

Targeting Covalently Closed Circular DNA (cccDNA): Emerging Therapeutic Strategies toward a Functional Cure for Chronic Hepatitis B

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Abstract

Chronic HBV won't be resolved in the immediate future. Almost 300 million individuals live with it [1], as well as it causes roughly 820,000 deaths annually [1]—mainly due to conditions such as cirrhosis, liver failure, or liver cancer. The usual therapies, such as nucleos(t)ide analogues and pegylated interferon-alpha, effectively manage the virus. However, conventional therapies fail to achieve complete viral eradication due to the persistence of covalently closed circular DNA (cccDNA) [2], an episomal viral reservoir residing in host hepatocytes. It hangs around within liver cells as a persistent minichromosome [2], silently acting as the template for each viral RNA required by the virus. Recently, though, there has been significant progress in addressing this virus reservoir directly. Scientists have begun testing CRISPR/Cas-based gene editing [18], RNAi (RNA interference) [23], ASOs (antisense oligonucleotides) [27], CAMs (capsid assembly modulators) [28], epigenetic suppression [31], as well as various forms of immunotherapy [33]. Among these, bepirovirsen, a type of ASO, has drawn notice—it succeeded in eliminating HBsAg in approximately 9–10% of patients in a Phase IIb clinical trial [27], which is highly significant in this area. The present review examines current knowledge of the biology of cccDNA [2] and outlines the top emerging therapeutic approaches. It also looks at the biggest hurdles left—like how to deliver these treatments safely—and evaluates what is actually required before we are able to classify CHB as curable [17].

Keywords: Hepatitis B virus; cccDNA; functional cure; CRISPR/Cas; RNA interference; antisense oligonucleotides; capsid assembly modulators; epigenetic silencing

1. Introduction

Chronic hepatitis B virus (HBV) infection remains a major global public health challenge. Currently, nearly 300 million individuals are affected by it [1], annually, over 800,000 people die due to complications such as cirrhosis,

liver failure, or liver cancer [1]. This is more than a local issue—certain areas, such as the Western Pacific and Africa, face a considerably heavier load [1]. In that place, the majority of infections occur early in life, at birth or in childhood. At this moment, it's reasonable to assume the data to be declining rapidly, because an effective vaccine has been available for more than four decades. In fact, the hepatitis B virus continues to cause approximately one-third of all cases of liver cancer around the world [3].

In terms of treatment, physicians generally choose one of two choices: nucleos(t)ide analogues (NAs) [4] or pegylated interferon-alpha (Peg-IFN- α) [6]. Nucleos(t)ide analogues, employing drugs including entecavir and tenofovir [4,5], inhibit the viral agent from replicating. Adherence to NA therapy routinely suppresses serum HBV DNA below detectable thresholds, and resistance rarely occurs, even following five years [5]. Peg-IFN-alpha functions in a different way. It is offered as a scheduled 48-week program [6] and stimulates your immune system to combat the virus. It occasionally eliminates surface antigen (HBsAg) a bit more efficiently than NAs, though not significantly—just around 5–10% of patients [6,7]. Both approaches come with drawbacks: NAs typically require lifelong treatment [4], and the virus is not truly eliminated, merely hiding. Pegylated interferon alpha is difficult for most patients to endure, but only a small number of patients are truly cured [7].

Here is the main issue: covalently linked circular DNA (cccDNA) [2]. These materials is the virus's base. It is a persistent fragment of DNA which embeds itself within your liver cells and functions as a source of fresh viral copies [2]. It lasts for months, occasionally years, while it keeps renewing itself [2], even when the rest of the virus has disappeared in the bloodstream. That is the reason, immediately after therapy ends, the disease returns aggressively. Destroying this sanctuary is the main obstacle to treating hepatitis B [2]. Currently, we describe a so-called "functional cure" as maintaining undetectable HBsAg levels and the absence of HBV DNA for a minimum of 6 to 12 months once therapy is discontinued [17].

Fortunately stands as the past ten years has completely changed research on hepatitis B inside out. Researchers are no longer merely trying to manage the pathogen any longer—their goal is to eradicate cccDNA directly [2]. We are observing an entirely new set of tools become effective: CRISPR/Cas for cleaving viral DNA [18], RNA interference along with antisense oligonucleotides (ASOs) to block its signals [23,27], capsid modulators to disrupt assembly [28], drugs that chemically deactivate cccDNA [31], and even immune therapies aimed at attacking infected cells [33]. Among all of these, the ASO drug bepirovirsen demonstrates considerable potential, assisting roughly 9 to 10 percent of patients clear HBsAg during advanced clinical trials [27]. In this analysis, I will explain our current understanding of cccDNA [2], analyze the existing and new treatments, emphasize the obstacles to come, and consider the future direction of the field in the pursuit of a definitive cure for chronic hepatitis B [17].

