

The Evolving Landscape of Drug Discovery for Hepatitis B: Recent Advances and Future Prospects

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ABSTRACT

The main cause of Hepatocellular Carcinoma and Liver Cirrhosis is an infection due to Hepatitis B virus (HBV) which remains a major global health concern. A complete cure with the help of Current therapies is very difficult due to the persistence of covalently closed circular DNA (cccDNA) although pegylated interferons and nucleos(t)ide analogues effectively suppress viral replication. Latest development in HBV drug discovery and highlighting novel therapeutic strategies targeting multiple stages of the viral life cycle is the main summary of this review. Entry inhibitors, cccDNA-targeted therapies, RNA interference-based therapeutics, hepatitis B surface antigen (HBsAg) secretion inhibitors, capsid assembly modulators, and gene-editing technologies such as CRISPR-Cas9 are some of the emerging approaches. Therapeutic potential of the mechanisms of action and current clinical development are discussed. Evidence shows that combination therapies mixing direct-acting antivirals with immunomodulatory agents may give the most potential path in achieving a visible cure. Current research and clinical translation of the above approaches are likely to elevate treatment outcomes and lessen the global load of chronic hepatitis B.

Keywords: Hepatitis B virus, Drug discovery, cccDNA, RNA interference, CRISPR-Cas9

1. INTRODUCTION

Viral hepatitis is one of the major challenges faced towards public health. Viral hepatitis is of five types from A-E. From all the types of hepatitis, hepatitis B is considered one the most sever ones. In 2024 WHO estimated that around 1,1 million people died from hepatitis B virus (HBV) -related cirrhosis and liver cancer and 240 million people were living with chronic HBV, which is equivalent to 2.9% of the global population. Indonesia, India, Nigeria, Vietnam, South Africa, the Philippines, Ghana, China, Ethiopia, Bangladesh are ten countries which accounted for 69% of the cases. Africa and Western Pacific regions showed highest mortality rates [1].

Hepatitis B is caused by HBV is a liver infection which is spread through infected blood and other body fluids. Children are at the highest risk of developing chronic hepatitis, globally 0.6 % of children showed prevalence of HBV [1]. Barunch Samuel Blumberg in 1965 identified Hepatitis B surface antigen (HBsAg) in serum of indigenous Australian and was called "Australian antigen"(AusAg) [2]. Despite the old history there is yet to be development of complete cure for hepatitis. The following review will discuss in detail the replication cycle of HBV, the treatments used currently to treat HBV and the status of new/novel drugs used in the HBV treatment and their prospects.

2.REPLICATION CYCLE: HBV

The Hepatitis B virus (HBV) which belongs to the hepadnavirus family, consist of following parts:

A partially dsDNA (genomic) which has a complete coding strand (negative strand) and an incomplete non-coding strand (positive strand). [3] It also contains a nucleocapsid and an envelope. It has a relatively small and incomplete dsDNA genome which is 3.2Kb [4]. Its envelope is composed of viral surface protein enclosed by a membrane which is made of lipid and is from a human host [5]. The HBV structure has been illustrated in figure 1.

