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REVIEW

Navigating the Viral Hepatitis Drug Landscape: New Discoveries and Enduring Challenges. A Narrative Review

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ABSTRACT

Viral hepatitis remains a significant challenge for global public health and a leading cause of liver-related morbidity and mortality worldwide, with most cases caused by five hepatotropic viruses: hepatitis A, B, C, D, and E. The World Health Organization has established a goal to eliminate viral hepatitis as a public health threat by 2030. In recent years, advancements in our understanding of its pathogenesis have significantly propelled the development of antiviral drugs, particularly for hepatitis C, for which we now have highly effective therapies with cure rates exceeding 95%. However, achieving complete cures for hepatitis B and D continues to pose challenges, and effective treatments for hepatitis A and E are still lacking. A comprehensive understanding of the latest treatment advancements is crucial for guiding future drug development. This article reviews the most recent advancements in pharmacological interventions for viral hepatitis, summarizes current treatment methods, and provides an outlook on future research and therapeutic strategies, with the aim of improving patient outcomes and alleviating the global burden of liver diseases.

Keywords: Hepatitis A virus; Hepatitis B virus; Hepatitis C virus; Hepatitis D virus; Hepatitis E virus; Treatment; Viral hepatitis

Key Summary Points

Viral hepatitis remains a major global public health threat with high liver-related morbidity and mortality. Therapeutic progress varies across viral types and faces challenges. This review synthesizes the latest pharmacological advances, summarizes current treatment strategies, and outlines future research directions to guide drug development and improve patient outcomes.

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For hepatitis B, novel therapeutic agents targeting different steps of the HBV life cycle are in clinical development, showing promising efficacy in reducing viral load and HBsAg levels.

Hepatitis D treatment has advanced with entry inhibitors (e.g., bulevirtide), assembly inhibitors (e.g., lonafarnib), and HBsAg inhibitors (e.g., REP 2139), and combination therapies have demonstrated superior virological response compared to monotherapy.

Pan-genotypic direct-acting antivirals have revolutionized hepatitis C treatment, achieving cure rates > 95%. Egypt's national elimination strategy provides a global reference for HCV prevention and control. No specific antivirals exist for hepatitis A and E, with supportive care as the mainstay; potential therapeutic candidates are under preclinical or clinical exploration.

Despite significant progress in the development of antiviral drugs for viral hepatitis, challenges such as the persistent presence of covalently closed circular DNA of the hepatitis B virus, the dependence of hepatitis D virus on the hepatitis B virus, and the limited accessibility of direct antiviral agents still need to be addressed through the optimization of combination therapies and global health initiatives.

INTRODUCTION

Viral hepatitis represents a significant public health challenge and is a leading cause of morbidity and mortality related to liver disease globally. It is primarily caused by five viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Each of these viruses is characterized by distinct biological structures, transmission routes, infection risks, and control measures (Table 1). The various types of viral hepatitis contribute to the high rates of morbidity and mortality. Estimates indicate that more than 250 million individuals worldwide are living with chronic hepatitis B (CHB), while more than 70 million are infected with the HCV, and more than 1.5 million cases of hepatitis A are reported annually. The estimated number of deaths attributed to viral hepatitis rose from 1.1 million in 2019 to 1.3 million in 2022 [1].

Most cases of acute hepatitis are self-limiting diseases that can resolve without treatment within a few weeks. However, a small proportion of infections lead to acute liver failure, resulting in patient death. HAV and HEV infections are the most common causes of acute viral hepatitis, whereas HBV and HCV infections have a high prevalence and often lead to chronic infections. Without timely intervention, these infections can progressively develop into end-stage liver diseases such as cirrhosis and liver cancer. Globally, approximately 3500 people die every day from HBV and HCV infections, posing a significant burden on global public health [2]. The clinical manifestations of viral hepatitis vary and are typically nonspecific at onset, including symptoms such as fatigue, abdominal discomfort, and loss of appetite. As the disease progresses to its terminal stages, patients can experience liver failure, hepatocellular carcinoma (HCC), and a series of complications, including gastrointestinal bleeding and hepatic encephalopathy.

Over the past few decades, groundbreaking advancements have occurred in the prevention and management of various types of viral hepatitis, leading to the emergence of multiple treatment methods. The World Health Organization (WHO) has set a goal to eliminate HBV and HCV infections by 2030, aiming to reduce global hepatitis-related mortality by 65% and new infections by 90% [3]. Due to the high prevalence and severe consequences of viral hepatitis, its treatment has been a consistent focus in liver disease research, with new and effective treatments gradually emerging. However, given the large population affected by viral hepatitis and the challenges associated with achieving a complete cure using existing drugs, significant progress remains to be made in the future. Notably, due to the extremely high prevalence of viral hepatitis, it is estimated that 89.7% of HBV infections and 78.6% of HCV infections remain undiagnosed. Current treatments often fail to

Table 1 Features of different hepatitis viruses

Feature	HAV	HBV	HCV	HDV	HEV
Family	Picornaviridae	Hepadnaviridae	Flaviviridae	Satelliviridae	Hepeviridae
Genus	*Hepatovirus*	*Orthohepadnavirus*	*Hepacivirus*	*Deltavirus*	*Orthohepevirus*
Genome	ssRNA(+)	Partially dsDNA	ssRNA(+)	ssRNA(−)	ssRNA(+)
Genome size (kb)	7–9	3–4	10–12	1.7	7–8
Transmission	Fecal–oral	Blood/body fluids, vertical	Percutaneous blood exposure	Requires HBV coinfection	Fecal–oral (genotypes 1/2) Zoonotic (genotypes 3/4)
Incubation period	15–50 days	30–180 days	14–180 days	Synchronous with HBV	15–60 days
Genotypes	6 (I to VI)	10 (A to J)	8 (1 to 8)	8 (1 to 8)	8 (1 to 8)
Serological markers	Anti-HAV IgM/IgG	HBsAg, HBeAg, Anti-HBc IgM/IgG	Anti-HCV, HCV RNA	Anti-HDV, HDV RNA	Anti-HEV IgM/IgG, HEV RNA
Treatment	Supportive care	Pegylated interferon-alpha and nucleoside/nucleotide analogues	DAA	Pegylated interferon-alpha	Supportive care Ribavirin in severe cases and immunosuppressed patients
Vaccination	Inactivated/live-attenuated	Recombinant vaccine	None	HBV vaccine prevents coinfection	Genotype 1 vaccine (China-approved)
Clinical outcome	Self-limited	Self-limited and chronic	Self-limited and chronic	Self-limited and chronic	Self-limited
High-risk populations	Children: subclinical	Vertical transmission cohorts	People who inject drugs	HBV carriers	Pregnant women
Chronicity risk	None	Adults: 5–10% Children: 90%	55–85%	Coinfection: < 5% Superinfection: 80%	Genotypes 1/2: None Immunocompromised: Persistent

dsDNA double-stranded DNA, *ssRNA* single-stranded RNA, *HBsAg* hepatitis B surface antigen, *HBeAg* hepatitis B e-antigen, *IgM* immunoglobulin M, *IgG* immunoglobulin G, *DAA* direct-acting antiviral agent

achieve a complete cure, highlighting the significant challenges that lie ahead in addressing this public health issue [4]. This review aims to summarize the current evidence for treating viral

hepatitis, with a particular focus on hepatitis B, which affects the highest number of patients, providing references for future treatment directions and potential research areas. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

NEW DISCOVERIES AND ENDURING CHALLENGES IN THE VIRAL HEPATITIS DRUG LANDSCAPE

Hepatitis B

HBV is the causative agent of hepatitis B. Current first-line treatments for hepatitis B include nucleos(t)ide analogs (NAs) and pegylated interferon alpha (PEG-IFN-α), both of which are widely utilized in the management of CHB. In recent years, indications for antiviral therapy for hepatitis B have expanded, with major guidelines updated to lower the treatment threshold. Initially relying mainly on alanine transaminase (ALT) levels and viral load, the criteria have now evolved to consider factors such as degree of liver inflammation and fibrosis, age, and family history, as summarized in Table 2. This evolution has broadened the population requiring treatment and refined the management of hepatitis B. Antiviral drugs can inhibit HBV replication, thereby reducing the likelihood of hepatitis B progressing to cirrhosis and liver cancer. However, due to their inability to target covalently closed circular DNA (cccDNA), achieving a functional cure—defined as hepatitis B surface antigen (HBsAg) levels below the detection limit of 0.05 IU/ml, accompanied by sustained HBsAg loss or seroconversion—remains challenging [5]. Only one-fifth of patients with CHB meet the criteria for initiating antiviral therapy, which necessitates long-term medication and carries a high risk of recurrence and severe consequences, such as liver failure, upon discontinuation. Furthermore, prolonged use of NAs can result in cumulative toxicities, including bone disease and kidney damage, and preclinical studies indicate entecavir may have carcinogenic effects [6]. If the current situation remains unchanged, the number of deaths worldwide due to HBV infection is projected to increase by 39% annually from 2015–2030. Consequently, there is an urgent need to explore new antiviral therapies with the potential to achieve a functional cure [7].