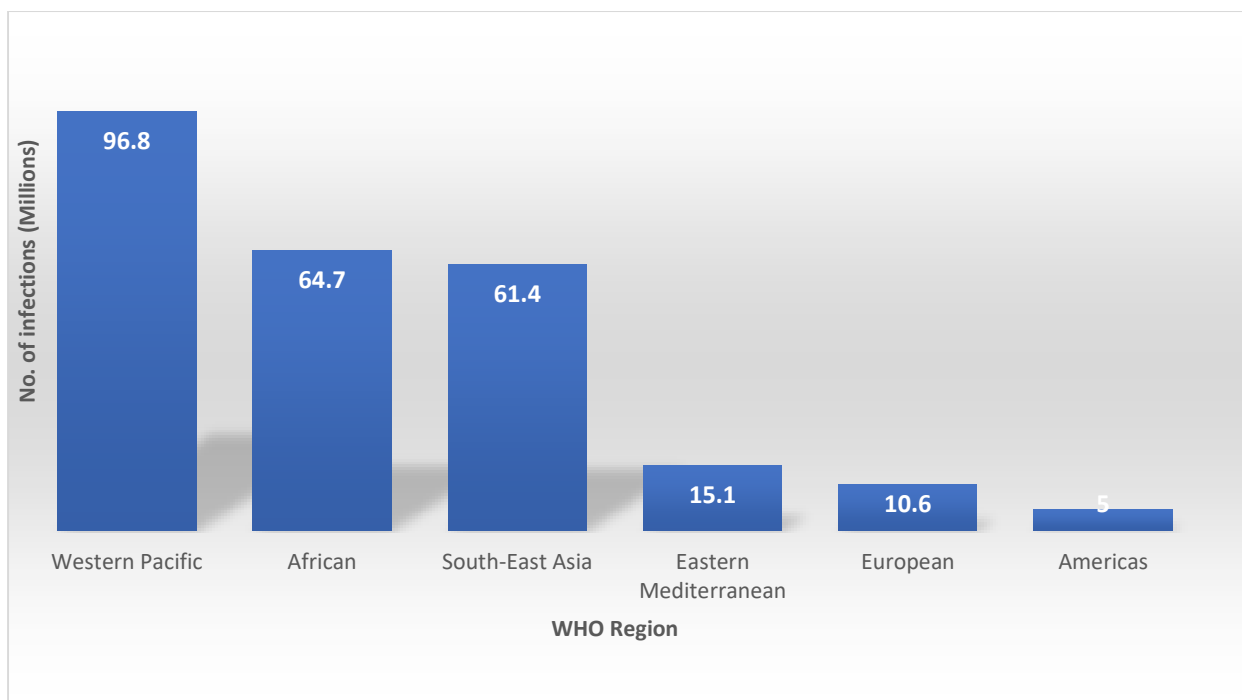


Figure 1: Global Prevalence of Chronic Hepatitis B by WHO Region

2. HBV Biology and cccDNA: Understanding the Viral Reservoir

2.1 HBV Structure and Genome

To understand why hepatitis B remains in the body, it is necessary to observe the way the virus is constructed. The contagious strain, referred to as the Dane particle, is quite small—approximately 42 nanometers in diameter [8]. Visualize a circular shell, abundant in lipids, having three varied proteins extending outward: surface proteins that are small, medium, and large [8]. Those are not merely ornamentation. These agents assist the pathogen bind with hepatocytes and get inside. Below the outer shell lies a strong core composed of the HBV core antigen [8]. Consider it as a protective layer, shielding what is most important: the viral DNA and a special enzyme known as polymerase. This virus is based on this arrangement to protect itself and achieve its goal. Without this, the hepatitis B virus would not persist for an extended period.

The HBV genome is a remarkable piece of biological engineering. It consists of a partially double-stranded, relaxed circular DNA molecule of approximately 3.2 kilobases in length [9]. This may seem small, but the virus makes extraordinarily efficient use of its limited genetic real estate. The genome contains four overlapping open reading frames, meaning that the same stretch of DNA can encode multiple different proteins simply by shifting the reading frame [9]. The S/Pre-S region encodes the various envelope proteins, the C/Pre-C region produces the core protein and the secreted e-antigen, the P region encodes the viral polymerase, and the X region produces a protein called HBx that is essential for maintaining the activity of cccDNA [10]. The overlapping nature of these reading frames imposes significant constraints on viral evolution. Because a mutation in one region can affect multiple genes simultaneously, the virus has less flexibility to develop resistance than it might otherwise have [11].