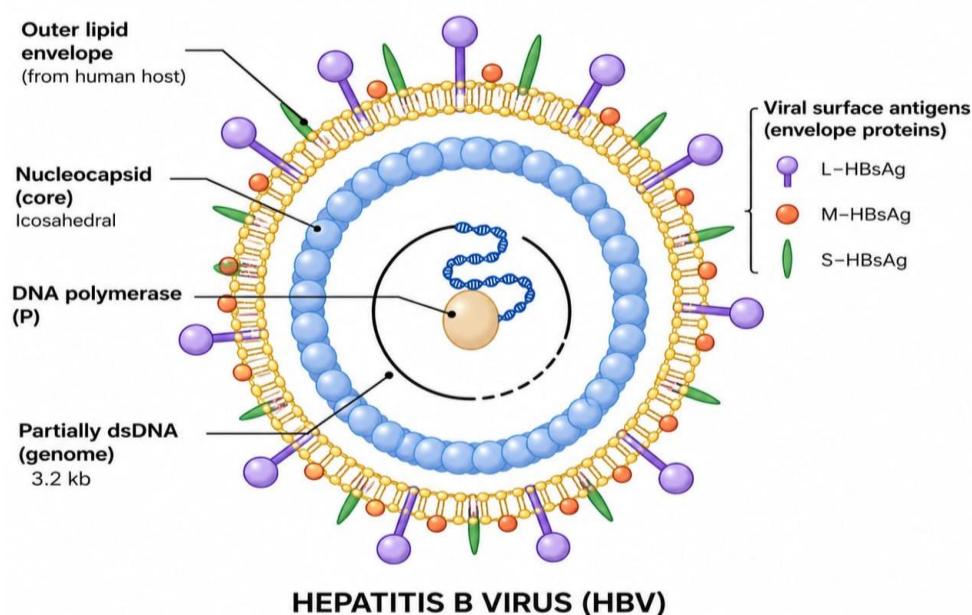


Figure 1: Hepatitis B virus Structure

The first step of HBV infection is the attachment of viruses to the host cell surface through heparan sulphate proteoglycans (HSPGs), such as glypican-5, in a nonspecific, low-affinity manner. This initial attachment is followed by specific, high affinity binding of the virus to its cellular receptor, which facilitates viral entry into the host cell [6,11,12]. In case of enveloped viruses, receptor binding is usually followed by fusion of the membrane, allowing the viral genome to enter the cell. This fusion can occur directly at the plasma membrane within an endosomal

compartment after the virus is taken up by endocytosis. [7]. After HBV enters the hepatocyte through endocytosis, the viral envelope fuses with the host membrane, releasing the viral nucleocapsid into the cytoplasm. The nucleocapsid contains the partially dsDNA, which remains covalently attached to the viral polymerase [8]. The single-stranded gaps present in the relaxed circular DNA (rcDNA) are repaired either by extension of the positive DNA strand, through the activity of the HBV polymerase, or by the host cellular DNA repair enzymes. This repair process converts rcDNA into covalently closed circular DNA (cccDNA), which exists in the nucleus as the nucleosome associated Mini chromosome. Studies in certain HBV transgenic (HBV-tg) mice have shown that cccDNA is not produced, highlighting that specific steps in cccDNA formation may require other viral or host factors that are absent or inactive in these models [9]. The episomal cccDNA functions as the transcriptional blueprint for all HBV RNA molecules. Viral RNA synthesis is controlled by host transcription factors, hepatocyte nuclear factors, chromatin-remodelling proteins, and the hepatitis B virus X (HBx) protein. Modifying enzymes (PCAF, HDAC1 etc). It regulates viral gene expression by interaction with the viral promoter.

These interactions between host and viral factors thereby regulate HBV gene expression. [10]. The viral RNAs are transported to the cytoplasm, where they are translated into viral proteins, including the core protein, polymerase, HBx protein, and surface proteins. These proteins are then used for nucleocapsid assembly and virion formation. After cccDNA is transcribed, the resulting pregenomic RNA (pgRNA) serves as the template for viral genome replication. The viral polymerase binds to the ϵ (epsilon) encapsidation signal on the pgRNA, and the complex is packaged into the assembling nucleocapsid [18,19]. Translation of the HBV polymerase and packaging of the pregenomic RNA (pgRNA) into viral nucleocapsids are closely linked processes. This coordination ensures that the assembly of the viral nucleocapsid and successful viral replication are done correctly [11,12,13]. The cellular molecules responsible for HBV attachment have not been fully identified. HBV is highly infectious in vivo liver cells grown in culture that show relatively less vulnerable to infection, making viral attachments difficult to study [16]. Research on duck hepatitis B virus (DHBV) using primary duck hepatocytes provided important insights. Studies by Kuroki et al. (1994, 1995) identified a 180 kDa glycoprotein in duck hepatocytes that binds to duck hepatitis B virus, indicating its potential role in viral attachment [22]. Inside the nucleocapsid, reverse transcription converts pgRNA into rcDNA by synthesizing the (–) DNA strand first, followed by the (+) DNA strand [20].

The mature nucleocapsid then either acquires an envelope containing HBV surface proteins and is secreted as an infectious virion or returns the rcDNA to the nucleus to replenish the cccDNA pool. [19,20] After rcDNA synthesis is complete, the mature nucleocapsid follows one of two pathways. It either acquires a viral envelope and is secreted as an infectious virion, or it transports the rcDNA back to the nucleus, where it is converted into cccDNA, thereby maintaining the nuclear cccDNA pool [21,22]. The replication cycle has been illustrated in figure 2.