The viral envelope of HBV surrounds a nucleocapsid that contains partially double-stranded circular DNA. After HBV enters the human body, it interacts with the key receptor on the surface of hepatocytes, the Na+-taurocholate cotransporting polypeptide (NTCP). Upon entering the cell, the nucleocapsid is released into the cytoplasm. The nucleocapsid subsequently releases the relaxed circular DNA (rcDNA) of the virus into the nucleus through the nuclear pore complex. Following this, the rcDNA undergoes a series of repair and circularization processes to be converted into cccDNA, which is then transcribed to produce pregenomic RNA (pgRNA), mRNA, and various other viral RNAs [8]. pgRNA is reverse transcribed to produce new rcDNA. Simultaneously, the core protein synthesized through mRNA translation assembles with rcDNA to form the nucleocapsid, which subsequently combines with the envelope protein. Following envelopment, mature viral particles are formed and released from the cell via exocytosis, allowing for further infection of other hepatocytes and thereby establishing a persistent infection in the body [9]. Every step of the HBV life cycle represents a potential therapeutic target for inhibiting HBV replication and reducing HBV infectivity (Fig. 1). Accordingly, potential therapeutic agents targeting each step are in development, as described in the following paragraphs and summarized in Table 3.

Capsid assembly modulators (CAMs)

CAMs, also known as core protein allosteric modulators (CpAMs), target the HBV core protein (Cp) to interfere with its assembly or stability, thereby inhibiting the normal formation of the viral capsid and blocking viral replication. Based on their mechanisms of action, CAMs are categorized into two types: CAM-As (class I) and CAM-Es (class Ⅱ). CAM-As induce abnormal capsid assembly, resulting in non-functional capsid

Table 2 Summary of the latest international guidelines for the management of CHB

Guidelines	APASL 2015	EASL 2017	AASLD 2018	WHO 2024
Indications	ALT level > 2 × ULN and HBV DNA > 2000 IU/ml (HBeAg-negative) or HBV DNA > 2000 IU/ml (HBeAg-positive) Liver cirrhosis with detectable HBV DNA	HBV DNA > 2000 IU/ml, ALT > ULN, and/or at least moderate liver inflammation, necrosis, or fibrosis HBV DNA can be detected in patients with cirrhosis Patients with HBV DNA > 20,000 IU/ml and ALT > 2 × ULN HBeAg positive, high HBV DNA levels, and age > 30 years Family history of HCC or cirrhosis and presence of extrahepatic manifestations	ALT level > 2 × ULN and HBV DNA > 2000 IU/ml (HBeAg-negative) or HBV DNA > 2000 IU/ml (HBeAg-positive) Liver cirrhosis with HBV DNA level > 2000 IU/ml Age > 40 years, family history of HCC, previous treatment history, and extrahepatic manifestations	Liver fibrosis ≥ F2, or clinical evidence of cirrhosis, regardless of HBV DNA and ALT levels HBV DNA > 2000 IU/ml and ALT > ULN (30 U/l for male patients and 19 U/l for female patients) Presence of any of the following conditions: co-infection, family history of liver cirrhosis or liver cancer, immunosuppression, comorbidities, HBV-related extrahepatic manifestations If HBV DNA testing cannot be performed, persistent ALT abnormality (defined as two instances of ALT > ULN at any interval within 6–12 months)
Recommended medications	ETV, TDF, and PEG-IFN-α or LAM, ADV, LdT	ETV, TDF, TAF, PEG-IFN-α	ETV, TDF, PEG-IFN-α	TDF, ETV, TAF

Table 2 continued

Guidelines	APASL 2015	EASL 2017	AASLD 2018	WHO 2024
Treatment discontinuation	HBsAg loss for ≥ 12 months HBeAg-positive non-cirrhotic patients with seroconversion and undetectable HBV DNA after at least 1 year of consolidation therapy Non-cirrhotic HBeAg-negative patients with undetectable HBV DNA for ≥ 2 years	HBsAg clearance Non-cirrhotic patients who are HBeAg-positive achieve stable HBeAg seroconversion, undetectable HBV DNA, and completion of at least 12 months of consolidation therapy Non-cirrhotic HBeAg-negative patients with CHB achieve long-term (≥ 3 years) virological suppression after NA therapy	HBsAg clearance Patients with clinical evidence of cirrhosis require lifelong treatment	Simultaneously meeting the following criteria: no clinical evidence of cirrhosis; ability to undergo long-term strict follow-up to monitor reactivation; for initial patients who are HBeAg-positive, continuation of consolidation therapy for at least 1 year after achieving HBeAg seroconversion; sustained normal ALT levels, and persistently undetectable HBV DNA Patients with clinical evidence of cirrhosis require lifelong treatment

APASL Asian Pacific Association for the Study of the Liver, *EASL* European Association for the Study of the Liver, *AASLD* American Association for the Study of Liver Diseases, *WHO* World Health Organization, *UNL* upper limit of normal, *ETV* entecavir, *TDF* tenofovir, *LAM* lamivudine, *ADV* adefovir dipivoxil, *LdT* Telbivudine, *TAF* tenofovir alafenamide

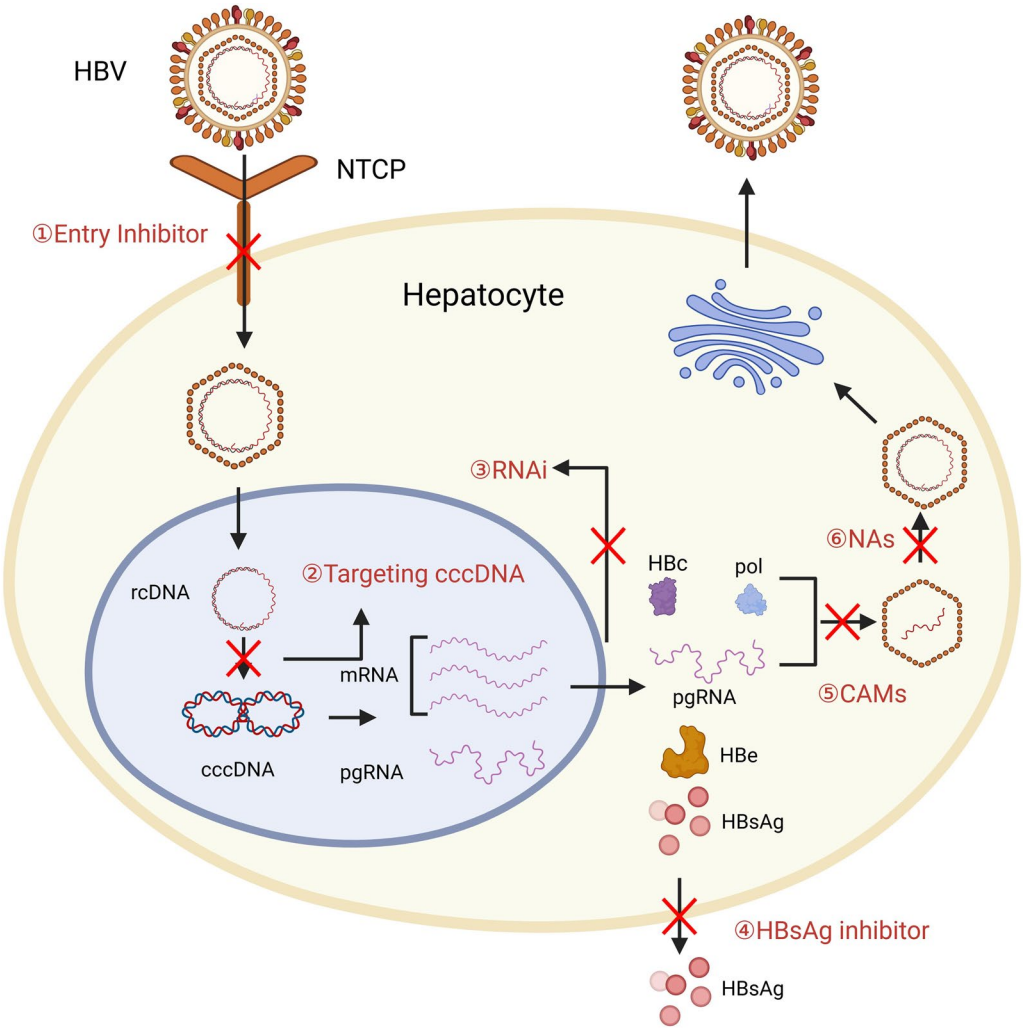

Fig. 1 Drug targets for disrupting HBV replication in hepatocytes. *HBV* hepatitis B virus, *NTCP* Na+-taurocholate cotransporting polypeptide, *rcDNA* relaxed circular DNA, *cccDNA* covalently closed circular DNA, *pgRNA* pregenomic RNA, *CAMs* capsid assembly modulators, *NAs* nucleos(t)ide analogs (created with BioRender.com, Agreement number: SP29B0AZW8)

structures that disrupt the packaging of pgRNA and the stability of nucleocapsids, thereby suppressing the replenishment of cccDNA. Additionally, they may eliminate the virus by activating host immune responses or directly inducing apoptosis in infected hepatocytes. CAM-Es promote excessive production of empty capsids, inhibit the packaging of pgRNA and polymerase, and reduce the conversion of rcDNA to cccDNA [10].