2.2 The Viral Life Cycle

The life cycle of hepatitis B provides numerous opportunities for therapeutic intervention [10]. The process begins when the virus attaches to the NTCP receptor on the surface of liver cells, triggering a process of endocytosis that brings the virus into the cell interior [12]. Once inside, the viral envelope is shed, and the nucleocapsid is transported toward the nucleus. The relaxed circular DNA is then released into the nucleus, where it undergoes a series of repair steps to become covalently closed circular DNA [2]. This conversion process, which is carried out by the cell's own DNA repair machinery, is critical for establishing a persistent infection.

The newly formed cccDNA is not simply a naked DNA molecule. Instead, it is wrapped around host histones to form a structure that closely resembles a cellular minichromosome [2]. In this form, it serves as the template for all viral transcription, producing a full complement of viral messenger RNAs that are then translated into viral proteins in the cytoplasm [10]. The pregenomic RNA, in particular, plays a central role in viral replication. It is packaged into newly forming nucleocapsids along with the viral polymerase, and within these structures, the polymerase reverse transcribes the RNA to produce new relaxed circular DNA [9]. Some of these newly formed nucleocapsids are enveloped and secreted as infectious virions, while others are transported back to the nucleus to replenish and maintain the cccDNA pool through a process known as intracellular amplification [2].