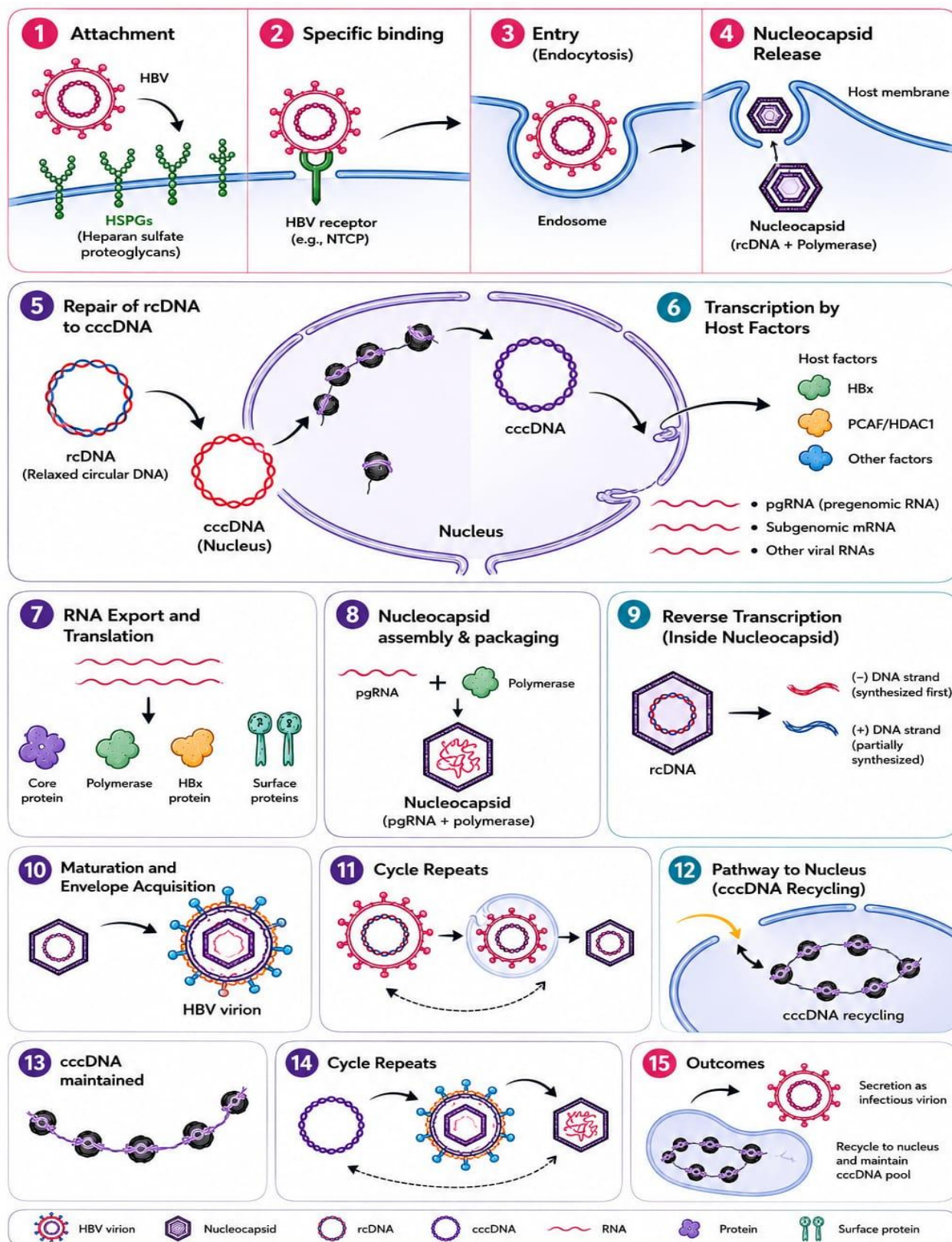


Figure 2: HBV replication cycle

3. CURRENT THERAPIES-

Treatment option of HBV includes treatment option for both adults and young children but there is no complete cure, treatment helps to manage the virus, prevent it from spreading in liver causing liver damage and liver cancer in patients. Current therapies for hepatitis B are of two general categories- immune modulating drugs, antiviral drugs. Immune modulating drugs are interferons which get rid of HBV, antiviral drugs stop the reproduction of the virus [23]. The first interferon α (INF- α) was approved in 1991 and pegylated interferon (PEG-INF- α) in 2001[23]. The first line treatment of chronic HBV is PEG-INF- α , two clinically approved PEG-INF- α are PEG-INF- α 2a (Pegasys® Roche) and PEG-INF- α 2b (Pegintron® Merck). They have longer half-life, and enhanced pharmacokinetics allowing weekly administration [24]. Adverse reaction caused by PEG-INF- α treatment are flu-like symptoms, fatigue, depression and patient compliance is low because it is given subcutaneously [25].

Nucleoside analogues (NAs) are anti-viral drugs which block the HBV reverse transcriptase and block HBV replication. There are eight NAs that have been approved out of which entecavir, disoproxil and alafenamide are recommended [26]. Lamivudine (3CT, LMV, Epivir®, Zeffix®, Heptodin® or Hepitec®) was the first approved drug in US in 1998. NAs are active