GLS4 is a class I CAM, and treatment with the combination of GLS4 and entecavir for 48 weeks inhibits HBV DNA replication and reduces HBV pgRNA [11]. Freethiadine, an enhanced variant of GLS4, exhibited favorable safety profiles and antiviral efficacy in phase I trials. After 28 days of administration, HBV DNA and pgRNA levels decreased [12]. Vebicorvir (ABI-H0731) interferes with HBV replication through multiple mechanisms, exhibits a good safety profile, is rapidly absorbed, and induces dose-dependent reductions in HBV DNA and RNA levels [13]. For treatment-naïve HBeAg-positive patients without cirrhosis, combination with entecavir

Table 3 Summary of pharmacotherapies for hepatitis B

Class	Mechanism	Drug name	Trial Number	Phase
NAs	Inhibition of reverse transcriptase Liver-target prodrug	ETV, TDF, TAF	Clinical use	Clinical use
CAMs	CAM-A	GLS4	NCT04147208	Ⅱ
		VNRX-9945	NCT04845321	Ⅰ
		RO7049389	NCT04225715	Ⅱ
		KL060332	CTR20200985	Ⅰ
		QL-007	CTR20190904	Ⅱ
		Freethiadine	NCT05391360	Ⅰ
	CAM-E	JNJ-6379	NCT04667104	Ⅱ
		ABI-4334	NCT05569941	Ⅰ
		ABI-H3733	NCT05414981	Ⅰ
		ALG-000184	NCT04536337	Ⅰ
		JNJ-440	NCT03439488	Ⅰ
		Vebicorvir	NCT03772249	Ⅰ
		EDP-514	NCT04008004	Ⅰ
		ZM-H1505R	CTR20221976	Ⅱ
		TQA3605	NCT06644417	Ⅱ
		GST-HG141	CTR20222978	Ⅱ
Entry inhibitors	NTCP receptor competitive antagonist	Bulevirtide	NCT03852719	Ⅲ
		Hepalatide	NCT04426968	Ⅱ
		HH-003	NCT05839639	Ⅱ
		HH-006	CTR20244743)	Ⅰ
		A7387	–	Preclinical
		AB543	–	Preclinical
		PRX202	–	Preclinical
		Burfiralimab	NCT05808335	Ⅱ

Table 3 continued

Class	Mechanism	Drug name	Trial Number	Phase
Translation inhibitors	siRNA	JNJ-3989	NCT05123599	Ⅱ
		VIR-2218	NCT05970289	Ⅱ
		Daplusiran/Tomligisiran	NCT06537414	Ⅱ
		Imdusiran	NCT04980482	Ⅱ
		RBD-1016	NCT05961098	Ⅱ
		HRS-5635	NCT06425341	Ⅱ
		TQA3038	NCT06452693	Ⅰb/Ⅱa
		BW-20757	ACTRN12623000708651	Ⅱ
	ASO	GSK3228836	NCT04676724	Ⅱ
		Bepirovirsen	NCT05630820	Ⅲ
		GSK3389404	NCT03020745	Ⅱ
HBsAg inhibitors	NAPs	REP2139	NCT02565719	Ⅱ
Immunomodulators		REP2165	NCT02565719	Ⅱ
	STOPs	ALG-010133	NCT04485663	Ⅰ
		GST-HG131	NCT06263959	Ⅱ
		GST-HG121	CTR20221651	Ⅰ
		LP-128	NCT05130567	Ⅰ
	TLR agonists	GS-9620	NCT02166047	Ⅱ
		RO7020531	NCT02956850	Ⅱ
		TQ-A3334	CTR20244362	Ⅱ
		Selgantolimod	NCT03491553	Ⅱ
		TQ-A3810	NCT06566248	Ⅱ
		HRS9950	CTR20231755	Ⅱ
		CB-06	CTR20240859	Ⅰ
		R848	–	Preclinical
		CL413	–	Preclinical

Table 3 continued

Class	Mechanism	Drug name	Trial Number	Phase
	ICIs	Nivolumab	NCT04638439	Ⅰ
		cemiplimab	NCT04046107	Ⅱ
		TQ-B2450	NCT04202653	Ⅱ
		Envafolimab	CTR20200363	Ⅱ
		GS-4224	ACTRN12618001957280	Ⅰ
	Therapeutic vaccines	VT-300	NCT04778904	Ⅱ
		BRII-179	NCT04749368	Ⅱ
		GSK3528869A	NCT03866187	Ⅱ
		ChAdOx1 HBV	NCT04297917	Ⅰ
		INO-1800	NCT02431312	Ⅰ
		HB-110	NCT03625934	Ⅱ
		CVI-HBV-002	NCT04289987	Ⅱ
		NASVAC	NCT01374308	Ⅲ
		TVAX-008	CTR20202547	Ⅱ
		ABX203	NCT02249988	Ⅲ
	Monoclonal antibodies	Lenvervimab	NCT03801798	Ⅱ
		Tobevibart	NCT05612581	Ⅱ
		KW027	CTR20234074	Ⅰ
		BJT-778	ACTRN12623000111673	Ⅱ
		HT-102	NCT06744686	Ⅰ

for 12 weeks reduces HBV DNA and pgRNA levels, demonstrating potent antiviral activity [14]. QL007 inhibits HBV replication dose-dependently, in vitro and in vivo, reducing HBV DNA, HBV RNA, and HBeAg while decreasing cccDNA synthesis [15]. The phase II clinical trial of CAM Neracorvir (ST-HG141) demonstrated potent antiviral efficacy. After 24 weeks of combination therapy with NAs, the proportion of patients with HBV DNA levels below the lower limit of quantification (LLOQ) exceeded that in the NA monotherapy group (low-dose group 84.0%, high-dose group 81.5% vs. placebo group 32.1%). Additionally, average reductions in HBV DNA and pgRNA exceeded 1 log10 IU/ml, prompting the initiation of phase III studies [16]. Another drug, ALG-000184, inhibits viral replication and cccDNA synthesis in vitro, resulting in significant reductions in HBV DNA and RNA levels [17]. A phase Ib study presented at the 2024 American Association for the Study of Liver Diseases (AASLD) meeting demonstrated that, after 72 weeks of 300 mg ALG-000184 monotherapy, 90% of the patients who are HBeAg-positive and 100% of patients who are HBeAg-negative achieved HBV DNA levels below 10 IU/ml. Additionally, HBV RNA, HBsAg, and HBeAg levels decreased significantly. The treatment was well tolerated, with no serious adverse events reported. In vitro experiments showed this therapy exhibits superior efficacy

in suppressing HBV DNA and HBeAg compared with entecavir.

Multiple next-generation CAM drugs are continuously advancing in clinical development. JNJ-6379 and EDP-514 effectively reduce HBV DNA and RNA levels, but neither has achieved HBsAg clearance; therefore, future studies should focus on exploring their potential for combination therapy with other mechanisms of action [18, 19]. JNJ-440 demonstrated good tolerability in both single and multiple doses in a phase I clinical trial (NCT03439488) involving healthy adults, while its antiviral efficacy requires further validation in larger-scale clinical trials. The new drugs ABI-4334 and ABI-H3733, as next-generation CAMs, can more efficiently inhibit pgRNA encapsidation and cccDNA formation through optimized mechanisms of action, and both drugs have entered phase I clinical trials (trial numbers NCT05569941 and NCT05414981, respectively). The development of TQA3605 and ZM-H1505R has progressed to phase II clinical trials, with study designs focusing on comparing the clinical efficacy differences between the two in combination with NAs versus NAs monotherapy for CHB; the relevant trial numbers are NCT06644417 and CTR20221976.