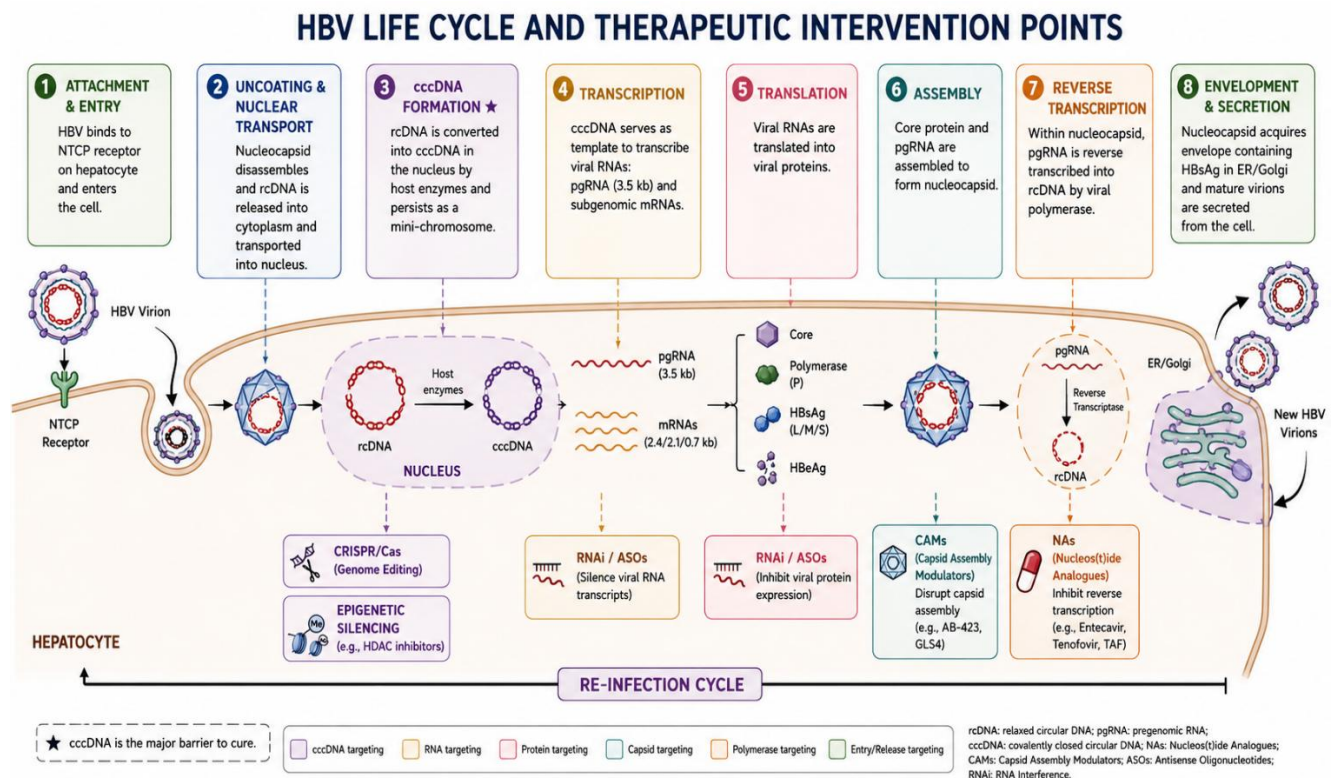


Figure 2: The HBV life cycle and sites of therapeutic intervention. The diagram illustrates the sequential steps of HBV replication within hepatocytes. Key therapeutic strategies are indicated at their respective sites of action: CRISPR/Cas and epigenetic silencing target cccDNA formation and transcription; RNAi and ASOs target viral mRNA; CAMs disrupt capsid assembly; and NAs inhibit reverse transcription. cccDNA represents the central viral reservoir and the primary target for curative strategies.

2.3 cccDNA: Formation, Structure, and Persistence

cccDNA doesn't simply emerge spontaneously—it demands an entire array of host enzymes to initiate the process. Initially, that viral polymerase stuck to the 5' end of the minus strand must be removed, and TDP2 enzyme intervenes to remove it [13]. Afterwards flap endonuclease 1 cuts out the RNA segment remaining after plus-strand synthesis [13]. Endogenous DNA polymerases repair all leftover gaps, and ultimately, DNA ligase enzyme joins all fragments into a continuous circle [13].

After formation, the cccDNA molecule does not merely drift freely. It assembles into a framework that appears very similar to chromatin [2]. Based on the histone modifications present, it may remain inactive or become active in transcription. If you spot acetylation on H3K27 and H3K4, that means cccDNA is switched on and cranking out RNA [16]. But once methylation shows up on H3K9 and H3K27, transcription just shuts down [16]. It really is this constant struggle between different modifications that calls the shots—either flipping the cccDNA "on" or pushing it into dormancy. The main twist, still, remains the persistent stability of cccDNA. Within cells that continue to divide, it remains present with a biological half-life approximately 50 to 100 days [2]. Within cells that do not divide, it can remain for a prolonged time [2]. The infectious agent does not simply accept the existing conditions—the internal replication mechanism enables it to sustain the cccDNA supply [2], thus preventing the viral reservoir from running out, regardless of adverse situations. Moreover, packaging cccDNA into chromatin reduces the innate immune system's ability to detect it, as well as retaining it within the nucleus shields it from cytosolic nucleases—enzymes that typically break down foreign DNA [2]. That's why cccDNA makes such a persistent, hard-to-erase viral footprint.