orally, they have good pharmacokinetics, better patient compliance as one pill is taken per day for therapeutic action. The level of viral particle in HbeAg positive patients was reduced to clinically undetectable level of 76% and 93% in HbeAg negative patients after one year regimen. The current first line NAs include ETV and prodrugs of TFV, TDF and TAF hemifumarate. They have excellent virological suppression with favourable safety profile [26].

In 2002 Adefovir dipivoxil (bis (POM) PMEA, Hepsera®, Preveon®) was approved, it's an oral pill taken once a day for a year or longer. This is a second line drug, and the patients must monitor their kidney function regularly [23]. In 2005 Entecavir (BMS-200475, ETV, Baraclude®) was approved, it has an excellent resistant profile and is considered a first line drug. Telbivudine (Ldt, TBV, Tyzeka® or Sebivo®) is a second line drug approved in 2006. In 2008 Tenofovir Disoproxil Fumarate (bis (POC) PMPA Fumarate, TDF, Viread®) was approved as a first line drug, showing excellent anti-viral activity. In 2016 tenofovir alafenamide fumarate (GS-7340-03, TAF, Vemlidy®) was approved as a first line drug with excellent activity. Besifovir dipivoxil maleate (ANA-380/LB)80380 maleate, BSV dipivoxil maleate, Besivo®) was approved in 2017 which showed less toxicity than tenofovir, all of these drugs are pills which are taken orally [23,26]. The figure 3 shows the timeline of HBV drug approvals.