Various CAMs can reduce HBV DNA and HBV RNA levels; however, their ability to clear HBsAg remains insufficient. Additionally, as direct antiviral agents, their standalone use can easily lead to viral mutations and the development of resistance. Some of these drugs are less effective than NAs and may have potential adverse reactions, which hinder their further development. For example, the study of NVR 3778 was discontinued due to insufficient efficacy and potential adverse effects. Combining drugs with different mechanisms of action to inhibit multiple steps in the HBV life cycle is an important strategy to improve the limitations of these drugs. Indeed, phase 2 clinical trials are underway to test various combination therapies involving RO7049389 with NA, small interfering RNA (siRNA), TLR7 agonists, or PEG-IFN. In the future, it may be possible to develop CAM molecules with a higher resistance barrier by drawing on the characteristics of highly resistant drugs like entecavir and tenofovir, ensuring their antiviral activity is sufficient to suppress related mutations and effectively inhibit HBV replication over extended periods, thereby enhancing the suppression of cccDNA and HBsAg.

Inhibitors of HBV protein synthesis/ translation

RNA interference (RNAi) is a gene silencing approach mediated by double-stranded RNA (dsRNA). siRNA drugs can bind to specific enzymes and proteins in the body to form an RNA-induced silencing complex (RISC), which recognizes, binds to, and degrades a target mRNA. This process can inhibit the expression of specific genes, block the synthesis of viral proteins, and subsequently suppress viral replication and assembly [20].

As monotherapy, JNJ-3989 significantly reduces HBsAg levels and shows favorable therapeutic effects when combined with PEG-IFN-α, JNJ-6379, and NAs [21, 22]. ALN-HBV and VIR-2218 are RNAi therapies targeting HBV transcripts. The former was discontinued due to elevated ALT levels in healthy populations, while the latter, an improved version, demonstrates enhanced safety. In a phase II study, VIR-2218 reduced HBsAg levels, and all 11 participants receiving IFN-α 2a combination therapy achieved HBsAg clearance [23]. Imdusiran (AB-729) is a novel pan-genotypic siRNA therapy that reduces HBsAg, viral antigens, and replication in patients with CHB, currently in phase II clinical studies [24]. RBD1016 targets the conserved HBV X gene region and inhibits all four HBV transcripts via RNAi, simultaneously suppressing HBV DNA replication and reducing HBsAg from cccDNA and integrated DNA. Currently, it is in phase II clinical studies to optimize dosage and administration frequency, exploring combination therapies [25]. HRS-5635 shows excellent antiviral activity against all HBV genotypes in preclinical studies and exerts durable antiviral effects in vivo. Its monotherapy and combination efficacy and safety are being evaluated in phase II CHB trials, with recruitment ongoing. The PIRANGA II study shows Xalnesiran, combined with PEG-IFN-α, significantly enhances functional cure rates. In the 200 mg Xalnesiran + PEG-IFN-α group, HBsAg seroconversion was 16.7% (5/30 cases)

at 48 weeks post-treatment [26]. In the phase Ib trial of siRNA drug HT-101 (NCT06746311), all dosing groups reduced HBsAg, with some achieving clearance.

Antisense oligonucleotides (ASOs) represent an alternative approach to suppress viral protein expression by binding complementary sequences of HBV mRNA, forming DNA:RNA or RNA:RNA duplexes that trigger RNase H-dependent degradation. GSK3228836 led to ≥ 3 log10 IU/ml HBsAg reductions in both treatment-naïve and treatment-experienced patients with CHB, with progression to phase IIb trials underway [27]. Bepirovirsen, a novel ASO, achieved sustained HBsAg and HBV DNA clearance in 9–10% of CHB cases in phase IIb trials [28]. In the phase III clinical trial presented at the 2025 European Association for the Study of the Liver (EASL) annual meeting, 2.5-year follow-up was conducted for patients achieving complete response (CR), defined as HBsAg < 0.05 IU/ml and HBV DNA below LLOQ. Among these, 73% attained functional cure sustained for 2 years. In contrast, GSK3389404 (a structural analog of bepirovirsen) induced dose-dependent HBsAg reductions after 12 weeks in patients with CHB, yet only 3 of 56 participants had > 1.5 log10 IU/ml declines, with no HBsAg seroclearance, demonstrating GSK3389404's inferiority to bepirovirsen [29]. AHB-137 is a novel therapy based on the ASO mechanism. Phase IIa trial data, presented at the 2024 AASLD Annual Meeting, revealed 62% of the 300 mg AHB-137 group achieved HBsAg seroclearance (HBsAg below LLOQ, 0.05 IU/ml) after 12 weeks. According to the existing clinical trial results, AHB-137 demonstrates greater HBsAg reduction and higher seroconversion rate compared to Bepirovirsen. Notably, the AHB-137 study only included HBeAg-negative patients treated with NAs, whereas the Bepirovirsen study included patients who were HBeAg-negative or HBeAg-positive. Therefore, efficacy differences in the same population require further investigation.

Current clinical studies indicate that ASO drugs may be superior to siRNA drugs in promoting HBsAg serological conversion. Among 24 patients with CHB treated with VIR-2218 for 48 weeks, none achieved HBsAg clearance [30]. In contrast, among patients treated with bepirovirsen for 24 weeks after NAs, 26% achieved HBsAg clearance, with a sustained clearance rate of 12% at 24 weeks post-treatment [28]. Due to the differences in baseline status, treatment duration, and dosage of ASO or siRNA in various clinical trials involving patients with CHB, it is currently difficult to determine the relative advantages of ASO and siRNA drugs in promoting functional cure for CHB. Future large-sample randomized controlled trials are needed to clarify this issue further. Two classes of drugs can inhibit viral RNA transcription and protein expression, but their effects on the clearance of cccDNA and integrated HBV DNA are relatively weak. Furthermore, these drugs may interfere with the normal expression of host genes, leading to a high risk of viral relapse after discontinuation. The high mutation rate of HBV polymerase may result in variations in target sequences, triggering viral escape. Additionally, the delivery systems are inadequate; viral vectors (such as adeno-associated viruses) may provoke an immune response, while non-viral vectors (such as lipid nanoparticles) suffer from insufficient targeting efficiency. The siRNA drug ARC-520 was discontinued due to carrier toxicity, which resulted in fatalities during non-human primate trials. Future efforts should accelerate the advancement of phase III clinical trials to validate the long-term safety and sustained response rates of these agents. It is essential to design strategies targeting multiple HBV mRNAs or to regulate host factors to reduce the risk of resistance. Development of oral formulations should be promoted, and the limitations of these drugs should be gradually addressed through technological innovations and precision medical strategies.

Entry inhibitors

Entry inhibitors, such as bulevirtide, target the NTCP receptor, which is crucial for the entry of HBV and HDV into hepatocytes. These medications can block viral entry but are ineffective against existing infections [31]. A phase Ⅱ clinical trial demonstrated that bulevirtide significantly reduced HBV DNA in patients co-infected with HDV; however, its ineffectiveness on HBsAg levels limits its role in HBV mono-infection.

Studies indicate that long-term use of NTCP inhibitors may lead to cholestasis, attributed to the role of NTCP in bile acid metabolism [32]. This suggests that these drugs must be used in combination with other medications to achieve broader efficacy. Future research should address challenges such as the impact on extrahepatic HBV infection, drug resistance, and patient safety. For instance, combination therapy with HBsAg inhibitors or immunomodulators may yield synergistic effects.

Hepalatide, a 47-amino-acid synthetic peptide derived from the HBV Pre-S1 domain, functions as a NTCP receptor-binding agent to block HBV cellular entry [33]. The NCT04426968 trial is investigating the dose–response relationship and safety of Hepalatide combined with PEG-IFN-α in patients who are HBeAg-positive. Preliminary findings indicate that the L47/PEG-IFN-α combination exhibits favorable safety and tolerability, with HBV DNA levels demonstrating dose-dependent reductions. Additionally, a randomized, double-blind, placebo-controlled, multicenter phase II trial (NCT05244057) is currently assessing the efficacy of triple therapy (Hepalatide + PEG-IFN-α + tenofovir alafenamide) in nucleos(t)ide-experienced patients with CHB with ≥ 2 years of prior antiviral therapy.

HH-003 targets the PreS1 region of the large envelope protein of HBV, directly blocking the binding of the virus to the NTCP receptor and preventing viral entry into hepatocytes. It has demonstrated good safety and antiviral activity in phase Ib clinical trials and is currently being tested in phase II clinical trials (NCT05839639, NCT05734807). HH-006, which shares the same target, is being evaluated in a phase I trial for its safety and tolerability in patients with chronic HBV infection (CTR20244743). hzVSF is a monoclonal IgG4 that targets vimentin, and previous in vitro studies showed that hzVSF can exert anti-HBV effects by inhibiting HBV entry into cells. A phase II clinical trial is currently evaluating the therapeutic effects of Burfiralimab (hzVSF-v13) in combination with NAs in patients with CHB (NCT05808335). JH-B10 is a novel entry inhibitor drug that potently inhibits NTCP, effectively blocking HBV infection and exhibiting no significant side effects, which positions it as a promising candidate for anti-HBV drug development.