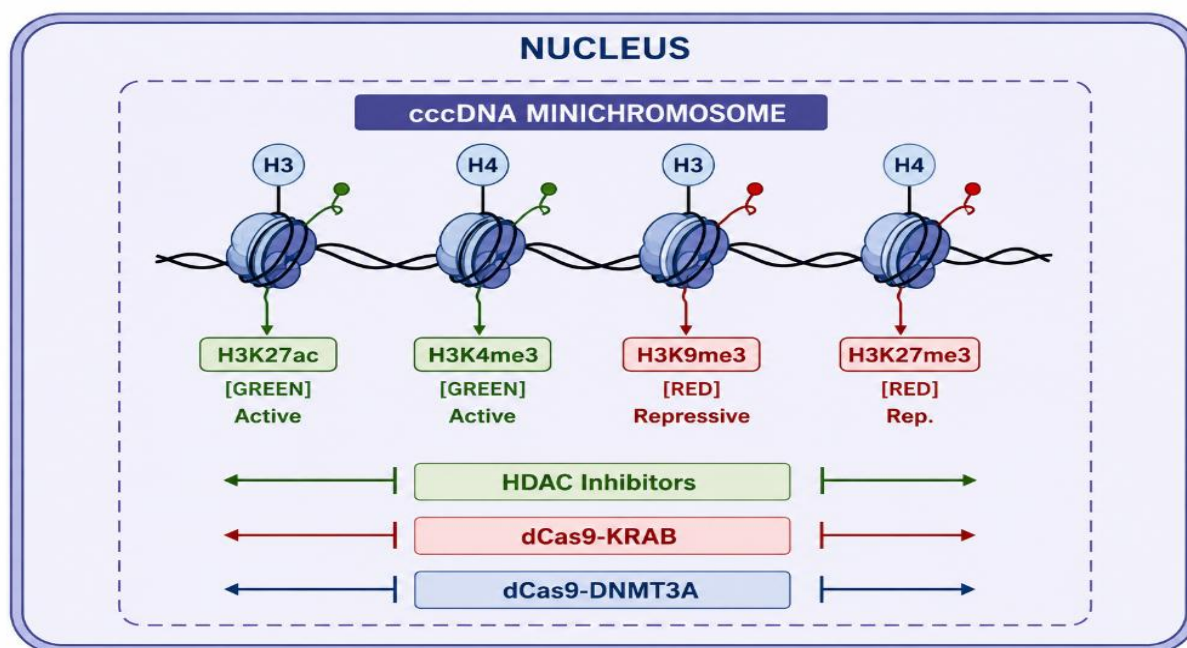


Figure 3: Epigenetic regulation of cccDNA minichromosome. The cccDNA is complexed with histones (H3, H4) to form a minichromosome. Active histone modifications (H3K27ac, H3K4me3) promote transcription, while repressive modifications (H3K9me3, H3K27me3) silence transcription. Therapeutic strategies such as HDAC inhibitors, dCas9-KRAB, and dCas9-DNMT3A aim to shift the balance toward a repressive state.

2.4 Why cccDNA is the Barrier to Cure

Covalently closed circular DNA is the primary barrier to eradicating HBV [2,17]. It's not simply stubborn—it is capable of reactivating after prolonged dormant phases [2]. This infectious DNA can restore itself, persisting despite conventional therapy is in place [2]. As antivirals fail to target episomal DNA and the immune system struggles to identify it, cccDNA evades both treatments and immune elimination [2]. As long as cccDNA is around, HBV infection never truly goes away [17]. Any treatment must eliminate cccDNA entirely or minimally permanently silence it so it won't trigger new infection [2].

3. Current treatment strategies: Their limitations

3.1 Nucleos(t)ide Analogues

Nucleos(t)ide analogs have served as the primary therapy against hepatitis B for many years—truthfully, the reason is obvious. They function effectively, the majority accept them without significant problems, and the chance of resistance remains minimal [4]. Entecavir and tenofovir are frequently selected [4,5]. They replicate the body's own DNA building blocks and essentially deceive the virus—they prevent the virus's ability to complete synthesizing its DNA [4]. If you use these medications consistently, hepatitis B infection typically falls to undetectable amounts within your bloodstream, and after a period of five years, only a small number of people develop resistance to the treatment [5]. Additionally, recent editions such as tenofovir alafenamide are effective while being gentler on your kidneys and bones than older tenofovir versions [14]. However, the main issue is: these medications do not affect the cccDNA pool—the resistant part within the hepatitis B mystery [2]. That indicates you have to keep using the medication for the rest of your life. As soon as you stop, the virus returns, rapidly. Moreover, these medications do not reduce the level of surface antigen, which causes the immune system to remain fatigued [4]. The virus sticks around, as well as your immune system never really get a fighting chance.

3.2 Pegylated Interferon-alpha

PEGylated interferon-alpha feels unusual. It's a predetermined path—injections every week for approximately one year—so it isn't a permanent treatment. It targets hepatitis B in two ways: it inhibits the virus immediately and boosts your immune system to respond more strongly [6]. By this strategy, 5 to 10% of patients are able to lose their surface antigen, a significantly higher chance of clearing the infection than nucleos(t)ide analogues [6,7]. For certain lucky individuals, this effect endures; they avoid the virus for many years following treatment [7]. However there is a catch. Interferon treatment has strong effects, unfortunately: many patients experience symptoms similar to the flu, severe exhaustion, depressive symptoms, and reductions in white blood cells and platelets [7]. Such side effects are so severe that a lot of people fail to endure the entire treatment—or avoid this treatment option entirely. The chances of success are still unfavorable, and if you suffer from decompensated cirrhosis or some other health issues, this is not a viable option for you [7].

3.3 Summary

The main point: Neither nucleos(t)ide analogues nor pegylated interferon-alpha are able to provide an effective cure for most patients. They fail to address the cccDNA store [2], and that is what causes hepatitis B persist stubbornly. More frequently, scientists concur: the upcoming breakthrough has to focus on cccDNA itself—lacking this, hepatitis B remains unattainable for a true cure [17].