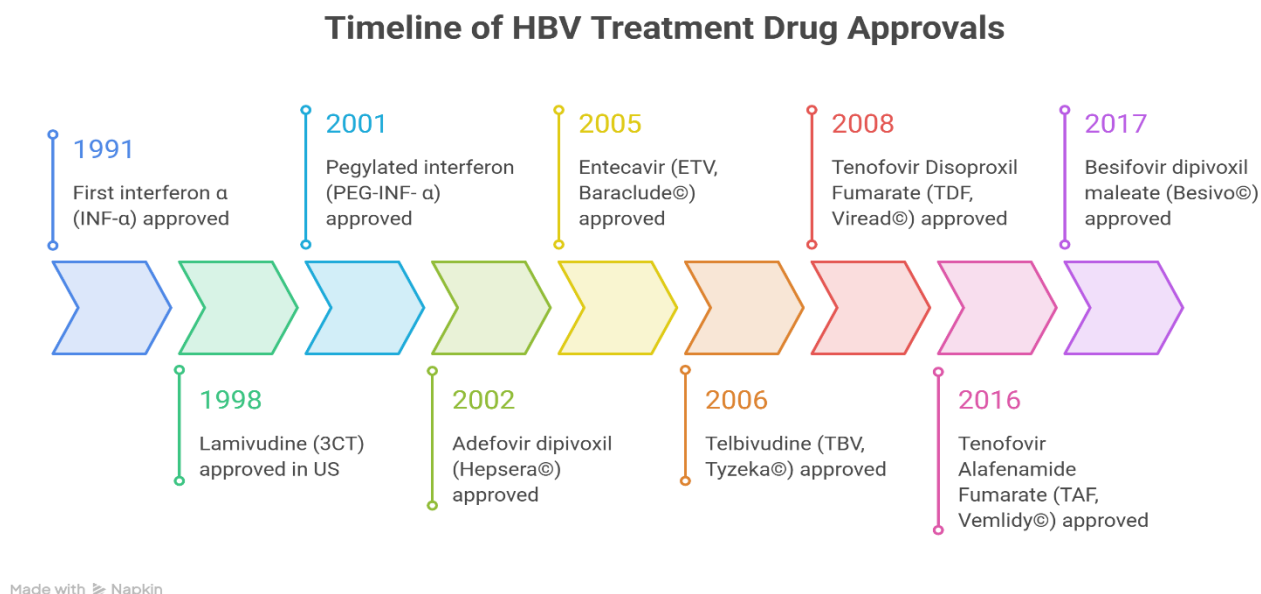


Figure 3: Timeline of HBV drug approvals.

5.NOVEL THERAPIES

5.1 ENTRY INHIBITORS

The first step of HBV entry into hepatocyte initiates with interaction of pre-S1 domain to sodium taurocolate cotransporting polypeptide (NTPC) [27]. Entry inhibitors are novel antivirals that inhibit HBV infection by targeting the viral particle [28]. The first in line drug of this class Bulivertide initially called Myrcludex B(Myrb) efficiently prevented the spreading of HBV from infected human hepatocytes [29]. It is a myristoylated peptide with 47 amino acids similar to the 2-48 amino acids of HBV pre surface protein [30]. Myrb showed great antiviral effect by blocking the NTCP in various in vivo models such as in mice it binds to the mice NTCP and block its BA-transporter, there was a significant reduction in level of HbeAg, HbsAg and HBV DNA [29,31]. Myrb has poor acidic stability and poor absorption through gastrointestinal barrier, this was overcome by making glycerylcaldityltertraether liposomal formulation [32,33]. Myrb is also in trial for chronic HBV, with the recent discovery of HBV-infected mice with humanized liver showed that a new HBV infection is required reactivate cccDNA. Myrb shows potential in combination therapies [34].

Another NTCP inhibitor Rapavir, inspired by rapamycin and FK506. After screening of 3918 rapafucin, 15 hits were identified from which rapafucin HP07-C6 showed the most inhibitory activity. To improve the potency structure activity relationship (SAR) was performed, 71 analogous rapafucin HP07-C6 were synthesised from which JH-B10 showed significant improvement and was named JH-B10 rapavir. The effect of rapavir was tested in vivo in mice which showed significant decreased levels of cccDNA and HBV RNA levels also was tested for hepatotoxicity and

nephrotoxicity in mice with a dose 16 mg/kg which showed no toxicity. The results showed that rapavir was able to exhibit enough liver cell protection against HBV infection in vivo [35]. Another research done identified a flavonoid epigallocatechin-3-gallate which can effectively block NTPC from green tea [36]. Other drugs which were recently approved by FDA are vanitaracin A, proanthocyanidin, zafirlukast and compound like B7[37,38-42]. The Table 1 contains drugs used as entry inhibitors.

Table 1: Novel drug used as entry inhibitors

Sr. No.	Class	Drug	Status	MOA
1	Entry inhibitor	Bulevirtide (Myrcludex B/MyrB)	U.S. FDA approved	Binds to NTCP, blocks HBV entry into the hepatocytes.
2	NTCP inhibitor	Rapavir (JH-B10)	In-vivo study	Inhibits NTCP-mediated HBV entry, further reducing cccDNA and HBV RNA levels.
3	NTCP inhibitor	Epigallocatechin-3-gallate (EGCG)	Identified	Blocks NTCP and inhibit HBV entry into hepatocytes.
4	Entry inhibitor	Vanitaracin A, Proanthocyanidin, Zafirlukast, Compound B7	Approved by FDA	Inhibit HBV entry by targeting NTCP.