Entry inhibitors can facilitate viral entry but are unable to eliminate existing infections, leading to an incomplete virological response. Currently approved entry inhibiting drugs, such as bulevirtide, are primarily used for patients co-infected with HDV, while the development of indications for isolated HBV infections is lagging. Additionally, HBV can infect extrahepatic cells through non-NTCP pathways, which entry inhibitors cannot prevent. Additionally, NTCP is involved in bile acid metabolism, and inhibiting its function may interfere with hepatic detoxification and lipid metabolism, posing a risk of cholestasis with long-term use. In the future, research on combination therapies, drug resistance, extrahepatic infections, and safety will be crucial for promoting the widespread application of such drugs.

Immunomodulators

The alpha-kinase 1 (ALPK1) agonist DF-006 has demonstrated favorable efficacy and safety in HBV-infected mice and primary human hepatocytes, effectively activating innate immunity and significantly reducing HBV DNA levels [34]. Inarigivir is a retinoic acid-inducible gene I agonist that exhibits both immunomodulatory and direct antiviral effects against HBV. In a phase II study, treatment-naïve patients experienced significant reductions in HBV DNA and RNA levels after inarigivir therapy, with enhanced reductions in HBsAg observed after transitioning to NA therapy [35]. The Farnesoid X receptor is involved in the transcriptional regulation of HBV cccDNA. Its agonist, Vonafexor, demonstrated potential antiviral effects and favorable safety in a phase Ib clinical trial. Monotherapy with Vonafexor led to a significant reduction in the HBsAg concentration, and its combination with PEG-IFN-α 2a resulted in decreased levels of hepatitis B core-related antigen (HBcrAg) and pgRNA [36].

Toll-like receptor (TLR) agonists regulate the effects of immunotherapy by inducing the production of IFN, pro-inflammatory cytokines, and chemokines. Agonists of TLR1/2 and TLR3 have been shown to inhibit HBV replication in

primary human hepatocytes [37]. The TLR7 agonist GS-9620 (Vesatolimod) has demonstrated antiviral effects in animal models of hepatitis B. Although its combination with NAs can restore protective T cell immunity, it does not significantly impact HBsAg levels. Several other TLR7 agonists, such as RO7020531 and TQ-A3334, have shown good safety and tolerability, indicating their potential in the treatment of CHB [38]. In a recent phase II clinical trial, patients with NAs receiving the weekly dose of the TLR8 agonist Selgantolimod showed a significant decrease in HBsAg levels after 24 weeks, with 5% of patients achieving HBsAg loss and 16% achieving HBeAg loss [39]. The TLR8 agonists TQA3810 and HRS9950 have also entered phase I and II clinical trials. Emerging evidence suggests that dual-action TLR7/8 (R848) and TLR2/7 (CL413) agonists are superior to single-target agonists in suppressing HBV replication. This enhanced antiviral activity underscores the unique mechanistic advantages of multi-targeted TLR activation, which may synergistically activate multiple innate immune pathways [40].

Immune checkpoint inhibitors (ICIs), which represent a pivotal breakthrough in cancer immunotherapy, act via unique immunomodulatory mechanisms and show emerging potential in the treatment of chronic viral infections. Research has confirmed that in patients with cancer with baseline HBsAg levels of less than 100 IU/ml, ICIs may accelerate the serological clearance of HBsAg [41]. At a low-dose, the programmed death-1 (PD-1) inhibitor nivolumab, when combined with the therapeutic vaccine GS-4774, led to a certain degree of HBsAg decline [33]. Another PD-1 inhibitor, Cemiplimab, has also been investigated in clinical trials for its therapeutic effects on hepatitis B (NCT04046107). TQ-B2450 is a programmed cell death ligand 1(PD-L1) antibody, and in a phase II study, the combination of a NA with TQA3334 and TQB2450 significantly reduced HBsAg levels in patients with CHB while demonstrating a favorable safety profile. Furthermore, high-dose TQA3334 triple therapy resulted in a more pronounced reduction of HBsAg levels among patients (NCT04202653). Envafolimab is currently being evaluated in combination with NUCs, and after 24 weeks of treatment, 21.1% of patients successfully achieved HBsAg clearance [42]. Two additional PD-L1 inhibitor drugs, AB-101 and GS-4224, are currently being evaluated in clinical trials for the treatment of hepatitis B (NCT05960240 and ACTRN12618001957280, respectively).

Therapeutic vaccines harness the host's immunity to elicit an anti-HBV response, enhancing the immune response of HBV-specific T cells and B cells to achieve a functional cure. HB-110 is a DNA vaccine that induces specific immune responses targeting HBsAg, HBcAg, and Pol. Approximately 19% (5/27) of patients exhibited multifunctional specific CD8+T lymphocytes that secrete TNF, IFN-γ, and CD107 [43]. BRII-179 targets three HBV surface proteins: HBsAg, pre-S1, and pre-S2, and in phase II trials, more than 30% of patients treated with BRII-179 exhibited an anti-HBs response. In patients with CHB, the combination of BRII-179 and elebsiran induces significant HBV-specific B-cell and T-cell responses [44]. In another trial, patients treated with therapeutic vaccine GS-4774 exhibited a significant increase in the production of IFN-γ, TNF, and interleukin (IL)-2 by HBV-specific CD8+T cells compared to baseline. In contrast, no increase was observed in the control group, confirming that GS-4774 has a strong immunostimulatory effect on CD8+T cells. However, neither BRII-179 nor GS-4774 resulted in a significant reduction in HBsAg, indicating these drugs may need to be used in combination with other antiviral medications to achieve an enhanced antiviral immune response [45, 46]. VT-300, a therapeutic vaccine utilizing an adenovirus vector encoding HBV alongside a poxvirus, can induce CD8+T cells and reduce HBsAg levels in phase II studies, a promising immunotherapy [47].

Passive immunization using monoclonal antibodies represents a viable treatment strategy for hepatitis B. In a prospective study, the monoclonal antibody GC1102 (Lenvervimab) can reduce HBsAg levels, thereby achieving a favorable sustained virological response. In a phase I trial, patients who are HBeAg-positive received single and multiple doses of Lenvervimab at four different doses (80,000 IU, 120,000 IU, 180,000 IU, or 240,000 IU). Notably, 10.3% of patients who received multiple doses of Lenvervimab achieved

HBsAg clearance during the treatment period [48]. The drug is currently being tested in phase III clinical trials. In the VIR-3434-1002 trial, a randomized, double-blind, placebo-controlled phase I single ascending dose study, a single dose of monoclonal antibody tobevibart (VIR-3434) led to a reduction in HBsAg and HBV DNA levels among patients [49]. In a phase 1b trial of another monoclonal antibody drug, HT-102, the vast majority of patients experienced a rapid decline in HBsAg levels, with reductions exceeding 2log within 2 days (NCT06744686). KW027 specifically binds to and clears HBsAg, achieving a significant reduction in serum HBsAg levels. Currently, its safety, tolerability, and immunogenicity characteristics are being evaluated in phase I trials involving both healthy individuals and patients with CHB.

The clinical selection of immunomodulators must closely align with the characteristics of the patient's immune microenvironment. For example, TLR agonists operate through the reactivation of the innate immune system, making them more suitable for patients with low-level viremia in whom innate immune pathways are still reactivatable. In contrast, the core function of immune checkpoint inhibitors is to reverse HBV-specific T cell exhaustion, with their advantages more pronounced in patients with high antigen load but dysfunctional immune responses. This mechanistic difference dictates the specificity of treatment choices. Therefore, precise stratification based on the patient's viral antigen levels and intrahepatic immune characteristics is the key prerequisite for optimizing immunomodulator treatment strategies and improving clinical response rates. Overall, immunomodulators represent a core direction for achieving functional cure of hepatitis B. Patients with CHB commonly exhibit HBV-specific T-cell exhaustion. However, existing immunomodulators struggle to fully restore T-cell function, and clinical trial results have been unsatisfactory. Potential immune-related toxicities as well as individual variability can significantly influence outcomes. In the future, leveraging blood transcriptomics or intrahepatic immune cell profiling may help identify patients who are sensitive to immunotherapy. By advancing multi-target combination therapies and emerging technologies, a comprehensive treatment regimen centered on immunotherapy, in conjunction with antiviral drugs, can be established to ultimately achieve the dual goals of immune activation and viral clearance.

