach to vaccine production—obtaining the immunizing antigen, HBsAg, directly from the blood of human carriers of the virus [7]. In the following decades, the HBV genome and replication cycle (Figure 2), HBV epidemiology, and its pathogenesis were elucidated.

A remarkable feature of HBV infection in humans noted since inception of the disease is the vagaries in host responses to infection [10]. The initial discovery of HBV was made through studies in asymptomatic carriers and persons with prior exposure who had developed antibodies [6–8]. It was then quickly realized that there are a variety of responses to infection with HBV in humans with several serological patterns [11]. These include acute hepatitis with complete recovery, acute hepatitis with progression to chronic hepatitis (CHB), CHB with progression to cirrhosis, liver failure or hepatocellular carcinoma (HCC) as well as the formation of immune complexes correlated with immune diseases such as polyarteritis nodosa [7]. It has been estimated that CHB affects up to 292 million people globally [12]. Furthermore, CHB with disease progression is estimated to occur in 15% to 40% of CHB patients, and remains a leading cause of morbidity and mortality in the US, and worldwide [3,13–16]. The global public health burden of CHB has led to the development of global guidelines by the World Health Organization (WHO), which recommends universal screening for HBV and provides guidance on important issues such as prevention, and surveillance [17].

## 3. HBV and HCC

For many years, investigators in Africa had hypothesized that hepatitis could be the cause of HCC. However, it was not until 1981 when the availability of sensitive tests for Au made it possible to test this hypothesis. In 1981, Beasley et al. published the first prospective study, demonstrating a striking association between HBV and HCC—supporting a causative role of HBV in HCC [18]. The results of their long-term prospective study of 22,707 Chinese men in Taiwan showed that the relative risk of HCC in HBsAg carriers compared to noncarriers was an astounding 223 [18]. The results of their study also suggested that although HCC typically occurs in patients with underlying cirrhosis, HBsAg carriers are at increased risk of HCC even without underlying cirrhosis—the first indication of another mechanism of hepatocarcinogenesis by HBV [18]. Further lending support of this association is the study of families of patients with chronic liver disease and HCC which observed that family members have a much higher prevalence of HBV infection as evidenced by HBsAg seropositivity [19]. HBV is now a well-established primary risk factor HCC, with hepatocarcinogenesis through CHB-related cirrhosis, or without underlying cirrhosis, through HBV genomic integration which leads to the activation of proto-oncogenes and the suppression of tumor-suppressor genes.

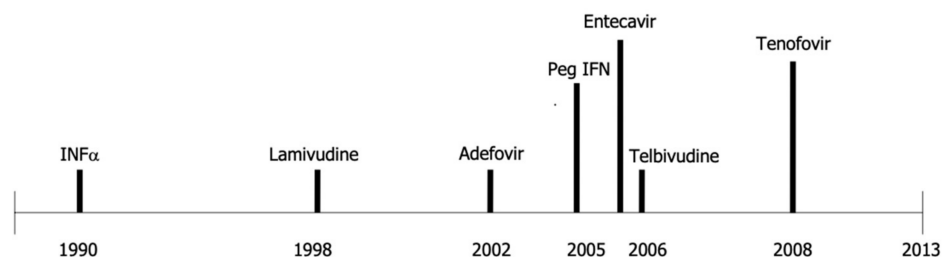
In 1985, HBV was associated with 85% of HCC diagnoses globally [20]. A recent study based on 2020 estimates shows that HCC is the sixth most common cancer and the third most common cause of cancer-related mortality with up to 56% cases being associated with HBV [1,21]. The decline in HBV-related HCC has been shown to be due to multiple advances including widespread vaccination programs [22,23] and effective antiviral therapies for CHB as has been shown with lamivudine [24,25], entecavir [26], and tenofovir [27]. In addition to the decreasing incidence of HCC, viral suppression with antiviral agents has been shown to improve survival and decreased HCC recurrence including after tumor ablation [28–31].

Nonetheless, with as much as 56% of cancer diagnoses being related to HBV infection, HBV-related HCC remains a significant public health burden [1]. Multiple factors have been implicated in this but perhaps, one of the most difficult enigmas for the experts is the occurrence and recurrence of HCC in CHB patients that have been “successfully” treated with antiviral therapies. Multiple studies have shown that patients are at risk of developing HCC despite successful antiviral therapy, which is defined as virologic suppression, even in patients without underlying cirrhosis as subsequently discussed herein [32–40]. Furthermore, and perhaps even more worrisome, are the reports from studies describing poorer survival being observed among CHB patients on antiviral therapy with HBV DNA suppression who develop HCC, compared to antiviral-naïve HBV-HCC patients [41].

#### 4. Treatment of HBV

Several antiviral therapeutic agents are available for CHB. However, the choice of agent is guided by patient factors such as the presence of liver fibrosis and the presence of coinfection with hepatitis C, hepatitis D, or HIV, and by viral factors such as genotype and resistance patterns [42]. There are also broader issues related to treatment in certain patient populations (for example, treatment in liver transplant recipients and patients on whom concurrent liver transplant evaluation should be initiated), including monitoring the response to therapy and the surveillance for HCC in persons with CHB [17]. There are various guidelines that address the initial evaluation and management of persons with HBV and address these important issues, such as the excellent resources from the American Association for the Study of Liver Diseases (AASLD) and WHO [17,42,43].