5.2 DIRECT-ACTING DRUGS ON cccDNA

cccDNA is a mini chromosome like moiety that is formed in the nucleus form relaxed circular DNA (rcDNA) by the host DNA polymerase enzyme [43]. cccDNA functions as the templet for the pregenomic RNA (pgRNA) and subgenomic messenger RNA (mRNA) that encode viral proteins like HBV polymerase, core proteins and other major proteins [44]. The life span of cccDNA is not yet known but may be less than the lifespan of hepatocytes [45]. After screening of a small molecule library consisting of 85,000 molecules, gave two disubstituted sulphonamide, CCC-0975 and CCC-0346 molecules which when assayed in HepG2 cell lines, showed to inhibit the conversion of rcDNA to cccDNA by the polymerase enzyme [46]. Interferons- α (INF α) can be used to eradicate HBV but they have severe side effects making them unusable, an alternate which can be used is lymphotoxin- β (LT β R). Activation of INF α and LT β R receptor causes up regulation of APOBEC3A and APOBEC3B deaminase, these deaminases cause non-hepatotoxic degradation of cccDNA[47].

Complete inactivation of cccDNA can be potentially done by using CRISPAR-Cas9 endonuclease system causing RNA guided disruption and mutagenesis of cccDNA. To inactivate cccDNA multiple sites on HBV need to be targeted [48,49,50]. There is a need to develop a delivery system that will transfer the CRISPAR-Cas9 to the site of action, there could be sever off-target effect that needed to be further analysed, editing of HBV DNA can result in

unpredictable effect [51]. Other methods which can destroy cccDNA utilise zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) [48,52]. The anti HBV effect of TALENs were tested in mouse model, they were injected with HBV DNA and control vector/plasmid encoding TALEN-L2/R2. The results showed significant decrease in the production of HbsAg showing that TALENs effectively inhibit viral transcription [53]. Other methods include directly targeting HBV X protein or using substitute sulfonamide which prevent the conversion of rcDNA to cccDNA [54,55,56]. The Table 2 contains the list of novel drugs acting directly on cccDNA.

Table 2: Novel drug directly acting on cccDNA

Sr. No.	Class	Drug	Status	MOA
1	cccDNA	CCC-0975, CCC-0346	In-vitro	Inhibits conversion of rcDNA to cccDNA by teh HBV polymerase
2	Host-targeting therapy	Interferon- α (IFN- α)	Available in Market	Leads to non-hepatotoxic degradation of cccDNA by activating the APOBEC3A and APOBEC3B deaminases.
3	Host-targeting therapy	Lymphotoxin- β receptor (LT β R) activation	Proposed	Leads to non-hepatotoxic degradation of cccDNA by activating the APOBEC3A and APOBEC3B deaminases.
4	Gene-editing therapy	CRISPR-Cas9	Experimental	Causes mutagenesis of cccDNA by targeting multiple HBV sites.
5	Gene-editing therapy	Zinc-finger nucleases (ZFNs)	Experimental	Destroys cccDNA through the targeted genome editing.
6	Gene-editing therapy	Transcription activator-like effector nucleases (TALENs)	Pre-clinical	Decreases HBsAg production by inhibiting the viral transcription.
7	HBx-targeting therapy	HBV X protein targeting	Under investigation	Suppresses the cccDNA activity by directly targeting the HBV X protein.
8	cccDNA inhibitor	Disubstituted sulfonamides	Under investigation	Prevent conversion of rcDNA to cccDNA

5.3 HbsAg SECRETION INHIBITORS

In a hepatitis infected patient HBV subviral particles (SVP) are present in major quantity as compared to infectious virions and are the reason for major source of HbsAg in blood. These HbsAg cause immune exhaustion and promote HBV chronicity [57,58]. Nucleic Acid Polymers (NAPs) are phosphorothioated oligonucleotide, these are antiviral agents with the ability to block HbsAg release. This action allows host mediated clearance of HbsAg from the circulation. This ability has an agonistic effect on other immunotherapies after anti-viral therapies is stopped. REP 2139 is a NAPs which showed activity on both HBV and hepatitis D virus [57,58,59]. NAPs have been tested in vitro in HepG2.2.15 cells, earlier in vitro and in vivo duck model for their inhibitory function [59]. NAPs REP 2139 and REP 2165 are NAPs which are under clinical investigation, phase II clinical trials of REP 2139 and 2EP 2165 in combination with tenofovir (TDF) and pegylated interferon alfa-2a (pegIFN). The study was done on 40 human participants in 2 parts, part 1 was monotherapy of TDF and pegIFN for 24 weeks. The criteria for the test were lower and higher level of HBsAg (5000 IU/ml), lower and higher level of HBV DNA (1.74×10^4 IU/ml) and age above and below 40 years. The result of the phase II randomized trials of the combination therapy of NAPs with TDF and pegIFN didn't affect the tolerability and significantly increased the decrease in level of HbsAg [60]. The Table 2 contains the list of novel drugs inhibiting the secretion of HbsAg.