HBsAg inhibitors

Nucleic acid polymers (NAPs) can inhibit the entry of HBV subviral particles from hepatocytes into the circulation, thereby reducing HBsAg levels. In a phase II trial involving 40 patients, after 24 weeks of tenofovir application, PEG-IFN-α and REP 2139 or REP 2165 were added for an additional 48 weeks. At the end of the treatment, 87.5% of the patients had achieved an HBsAg reduction greater than 1.0 log10 IU/ml, 60% of the patients had HBsAg levels suppressed to < 0.05 IU/ml, and 39% of the patients met the criteria for functional cure for more than 24 weeks after the end of treatment [50]. S-antigen traffic-inhibiting oligonucleotide polymers (STOPs) represent a new class of oligonucleotides that are structurally similar to NAPs. Investigation of ALG-010133 has completed a phase 1 trial (NCT04485663) that demonstrated its favorable safety and tolerability in healthy volunteers. GST-HG131 is a novel inhibitor of HBsAg production that can induce the degradation of HBV-RNA, and an ongoing evaluation of its safety and efficacy in patients with CHB (NCT06263959) is being conducted [51]. Two additional potential drugs targeting HBsAg, GST-HG121 and LP-128, are currently undergoing testing in phase I studies (CTR20221651 and NCT05130567, respectively).

Similar to entry inhibitors, HBsAg inhibitors do not affect viral replication, resulting in limited therapeutic effects. Therefore, they must be used in combination with other medications to effectively block the viral life cycle through multiple pathways. Certain drugs interfere with host transmembrane transport proteins, which may lead to nonspecific liver damage or disrupt other hepatic metabolic functions. In the future, it is essential to develop drugs that very selectively target specific targets.

Others

Recent advancements in the field of biotechnology have enabled the application of emerging therapeutic approaches to hepatitis B treatment, such as gene editing technology, which offers a new direction for the functional cure of HBV infection by directly targeting the viral genome or host integration sites. Zinc-finger proteins can recognize and cleave specific DNA sequences through their zinc finger structures, primarily including zinc-finger antiviral protein and zinc-finger nuclease. In vitro experiments have demonstrated significant inhibition of HBV replication; however, in vivo experimental data are lacking [52]. Transcription activator-like effector nucleases (TALENs), derived from plant pathogenic bacteria, target the S gene of HBV to block the expression of viral envelope proteins and cleave HBV DNA through specific protein–DNA binding. Studies have shown that TALENs can effectively inhibit HBV replication, significantly reduce the levels of HBsAg and HBeAg in vivo, and are effective against different HBV genotypes. However, their efficacy is time-dependent, and their antiviral effects have varied across different studies. Targeting cccDNA also presents a challenge [53]. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 represents the third-generation gene editing technology, that allows the design of guide RNA to target conserved regions of the HBV genome, such as the S, C, and X genes, or cccDNA. This technology can effectively allow inhibition of HBV protein expression and reduction of levels of HBsAg, HBcAg, and cccDNA. The representative drug EBT-107 has demonstrated certain antiviral effects in both in vitro and in vivo experiments. Combining CRISPR/Cas9 with siRNA or other gene editing tools, such as APOBEC3B, can further enhance the elimination of cccDNA [6]. To date, relatively few clinical trials have evaluated gene editing technologies, and various factors contribute to the challenges faced in clinical application. Existing delivery vectors, such as AAV and lipid nanoparticles, struggle to efficiently target liver cells. Also, the gene editing process may inadvertently harm the host genome, increasing the risk of carcinogenesis. Additionally, it may provoke immune responses, raising a series of ethical concerns. The locked nucleic acid technology utilizes liver-targeting single-stranded oligodeoxyribonucleotides that are complementary to cccDNA-derived mRNA. RO7191863, a liver-targeting PD-L1 single-stranded oligonucleotide drug modified using this technology, was designed to treat hepatitis B by blocking the PD-1/PD-L1 pathway and has been tested in a phase II clinical trial (NCT04225715).

Engineered T cells represent an emerging therapeutic strategy that achieves genetic reprogramming via T-cell receptor gene transfer or the utilization of chimeric antigen receptor (CAR) T cells. This method generates functional T cells capable of eliminating HBV-infected hepatocytes and has demonstrated efficacy in inhibiting HBV replication both in vitro and in mouse models [5]. Based on this principle, the drug SCG101 has received approval for clinical testing and has demonstrated dual antiviral and antitumor activity in patients with advanced HBV-related HCC. Recent data presented at the 2025 EASL meeting indicated that all 17 patients treated with SCG101 experienced a significant reduction in HBsAg, with four cases achieving complete clearance and 47% of patients showing tumor regression.

Hepatitis D

HDV, a defective RNA virus requiring HBV coinfection for replication and propagation, exclusively infects individuals with concurrent or pre-existing hepatitis B. Epidemiological data indicate that 10.58% of HBsAg carriers are coinfected with HDV. This dual infection accelerates disease progression, leading to earlier development of hepatic fibrogenesis, a higher cirrhosis incidence, and an elevated risk of HCC compared to HBV monoinfection [54]. IFN-α remains the sole guideline-recommended therapy for hepatitis D, exerting partial suppression of HDV replication through immunomodulatory mechanisms. However, its clinical utility is constrained by suboptimal efficacy—less than 25% of treated patients achieve a sustained virologic response (SVR, defined as undetectable HDV RNA 24 weeks post-treatment)—and significant

adverse effects, necessitating novel therapeutic paradigms [55].

Entry inhibitors

Bulevirtide is a novel peptide derived from the preS1 region of the large envelope protein of both HBV and HDV. It was approved by the European Medicines Agency (EMA) in 2020 for the treatment of HDV infection. A phase II trial (MYR202) demonstrated that combination therapy with bulevirtide and TDF significantly reduced HDV DNA levels within 24 weeks, with patients exhibiting good tolerability. However, nearly all patients experienced a rebound in HDV RNA concentration following the discontinuation of bulevirtide treatment [32]. After 48 weeks of combination therapy with PEG-IFN-α 2a, 53% of patients in the bulevirtide 2 mg + PEG-IFN-α 2a group exhibited undetectable levels of HDV RNA at 24 weeks post-treatment. This outcome was significantly superior compared with that in the PEG-IFN-α 2a monotherapy group, in which 0% of cases had undetectable HDV RNA [56]. Similarly, another entry inhibitor, Hepalatide, is currently undergoing testing in phase II clinical trials to evaluate its efficacy and safety in the treatment of hepatitis D (NCT06505928). Ezetimibe is a cholesterol-lowering drug that inhibits NTCP. In a phase II trial, the treatment of patients with chronic hepatitis D using ezetimibe resulted in a 1-log reduction in viral load for 43% (18/42) of the patients who completed the 12-week treatment [57]. HH-003 has been shown to significantly reduce HDV RNA levels and normalization of ALT in patients with chronic HBV and HDV co-infection when administered at a dose of 20 mg/kg, thus providing a new treatment option for this patient population (NCT05674448). Another phase II clinical trial is currently assessing its efficacy (NCT05861674).

Assembly inhibitors

Lonafarnib is an orally administered farnesyltransferase inhibitor that inhibits viral assembly of HDV, resulting in dose-dependent reductions in HDV RNA levels in the serum of treated patients [58]. The LOWR-2 study evaluated the efficacy of lonafarnib or ritonavir, with or without PEG-IFN-α. The results indicated that at 24 weeks of treatment, patients receiving the regimen of 25/50 mg lonafarnib combined with 100 mg ritonavir and PEG-IFN-α achieved the highest viral response rate, with 89% (8/9) of patients exhibiting undetectable HDV RNA or a reduction of more than 2 log10 IU/ml from baseline [59].

HBsAg inhibitors

REP 2139 is a nucleic acid polymer that effectively inhibits the viral load in patients with HBV and HDV coinfection. In a phase 2 clinical trial of 12 patients with chronic hepatitis D, patients underwent 15 weeks of monotherapy with REP 2139, followed by 15 weeks of combination therapy with PEG-IFN-α, and then a subsequent 33 weeks of PEG-IFN-α monotherapy. The results indicated that at the conclusion of the treatment, nine patients had achieved undetectable levels of HDV RNA, and seven patients maintained these undetectable levels for 1 year post-treatment. Furthermore, these patients were monitored for 3.5 years, during which the seven patients who attained a virological response continued to exhibit undetectable HDV RNA levels, and no safety concerns were noted in any of the patients [60].