Currently, there are six approved agents for the treatment of HBV [3,5,12,44]. These are pegylated-interferon (IFN) $\alpha$ -2a and the oral nucleo(t)ide analogues (NA) lamivudine, adefovir, entecavir, telbivudine, and tenofovir (Figure 3) [3,44]. IFN was the first approved agent but it was less desirable due its poorly tolerated side-effects and the need for injection. The advent of the effective oral antiviral NAs which overall have a good safety profile across a wide spectrum of persons with CHB, including those with decompensated cirrhosis and those with a post-transplant status soon followed [42]. These anti-HBV agents are extensively reviewed elsewhere [3,42,44]. It has been shown that HBV DNA suppression with NAs reduces the progression of CHB to cirrhosis, liver failure, and HCC [12]. However, even with sustained HBV DNA suppression, the risk of long-term complications, particularly HCC, remains [5,12,36–38,45].



**Figure 3.** Timeline of approved therapies for chronic hepatitis B infection (CHB) [1].

Additionally, the current goal of treatment for CHB which is a “functional cure” (Table 1) [46], defined as the durable loss of HBsAg, is rarely achieved in NA therapy, and loss of response to therapy with virologic relapse is nearly unanimous even after prolonged viral suppression [12,47–49]. In fact, although the term “cure” is being increasingly used in HBV therapy, there currently is no cure for HBV [5,12,44,48]. The clearance of the transcriptionally active cccDNA mini-chromosome in the nucleus of all infected hepatocytes, which is not directly targeted by the approved antiviral therapies, is required to achieve a true complete cure for HBV [5,46]. Clearance of cccDNA would then allow the cessation of treatment and prevent reactivation in case of a loss of immune control [5,46]. The requirement to eradicate an intranuclear reservoir is a clear distinction from the treatment of hepatitis C virus infection, where the entire viral replication cycle occurs within the cytoplasm of the infected hepatocytes [5]. The varying source of HBsAg depending on the disease stage and the persistence of integrated HBV genomes also limit the achievement of a functional cure in CHB therapy [50].

**Table 1.** Serologies in complete cure versus functional cure treatment of chronic hepatitis B infection. Cure of HBV requires clearance of intra-nuclear cccDNA from all infected hepatocytes. Functional cure corresponds to a resolved acute infection where there is sustained HBsAg loss (with or without seroconversion to anti-HBs), undetectable serum DNA with persistence of cccDNA [5,46]. The goal of therapy with currently available antiviral agents is achieving functional cure.

	HBsAg	Anti-HBs	Viremia	cccDNA
Functional Cure	–	+ or –	–	+
Complete Cure	–	+	–	+

The difficulty in achieving a functional cure leads to indefinite courses of antivirals in most patients. The need for long-term therapy, in turn, leads to significant challenges in the treatment of CHB including difficulty with long-term compliance, drug safety, and financial and emotional burdens to patients and their caregivers [5,12]. Limited access to HBV treatments and prophylactic vaccines in many highly endemic regions, together with the persistent risk of HCC despite viral suppression with currently available therapies present additional challenges in the treatment of HBV. These concur to explain why, still, more than 240 million people in the world have CHB and why millions of patients die every year from HBV-related cirrhosis and HCC [5,12].

## 5. HBV Cure Efforts

Despite all the aforementioned limitations, the availability of prophylactic anti-HBV vaccines and effective antiviral agents which can potentially control HBV transmission make HBV eradication, in principle, an achievable objective [5]. Furthermore, the search for a HBV cure, appropriately, represents an area of burgeoning investigation. Research is on-going for novel antiviral and immune-therapeutic approaches and serum markers for HBV.

Recent advances in understanding the molecular biology and replication cycle of HBV [51] have provided new insight into potential new therapeutic targets. Multiple strategies targeting all steps of the HBV replication cycle, including HBV entry and cccDNA, and/or targeting HBV-stimulated immune responses are currently being investigated (Figure 2), as reviewed extensively by Levrero et al. [5]. Vebicorvir is an investigational orally administered inhibitor of the HBV core protein that interferes with multiple aspects of HBV replication, including the formation of viral nucleocapsids containing pgRNA and the trafficking of incoming nucleocapsids to the nucleus to form new cccDNA molecules [52]. The results of this study showed that combination therapy with VBR and ETV provided additive antiviral activity and viral suppression in monotherapy with ETV in treatment-naïve patients with CHB, with a favorable safety and tolerability profile [53,54]. Combination therapies are also being explored and are currently yielding promising results, as described

in a recently completed phase II clinical trial that evaluated the safety and efficacy of vebicorvir (VBR) in combination with entecavir (ETV) in treatment-naïve patients with CHB [53].

Potential markers to better assess disease status and the response to therapies being explored include HBV RNA and the hepatitis B core-related antigen (HBcrAg). Serum HBV RNA has been shown to correlate with cccDNA transcriptional activity or cccDNA levels [55]. Serum HBcrAg, which is secreted HBV antigens, is being explored as it may correlate with levels of cccDNA in hepatocytes [56,57].

## 6. Conclusions

There have been multiple significant scientific advances since the discovery of HBsAg in 1965. These include the delineation of the HBV virion, epidemiology, pathogenesis and hepatocarcinogenesis. The progress in therapeutics has led to the advent of highly effective HBV vaccines and antiviral medications, with a resultant reduction in the incidence of CHB and HBV-related HCC. Despite these advances, CHB and HBV-related HCC remain a major public health concern with significant morbidity and mortality, affecting over 200 million individuals globally. This has been attributed to multiple factors including the fact that the currently available antiviral agents are not curative. It is well-established in the literature that despite successful viral suppression with anti-HBV agents, the risk of occurrence and recurrence of HCC persists. Furthermore, poorer survival has been reported in patients who develop breakthrough HCC despite achieving successful viral suppression with antiviral therapy.

Multiple studies on the mechanism of the persistence of the risk of HCC despite viral suppression are in progress, as are studies exploring new potentially curative therapeutic targets and combination therapies for HBV. When the results of these are available, HBV cure and elimination of HBV can become possible.

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