Table 3: Novel drug used as HbsAg secretion inhibitors.

Sr. No	Class	Drug	Status	MOA
1	HBsAg Secretion Inhibitor (NAP)	REP 2139	Phase II clinical trial	Inhibits HBsAg release from the affected hepatocytes, allowing clearance of circulating HBsAg.
2	HBsAg Secretion Inhibitor (NAP)	REP 2165	Phase II clinical trial	Inhibits HBsAg release from the affected hepatocytes, allowing clearance of circulating HBsAg.

5.4 RNA INTERFERENCE: siRNA and ASOs

RNA interference (RNAi)-based therapeutics, including small interfering RNAs (siRNAs) and the anti-sense oligonucleotides the ASOs, were developed to decrease the viral antigen load by targeting the HBV transcripts, in addition to all this these agents suppress HBV replication by cutting down on the availability of viral RNA templates and the essential replication-associated factors. the siRNA are the double stranded RNA molecules that are very specifically recognizing the HBV messenger RNAs and integrate into the RNA induced silencing complex further argonaute-2 within the RISC complex degrades HBV RNA and then it inhibits its translation while the ASOs

promote the RNase H-mediated degradation of the complimentary HBV RNA. The liver targeting delivery systems and dosage forms also the chemical modification enhance the stability and durability of such therapies, leading to the sustained HBsAg reduction. Currently several siRNA therapeutics, that include JNJ-3989, AB-729, RG-6346, and the VIR-2218 are currently in the phase II of the clinical development [61].

ARC-520 has been discontinued because of the toxicity observed in the preclinical trials (cynomolgus monkeys), there's an uprise in the development of an RNAi therapy that could be delivered by a subcutaneous injection, by arrowhead [62]. Next came the JNJ-3989 in the siRNA evolution made to target the different HBV genome sites, it is safe and is administered subcutaneously, serious drug-drug interaction was not observed. [63,64,65]. RG7834 is an HBV inhibitor which has been studied for its complex nature in hepatitis B and it's been proved to not act as an RNAi molecule rather it operates as an HBV transcription suppressor in an unknown manner [66,67]. Also, RG7834, entecavir, and PEG-IFN- α when come together it's observed to decrease HBV DNA and HBsAg levels significantly [48]. Another siRNA molecule AB-729, its administered subcutaneously in conjugation with NAG, this compound has shown a very important suppression of HBsAg in the preclinical trials (mice models) infected by HBV [64]. The Table 4 contains the list of novel drugs acting on replication and translation of RNA.

Table 4: Novel drug which act on viral RNA.

Sr. No	Class	Drug	Status	MOA
1	siRNA	JNJ-3989 (ARO-HBV)	Phase II	Targets HBV transcripts, inducing RISC, leading to degradation of HBV RNA and inhibition of translation.
2	siRNA	AB-729	Phase II	SiRNA that supresses the HBsAg by destroying HBV mRNA via RISC path.
3	siRNA	RG6346 (DCR-HBVS)	Phase II	Points at HBV mRNA through the RISC, suppressing the expression of viral antigen
4	siRNA	VIR-2218	Phase II	Degardes HBV RNA by the RISC, amount of viral antigen produce is decreased.
5	siRNA	ARC-520	Discontinued	Targets the HBV mRNA through RNA interference
6	Transcription inhibitors	RG7834	Preclinical	HBV transcription is stopped by an unknown mechanism

5.5 CAPSID ASSEMBLY MODULATORS (CAM)

Capsid assembly is an important step which occurs in the HBV life cycle, it involves core proteins as the major component to form a capsid which houses the reverse transcription of pgRNA by HBV polymerase. CpAMs the core protein allosteric modulators stop this process by inducing the formation of unstable capsids or the empty capsids, which then decreases the viral particle production and hinders the nuclear trafficking of rcDNA containing capsids results into decrease in the accumulation of cccDNA within the hepatocytes [68,69]. JNJ-6379 observed in a Phase Ib clinical trial, decreased the HBV DNA levels after 28 days under undisturbed treatment although no changes in the levels of HbsAg levels were seen [70].