Others

HDV requires HBsAg to form infectious viral particles. The siRNA agent JNJ-3989 has been shown to reduce HBsAg levels in patients with CHB. In the REEF-D study (NCT04535544), JNJ-3989 resulted in a reduction of HBsAg and HDV DNA. A study of RNAi-based drug, VIR-2218, which reduces HBsAg and HDV RNA, is recruiting patients to evaluate the effect of VIR-2218 in combination with the monoclonal antibody VIR-3344 for treating HDV infection (NCT06903338). A phase II clinical study of the monoclonal antibody BJT-778, presented at the 2024 EASL conference, demonstrated potential in the treatment of chronic hepatitis D. In the 300-mg once-weekly subcutaneous injection group, 100% of patients achieved a virological response by week 28, with 50% having HDV

RNA levels below the detection limit by week 24 and 67% experiencing a return to normal ALT levels. In the 600-mg group, 80% of participants achieved a virological response by week 12, and all dosage levels exhibited safety profiles, with no serious adverse events reported.

The core challenges of HDV therapy lie in its dependence on HBV infection, immune tolerance, and limitations of existing pharmacological agents. Currently, the only approved combination therapy is bulevirtide combined with PEG-IFN-α; however, this regimen is poorly tolerated, with only a small proportion of patients completing the course. The high mutation rate of HDV RNA polymerase, which lacks proofreading capability, poses a risk for resistance during long-term monotherapy. Future efforts must focus on exploring novel agents that directly target HDV, designing multi-target combination strategies, and implementing interventions based on host factors. Additionally, enhancing resistance detection and managing HBV/HDV co-infection in a manner is crucial for achieving control of the viruses and thereby advancing towards the goal of cure or eradication.

Hepatitis C

HCV infection is one of the leading causes of liver cirrhosis and liver cancer worldwide. According to WHO estimates, approximately 50 million people globally have chronic HCV infection, with about 1 million new cases occurring annually [2]. The primary goal of treating HCV infection is to achieve a SVR. IFN and ribavirin were the initial treatment drugs used for hepatitis C; however, due to their low success rates and various adverse reactions, achieving a complete cure for hepatitis C proved challenging [61, 62].

Since 2013, the interferon-free direct-acting antiviral agent (DAA) regimen has revolutionized HCV treatment. In recent years, with the development and widespread application of DAAs, hepatitis C treatment has entered a new era, transitioning from 'disease control' to 'achieving a cure,' with the current cure rate elevated to approximately 95%. DAAs target critical points in the HCV life cycle, directly inhibiting viral replication. Based on their different target sites, they can be classified into non-structural protein 3/4A (NS3/4A) protease inhibitors, NS5A protein inhibitors, and NS5B polymerase inhibitors [63]. The latest third-generation DAAs offer significantly reduced side effects and drug interactions, shortened treatment durations, expanded genotype coverage, and consistently improved cure rates. The development of pan-genotypic DAAs represents a major breakthrough in the history of hepatitis C treatment, targeting multiple genotypes with SVR rates exceeding 95%, thus establishing them as the first-line treatment for hepatitis C. Glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are currently representative pan-genotypic DAAs, suitable for a broad range of patients who are HCV-infected, including those with cirrhosis who were previously difficult to treat and those who have previously experienced treatment failure [64].

Egypt is a representative of the application of DAAs for the elimination of hepatitis C. It was once one of the countries with the highest prevalence of HCV globally, with adult HCV seroprevalence rate exceeding 40% in 1996. To address the disease burden posed by hepatitis C, the Egyptian Ministry of Health established the National Committee for Control of Viral Hepatitis in 2006, which standardized syringe use and established specialized centers for hepatitis. Advent of DAAs marked a turning point in Egypt's HCV prevention and control efforts, as DAAs can cure various genotypes of HCV, particularly the predominant genotype 4 in Egypt. In 2014, Egypt became one of the first countries globally to introduce sofosbuvir, ensuring more patients could access treatment through drug price negotiations and local production. Furthermore, Egypt launched awareness campaigns to ensure every citizen had access to information on hepatitis C prevention and treatment, implementing a universal screening and treatment strategy [65]. After years of effort, incidence of hepatitis C has decreased from 300 per 100,000 to 9 per 100,000, achieving standards set by WHO by end of 2023, making Egypt first country in the world to receive "gold level" certification for Path to Elimination (PTE) of hepatitis C [66]. Egypt's practices in prevention and control of hepatitis C provide valuable experience

and replicable model for other countries with high HCV infection rates globally: by mobilizing public awareness campaigns to enhance public's understanding of hepatitis C and participation in prevention and control efforts; establishing comprehensive and cost-effective screening network to ensure early detection and diagnosis of patients with hepatitis C; utilizing effective and low-toxicity DAA drugs to lower treatment thresholds and simplify clinical processes, ensuring accessibility to treatment and adherence; while addressing both universal prevention and precision interventions for high-risk populations, thereby constructing comprehensive and multi-layered hepatitis C prevention and control system.

The current limitations primarily arise from inadequate screening and diagnostic tools for HCV infection, the economic burden associated with DAAs, and the potential for drug resistance. Future developments should focus on personalized treatment strategies targeting HCV infection to optimize therapeutic outcomes. Currently, no significant differences in the efficacy of DAAs have been observed based on gender or age. However, among injection drug users, the prevalence of HCV is higher in female patients than in male patients, while the treatment uptake rate is lower in female patients, highlighting the need for targeted interventions for this population. The safety and efficacy of DAA therapy in older patients are comparable to those in younger patients; however, comorbidities, such as chronic kidney disease, must be taken into consideration. Glecaprevir/pibrentasvir is the preferred treatment option for patients on dialysis. In chronic kidney disease patients receiving the sofosbuvir regimen, elevated levels of the metabolite GS-331007 have been linked to an increased risk of adverse events, although current trials assessing safety show the risk remains within acceptable limits. For patients with hepatitis C co-infected with HIV, it is crucial to coordinate the timing of antiretroviral therapy with DAAs to prevent potential drug interactions [67].

Bemnifosbuvir (BEM, AT-527) is a novel oral antiviral drug that is metabolized into AT-9010, an active guanosine triphosphate analog, which effectively and selectively inhibits multiple viral RNA polymerases, including the HCV NS5B polymerase. In vitro studies have shown that BEM is approximately 10× more potent than sofosbuvir in treating HCV [68]. Early clinical trials have demonstrated effective pan-genotypic antiviral activity in participants with chronic HCV infection [69]. A clinical study (NCT05904470) was conducted to evaluate the safety and efficacy of BEM and ruzasvir in patients with chronic HCV. Additionally, a phase III study (NCT06868264) is currently comparing the efficacy of the BEM-ruzasvir combination with that of the sofosbuvir–velpatasvir regimen.

Despite the significant advancements in the pharmacological treatment of HCV, the number of infected individuals continues to exceed that of cured patients each year. This discrepancy is attributed to the limited number of patients receiving DAA treatment and the occurrence of reinfection in some patients after achievement of a cure. Consequently, the development of a preventive vaccine has become a crucial strategy for the elimination of hepatitis C. The envelope glycoproteins E1 and E2 of HCV are the primary targets for neutralizing antibodies, and vaccines leverage B-cell immunity function by inducing neutralizing antibodies against E1 and E2. The recombinant E1/E2 glycoprotein vaccine has demonstrated protective potential in a chimpanzee model and exhibited good safety in phase I trials. It successfully induced cross-neutralizing antibodies against genotypes 1a, 1b, and 2a; however, only a small number of vaccinated individuals produced high-titer antibodies, and antibody levels declined over time [70]. In recent years, the development of a vaccine for the hepatitis C virus has made continuous progress through technological optimization. This has been achieved by focusing on E1/E2 antigens and T cell targets, as well as optimizing vectors and adjuvants to enhance immunogenicity [71].

T cell-based vaccines function by targeting HCV non-structural proteins (NS3-NS5), thereby activating CD4+ and CD8+ T-cell responses. Vaccines utilizing chimpanzee adenovirus (ChAd3) and modified vaccinia virus (MVA) as vectors can induce rapid and durable T-cell responses, reduce viral load, and delay

the progression to chronic infection. Clinical trials have demonstrated that such vaccines can induce HCV-specific T-cell proliferation and multifunctionality; however, they have not been able to completely prevent chronic infection. For instance, the ChAd3-NSmut/MVA-NSmut vaccine resulted in a reduction in peak HCV RNA levels among vaccinated individuals, yet 14% of the vaccinated group still developed chronic infection [72]. The development of HCV vaccines is highly challenging due to the virus's high variability and the complexity of immune protection mechanisms. Nevertheless, by targeting conserved epitopes, optimizing antigen delivery systems, and incorporating novel adjuvants, potential has been demonstrated in animal models and early clinical trials. Future efforts must further address challenges related to genotype coverage, immune response intensity, and production processes. In conjunction with global prevention and control needs, these efforts will facilitate the early application of preventive vaccines.