Table 1: Comparison of Current Therapies

Comparison of Current Therapies					
Therapy	Mechanism	Route	Duration	HBsAg Loss	Side Effects
NAs	Inhibits reverse transcriptase	Oral	Lifelong	<5%	Minimal
Peg-IFN-α	Immunomodulatory	Injection	48 weeks	5-10%	Flu-like symptoms

4. Emerging Therapeutic Strategies Targeting cccDNA

4.1 CRISPR/Cas Gene Editing

CRISPR/Cas-based gene editing has genuinely ignited enthusiasm among researchers and laypeople alike since it allows us to modify genes with remarkable accuracy [18]. In the case of hepatitis B, the primary expectation is that we might permanently deactivate covalently closed circular DNA by performing targeted cleavages in the viral DNA [18]. This system consists of two primary components: the Cas complex, operating similarly to molecular scissors, together with a guide RNA which directs those scissors precisely where to cut on viral DNA [18]. By creating these guide RNAs to reach important regions inside the HBV genome, researchers improve their odds of disabling the cccDNA [19].

Experiments involving animals, notably in mice, have provided encouraging findings. By means of CRISPR/Cas9, experts were able to decrease amounts of cccDNA by nearly 90% [19]. This type of reduction may be adequate for attaining a functional cure. However there is a considerable way to go prior to this benefiting people. Currently, introducing the CRISPR tools inside every infected liver cell is difficult—present delivery approaches cannot reach 50% of the target cells [20]. We must also consider the problem of non-specific effects, where the system unintentionally cuts the patient's own genetic code, which causes serious safety concerns [21]. Besides all that, numerous individuals already show immune system responses versus the Cas9 protein, which has the potential to disrupt the treatment [21]. Although CRISPR cuts the circular DNA, at times the cell's repair machinery only reattaches the broken pieces, causing the virus to return [21]. So, while the technology is promising, there are still plenty of hurdles researchers need to clear.

4.2 RNA Interference

RNA interference is a naturally occurring process in which small RNA molecules silence gene expression by targeting messenger RNA for degradation [23]. Researchers have harnessed this mechanism to develop therapies that degrade viral transcripts, thereby reducing the production of viral proteins, including the surface antigen [23]. Several RNA interference drugs have advanced to clinical trials. JNJ-3989, developed by Arrowhead and Janssen, has demonstrated substantial reductions in surface antigen in Phase IIb trials, with approximately 19 percent of patients meeting the criteria to discontinue nucleos(t)ide analogues [24]. VIR-2218, another RNA interference drug, has shown similar promise, reducing surface antigen by 1.5 to 2.0 log units [25]. However, a significant limitation of this approach is that it does not eliminate the cccDNA itself; it merely degrades the transcripts produced from it [23]. If treatment is stopped, the cccDNA can resume transcription, leading to a return of viral

production. Additionally, surface antigen produced from integrated HBV DNA is not affected by RNA interference [23].

4.3 Antisense Oligonucleotides

Antisense strands are fundamentally small, carefully engineered strandchains of nucleic acid. They connect with designated RNA segments then engage RNase H to cleave them. The drug Bepirovirsen is the leading candidate within this domain, to be honest, the clinical evidence obtained in its trials draws attention. Throughout the B-Clear Phase IIb trial, individuals were administered a 300 mg amount of bepirovirsen once a week throughout 24 weeks. About 9 to 10 percent experienced sustained loss of envelope antigen along with HBV DNA [27]. That was the case no matter if they were at that time receiving nucleos(t)ide analogue therapy [27].

That's an important breakthrough—it's the first concrete proof that nucleic acid–based therapies can produce a substantial effect for hepatitis B. However, there remain downsides. It must be delivered by subcutaneous injection, it comes at a high price, as well as people react differently to it. A number of people detect a spike in their liver enzyme levels for a short time (referred to as ALT flares), hence, doctors are required to observe them attentively [27].

4.4 Capsid Assembly Modulators

Capsid assembly modulators are a class of drugs that interfere with the formation of the viral nucleocapsid, a step that is essential for the production of new infectious virions [28]. These drugs come in two main varieties. Type I modulators accelerate the assembly of capsids, but they do so in a way that leads to the formation of empty capsids that lack viral genetic material [28]. Type II modulators cause the capsid proteins to misassemble into aberrant structures that are incapable of supporting viral replication [28].

Several capsid assembly modulators are now in clinical development. GLS4, JNJ-56136379 (bersacapavir), and ABI-H0731 (vebicorvir) have all shown antiviral activity in early trials [29]. More recently, AB-836 demonstrated a remarkable reduction in HBV DNA of more than three log units in Phase I trials [30]. The primary advantages of these drugs are their novel mechanism of action, their ability to be taken orally, and their synergy with nucleos(t)ide analogues [28]. However, they do not reduce surface antigen or clear cccDNA, and resistance mutations are beginning to emerge [30].