Class II CpMAs, like EDP-514 and ALG-000184 are in Phase I trials although they are yet to show any significant effects on the HBsAg levels [71,72]. AL-3778, first class HBV inhibitor said to inhibit various core mediated HBV life cycle functions [73]. AL-3778, entecavir or Peg-IFN in a mouse model study (compared monotherapy) to NVR 3-778 + entecavir or NVR 3-778 + Peg-IFN (combination therapy), it was observed that serum HBV viral load reduction with NVR 3-778 monotherapy was relatively similar to what was observed in the with entecavir monotherapy, highest reduction was seen with NVR 3-778 + Peg-IFN combination therapy [74]. ABI-H0731, RO7049389, vebicorvir (VBR), JNJ-56136379 and GLS4 have been observed to reduce HBV DNA and HBV RNA after 28 days [75,76,70,77,78]. CAMs including sulphonamides [79], NVR 3-778, AB-423, AB-506, JNJ-440, JNJ-56136379, ABI-H0731, Bay41-4109, QL-007[80], ZW-1841, ZW-1847 [81], GLP-26 [82,83] are currently under investigation. The Table 5 contains the list of novel drugs acting as CAMs.

Table 5: Novel drug which are used as capsid assembly modulators.

Sr. No	Class	Drug	Status	MOA
1	CAM	JNJ-6379	Phase Ib	Causes the formation of unstable or empty capsids, it reduces the viral particle production.
2	CAM (Class II)	EDP-514	Phase I	Induces unstable/empty capsids formation, blocking HBV replication
3	CAM (Class II)	ALG-000184	Phase I	Reduces viral particle production.
4	CAM	AL-3778	Under investigation	Inhibits various core HBV life cycle functions.
5	CAM	NVR 3-778	Under investigation	Decreases HBV replication.

6	CAM	ABI-H0731, RO7049389, Vebicorvir (VBR), JNJ-56136379, GLS4	Under investigation	Decreases HBV RNA and DNA levels.
7	CAM	Sulfonamides, AB-423, AB-506, JNJ-440, Bay41-4109, QL-007, ZW-1841, ZW-1847, GLP-26	Under investigation	Inhibits viral replication of HBV DNA or HBV RNA.

6. FUTURE PROSPECTS

Several drugs are in the early phases of the clinical trials, that can be delivered via various routes of administration like subcutaneously or intravenously [84]. Personalized approaches and regular monitoring is expected as the immunotherapies rise [85]. Unlike HCV, HBV carries a lifelong risk of HCC development although cirrhosis is absent [86]. cccDNA and integrated HBV DNA residues at an annual rate of between 0.3% to 0.6%, even if there's absence of cirrhosis [87,88]. Various clinical trials indicate that monotherapy might be insufficient to reach the serological clearance of HBsAg, reason being the future treatments should be targeted on multidrug combination including siRNA or ASO drugs along with immunomodulators riding on top of nucleo(t)ide analogues or capsid modulators (antivirals) [89]. However, the drugs and vaccines are hard to access as most of the suffering population lies in the developing and sub-Saharan countries, Africa or southeast Asia [90]. Hence, the development of an affordable and readily deliverable cure for hepatitis B should be a top priority. It will require combination therapy using agents that target multiple viral targets plus immune modulators that harness the power of the patient defenses against the virus [91,92].

7. CONCLUSION

In conclusion, recent advances in our knowledge of the biology of hepatitis B virus (HBV), including its replication cycle and interaction with the host immune system, accelerated the development of novel therapeutic strategies. While the ultimate goal is the complete elimination of HBV by removal of covalently closed circular (cccDNA) and integrated viral DNA, the available evidence points towards functional cure as a more achievable goal. This will likely need combination therapies that not only inhibit viral replication by novel direct acting antivirals but also re-establish effective innate and adaptive immune responses by immunomodulatory agents. These next generation therapies must be safe, well tolerated, accessible, and affordable to dramatically reduce the global burden of chronic hepatitis B, especially in low- and middle-income countries with the highest HBV prevalence. Continued research and clinical development should move effective functional cure strategies closer to routine clinical practice.

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