Hepatitis A and E

HAV and HEV are the predominant etiological agents responsible for acute viral hepatitis worldwide. Because HAV and HEV infections typically manifest as self-limiting illnesses, with most patients achieving spontaneous resolution within weeks through immune-mediated clearance, antiviral therapy is generally not required. Current clinical management focuses on symptomatic relief and supportive care [73]. Nevertheless, for high-risk populations such as pregnant women and immunocompromised individuals, these infections may precipitate acute liver failure or chronic sequelae, underscoring the need for continued development of targeted antiviral therapies.

Hepatitis A is the most common acute viral hepatitis. An estimated 100 million HAV infections and 1.5 million symptomatic cases occur yearly globally, causing 15,000–30,000 annual deaths. Two HAV vaccines are available: an inactivated one developed in the US and Europe, and a live attenuated vaccine used only in China, Bangladesh, Guatemala, the Philippines, Thailand, and India. The inactivated vaccine induces long-term immunity and is easily accessible, making it the most commonly used one currently [74, 75]. No specific treatment exists for hepatitis A. Experimental evidence shows that type I INFs (IFN-α/β) inhibit HAV replication in vitro, while in vivo studies demonstrate their potential to ameliorate hepatic function. Notably, type III INFs (IFN-λ) have comparable antiviral efficacy against HAV with less systemic toxicity than type I IFNs, making IFN-based therapies promising for severe HAV infections [76]. Repurposed antiviral agents for other viral hepatitides, such as sofosbuvir and amantadine, reduce HAV RNA levels in infected cell cultures in vitro [77, 78]. For acute HAV-induced hepatic injury, corticosteroid therapy is a potential intervention. A clinical study of pediatric fulminant with hepatitis A reported lower mortality after corticosteroid use, though controlled trials are needed for further validation [79]. Orally administered RG7834, a dihydroquinolizinone TENT4 inhibitor, blocks HAV replication and inhibits pathogenesis in murine hepatitis A models. However, significant toxicity in animal studies limits its clinical application. Therapeutic interventions using RG7834 or similar compounds with reduced toxicity may benefit patients with hepatitis A, though they have not yet been validated in clinical trials [80]. Recent investigations have identified heme oxygenase-1 (HO-1) as a potent suppressor of HAV replication in vitro. The HO-1 inducer hemin dose-dependently inhibits viral RNA and protein synthesis in infected hepatocytes, suggesting the potential as a novel host-directed antiviral strategy. These findings require further exploration in physiologically relevant models to assess translational feasibility.

Similar to that of hepatitis A, the treatment of hepatitis E is primarily supportive. Hecolin® is the world's first approved HEV vaccine, currently approved in China and Pakistan. In 2022, a large-scale vaccination campaign in South Sudan targeted 27,000 residents, effectively curbing the spread of the HEV epidemic. In a large Chinese randomized trial (NCT01014845), the vaccine demonstrated 100% efficacy after three doses. Upon evaluating long-term efficacy,

it maintained 86.8% effectiveness after 4.5 years [81]. However, this vaccine is not widely included in national immunization programs, leading to relatively low vaccination rates. It is also unapproved in other countries, with insufficient evidence for its efficacy in special populations. Future efforts should focus on targeted promotion among high-risk groups and larger-scale real-world studies globally. Furthermore, clinical investigations of alternative candidates are ongoing (NCT00287469, 2012L01657). For patients with specific conditions, such as immunosuppressed individuals with chronic infections, ribavirin may be a potential therapeutic agent. In acute hepatitis E and acute-on-chronic liver failure, ribavirin treatment normalizes liver enzymes and clears HEV RNA in patients who are infected [82]. In Mulder et al.'s study, ribavirin was given to 92 adult transplant recipients with chronic HEV infection, achieving a 60% sustained virological response after 3 months [83]. In hepatitis E cases for which ribavirin therapy fails, sofosbuvir represents a potential alternative. Biliotti et al. reported complete HEV clearance with sofosbuvir/ribavirin combination therapy in patients who are acutely infected [84]. INF-α is a potential therapeutic agent currently deemed suitable only for chronic HEV infection in patients with HIV or those who have undergone liver transplantation. However, data regarding its use to treat hepatitis E are limited, and its efficacy remains undetermined [73]. Additionally, 2′-C-methylguanosine inhibits the growth of HEV in cells and exhibits a synergistic effect with ribavirin and INF; however, its efficacy and safety in animal models and human trials have yet to be established [85]. Silvestrol, NITD008, and GPC-N114 all inhibit HEV replication in animal or in vitro studies, indicating their therapeutic potential but still requiring testing in human hepatitis E cases [86].

SUMMARY AND FUTURE DIRECTION

In the review, we provided a comprehensive overview of the advancements in pharmacological treatments for five types of viral hepatitis. Recent years have witnessed significant developments in drug formulations, which have expanded treatment options for patients, offering renewed hope for improved prognoses and potential cures for hepatitis. Nevertheless, numerous challenges persist in the management of viral hepatitis. Hepatitis A and E pose a risk of acute severe cases; however, only supportive treatments are currently available, with no specific antiviral drugs. The diagnostic rates for hepatitis C remain inadequate, and the cost of DAAs medications poses a difficulty for patients in low- to middle-income countries. Furthermore, the genetic diversity of the virus can lead to resistance against DAAs in certain patients. Treatment of HDV infection, which depends on replication of HBV, necessitates concurrent targeting of both viruses for effective treatment. The substantial population of patients with hepatitis B presents a challenge, as cccDNA remains persistently latent within the cell nucleus, complicating the elimination of treatment drugs. Chronic infections result in T-cell exhaustion, hindering the immune system's activation for viral clearance and contributing to the persistence of the virus. Additionally, individual patient variations, including age, sex, immune status, and comorbidities, can influence drug efficacy. Furthermore, most clinical trials to date have been phase I and II studies, which complicates the analysis of individual differences among patients and personalized treatment.

Despite achievements, research efforts to develop effective therapies must persist. Pan-viral therapies and pan-viral vaccines may represent research directions, while studies are needed to optimize delivery systems, reduce immunogenicity, and improve drug targeting. Another critical aspect is the development of precision diagnostic and monitoring methods to assess disease progression, which will facilitate early detection and timely intervention. Furthermore, evaluation of drug efficacy should not be limited to short-term improvements in liver function or biomarkers; long-term follow-up studies are crucial for assessing durability of treatment effects and preventing disease progression to cirrhosis and HCC [87]. For hepatitis A and E, research to develop antiviral drugs is crucial, along with efforts to study preventive vaccines and reinforce vaccination among

high-risk populations. For hepatitis C, pressing needs include further optimization of pan-genotypic DAAs and development of next-generation drugs effective against resistant mutations. Additionally, efforts should focus on simplifying treatment regimens to alleviate medication burden and expediting clinical application of HCV vaccines. For treatment of hepatitis B and D, it is essential to accelerate late-stage trials to verify long-term safety and durability of response rates to drugs, while expanding sample diversity and ensuring long-term follow-up. Moreover, promoting rapid translation of experimental drugs for clinical use is imperative. Furthermore, exploration of combination therapies that utilize drugs with different mechanisms should be pursued to achieve optimized treatment regimens. The future of viral hepatitis treatment will revolve around precise viral clearance, immune reconstruction, and global accessibility, and thus, it is necessary to optimize existing therapies and advance new technologies into clinical practice, toward ultimate goal of achieving global elimination of viral hepatitis through comprehensive vaccination and early intervention. Multiple stakeholders, including clinicians, basic researchers, and pharmaceutical companies, must work together to strengthen new drug research, public health, and patient management, through enhanced interdisciplinary collaboration and translation of innovative technologies, thereby contributing to global mission of eliminating viral hepatitis by 2030.

CONCLUSIONS

This review systematically outlines the current landscape of antiviral therapies for viral hepatitis, revealing the differential challenges and advancements associated with various virus types. Although breakthroughs in treatment represented by DAAs have rendered HCV infection a curable disease and provided a realistic pathway for elimination efforts, achieving a functional cure for HBV and effective control of HDV remains a core challenge in current research. Additionally, the lack of specific antiviral medications for HAV and HEV necessitates urgent solutions. The path to fundamental breakthroughs lies in a dual strategy targeting both the virus and the host: on one hand, it is essential to develop next-generation direct antiviral agents and explore optimal combination strategies to achieve deep suppression of viral replication and reservoirs; on the other hand, therapeutic regimens must be designed to precisely disrupt immune tolerance and rebuild effective immune surveillance. Concurrently, global screening, vaccination initiatives, and drug accessibility programs should be implemented, fostering interdisciplinary collaboration and innovative technology transfer to continuously advance and upgrade treatment strategies, ultimately alleviating the significant public health burden posed by viral hepatitis.

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Declarations

Conflict of interest. He-ming Sun, Xing-yu Wang, Hong-qin Xu and Yan-hang Gao have nothing to disclose.

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