4.5 Epigenetic Silencing

Epigenetic repression uses an alternative method to deactivating ccc DNA. It does not cut nor break the DNA strand. Alternatively, it switches the deactivation switch through altering the chemical markers attached to histones. As researchers introduce repressive modifications such as H3K9me3 or H3K27me3, they are able to lock cccDNA in a silent, stable state—the genetic sequence simply remains silent.

Recent tools such as dCas9 linked to epigenetic modifiers (for instance DNMT3A) are already demonstrating significant potential in laboratory experiments. Such as, Wang and colleagues succeeded in silencing cccDNA gene transcription and reduce expression of viral genes through this type of approach [31]. The main advantage here is that this approach avoids breaking the DNA directly, therefore it reduces unintended mistakes in other parts of the genome [31].

However, there exist major challenges. It's difficult to deliver these gene-editing tools into each infected liver cell, and there is always a chance that some of these epigenetic alterations might affect the wrong site [31]. So while the science is moving forward, there's more work to do.

4.6 Therapeutic Vaccines

Therapeutic vaccines aim to stimulate the individual's immune response to identify and eliminate cells infected with HBV. The researchers have evaluated various types—protein-derived vaccines including NASVAC and GS-4774, DNA-based vaccines, and viral vector vaccines like TG-1050 [32]. The primary goal is to initiate an effective T-cell response, so that these immune cells can either eliminate infected liver cells themselves or produce antiviral signals which aid in clearing the infection [32].

So far, clinical results have been disappointing. None of the vaccines tested to date have shown significant efficacy in clearing surface antigen compared to placebo [32]. The primary explanation for this failure appears to be the profound immune exhaustion that characterizes chronic hepatitis B infection. After years of exposure to high levels of viral antigens, the patient's T-cells become functionally impaired and are difficult to reactivate [32].

4.7 Immune Modulators

Immunomodulatory agents are drugs which adjust immune responses so it fights viral infections more effectively. For example, TLR agonists such as GS-9620 and GS-9688 enhance our natural immunity [33]. Next, there are checkpoint inhibitors—consider drugs targeting PD-1 or PD-L1—aiming to revive exhausted T-cells [33]. Certain ideas here have shown potential in preclinical trials, but the outcomes in humans have not quite met expectations. A single medication, inarigivir, a RIG-I receptor agonist, was ultimately withdrawn from trials due to causing liver toxicity [33]. Truthfully, that is the issue with the majority of immune-based treatments: there is consistently a danger of harming the liver, which is currently being compromised [33].

4.8 Combination Therapies

The majority of specialists concur at this point—not one medication will be able to cure HBV infection by itself. The best approach depends on combinations targeting the virus from multiple angles at once [33]. Currently, scientists are evaluating a wide range of pairs: RNA interference agents with nucleos(t)ide analogues, antisense oligonucleotides combined with nucleos(t)ide analogues, and even capsid assembly modulators combined with the standard nucleos(t)ide drugs [33]. Consider the REEF-1 trial, as an example—it combined JNJ-3989, JNJ-56136379, and nucleos(t)ide analogues, and patients experienced a significant drop in surface antigen levels [24]. What is beginning to become clear is a sequential method: first, lower the amount of virus and surface proteins through RNA interference or antisense oligonucleotides; next, introduce immunotherapy to eliminate remaining infected cells; and finally, maintain control using vaccines to prevent the virus from coming back [33]. That's where the research is heading.

Table 2: Comparison of emerging therapeutic strategies targeting cccDNA.

Therapy	Mechanism	Target	Stage	Key Advantage	Key Limitation
CRISPR/Cas	Gene editing	cccDNA	Preclinical	Potential permanent cure	Off-target effects
RNAi	mRNA degradation	Viral RNAs	Phase II	Potent HBsAg reduction	No cccDNA clearance
ASOs	mRNA degradation	Viral RNAs	Phase III	9–10% HBsAg loss	Response variability
CAMs	Capsid disruption	Assembly	Phase II	Novel antiviral mechanism	Minimal HBsAg reduction
Epigenetic Therapy	Transcriptional silencing	cccDNA	Preclinical	No DNA cleavage	Delivery challenges
Immunotherapy	Immune restoration	T cells	Phase II	Potential durable response	Limited efficacy

The table compares six major therapeutic approaches based on their mechanism of action, target, current stage of clinical development, key advantages, and limitations.

5. Ongoing Clinical Trials

A number of promising therapies are now in clinical development. Bepirovirsen has advanced to Phase III trials following its successful Phase IIb results [27]. JNJ-3989 has completed Phase IIb trials and shown substantial reductions in surface antigen [24]. VIR-2218 and RG6346 are in Phase II trials [25,26]. Capsid assembly modulators, including GLS4, JNJ-56136379, AB-836, and ABI-4334, are progressing through various stages of development [29,30]. Researchers are additionally evaluating immunological treatments such as GS-9688 and the therapeutic vaccine NASVAC [32,33].

Table 3: Summary of major ongoing clinical trials for chronic hepatitis B.

Drug	Class	Company	Phase	HBsAg Reduction	Status
Bepirovirsen	Antisense Oligonucleotide (ASO)	GSK	Phase III	9–10% HBsAg loss	Ongoing
JNJ-3989	RNA Interference (RNAi)	Janssen	Phase IIb	>95% HBsAg reduction	Ongoing
VIR-2218	RNA Interference (RNAi)	Vir Biotechnology	Phase II	1.5–2 log HBsAg reduction	Ongoing

RG6346	RNA Interference (RNAi)	Roche	Phase II	Significant HBsAg reduction	Ongoing
GLS4	Capsid Assembly Modulator (CAM)	HEC Pharma	Phase II	HBV DNA suppression	Ongoing
JNJ-56136379 (Bersacapavir)	Capsid Assembly Modulator (CAM)	Janssen	Phase II	Synergistic antiviral activity	Ongoing

The table lists key drugs in clinical development, their class, sponsor, phase, and reported HBsAg reduction.

6. Problems and Drawbacks

Despite all the progress made up to now, several major obstacles remain in the path. Delivering nucleic acid-based therapies to effectively reach the liver remains a significant challenge. Current delivery systems achieve less than 50 percent transduction of hepatocytes [20], and the presence of sinusoidal endothelial cells and Kupffer cells further complicates delivery [20]. Off-target effects, particularly with CRISPR-based approaches, remain a significant safety concern [21]. Resistance to antiviral drugs, particularly capsid assembly modulators, is beginning to emerge [30]. Safety concerns such as ALT flares and hepatotoxicity remain a significant concern with many of the new agents [27].

7. Future Perspectives

Recent technologies like prime editing, base editing, and CRISPR-Cas13 technology are beginning to demonstrate true potential to target cccDNA with high accuracy [33]. Patient-specific treatment is attracting growing interest—currently, physicians rely on indicators such as HBsAg, HBV DNA, and ALT to customize therapies for individual patients [17]. The present approach to achieve a functional cure seems quite reliable: initiate treatment using RNA interference or antisense oligonucleotides, then proceed with immunotherapy to enhance those outcomes, and finally maintain stability with vaccines [33]. If these methods cooperate as people expect, we could witness the earliest effective treatments over the next three to five years [33].

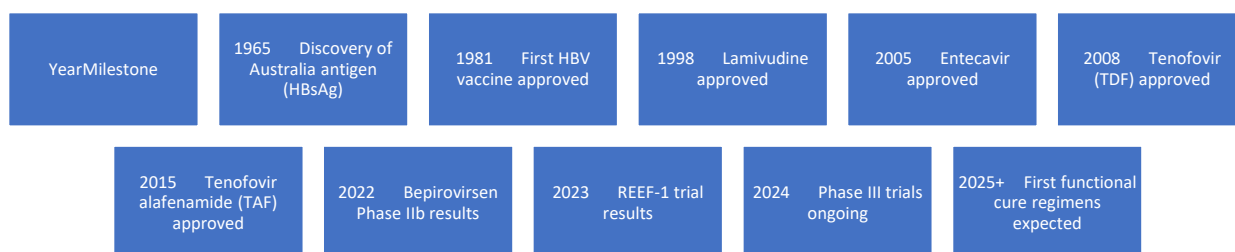


Figure 4: Timeline of HBV therapeutic development. Key milestones from the discovery of the Australia antigen in 1965 to the projected availability of functional cure regimens beyond 2025.

8. Conclusion

Long-term hepatitis B continues to affect nearly 300 million individuals globally [1]—and the persistence of cccDNA is the primary cause a true cure has not been found yet [2]. Current therapies are able to manage the infection, yet they fail to eliminate that unseen reservoir [2]. Over the past decade, however, there has been an influx of innovative ideas. Antisense oligonucleotides and RNA interference are leading the charge within clinical studies [23,27]. Capsid assembly regulators offer a novel approach for targeting the virus [28], and CRISPR-driven techniques might effectively remove cccDNA permanently [19]. Certainly, challenges remain: administering the therapies, maintaining their safety, and overcoming resistance [20,21]. However the true future of hepatitis B treatment is in addressing the issue from all perspectives, at the same time [33]. As of now, it's not a question of whether we will discover a cure—it's simply a question of when [33].

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