

# World Journal of *Gastroenterology*

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## Update on the management and treatment of viral hepatitis

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### Abstract

This review aims to summarize the current evidence on the treatment of viral hepatitis, focusing on its clinical management. Also, future treatment options and areas of potential research interest are detailed. PubMed and Scopus databases were searched for primary studies published within the last ten years. Keywords included hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus, hepatitis D virus (HDV), hepatitis E virus, and treatment. Outcomes reported in the studies were summarized, tabulated, and synthesized. Significant advances in viral hepatitis treatment were accomplished, such as the advent of curative therapies for hepatitis C and the development and improvement of hepatitis A, hepatitis B, and hepatitis E vaccination. Drugs that cure hepatitis B, going beyond viral suppression, are so far unavailable; however, targeted antiviral drugs against HBV (immunomodulatory therapies and gene silencing technologies) are promising approaches to eradicating the virus. Ultimately, high vaccination coverage and large-scale test-and-treat programmes with high screening rates may eliminate viral hepatitis and mitigate their burden on health systems. The development of curative hepatitis C treatment renewed the enthusiasm for curing hepatitis B, albeit further investigation is required. Novel therapeutic options targeting HDV life cycle are currently under clinical investigation.

**Key Words:** Viral hepatitis; Hepatitis A virus; Hepatitis B virus; Hepatitis C virus; Hepatitis D virus; Hepatitis E virus

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**Core Tip:** Viral hepatitis is a major global public health problem due to the risk of progression to chronic hepatitis, cirrhosis, and hepatocellular carcinoma development. The clinical management and treatment of these infections have evolved over the last decade. Even though remarkable achievements have been accomplished, such as the development of curative hepatitis C treatment, drugs that cure hepatitis B are still missing. In addition, programmes to enhance viral hepatitis testing and treatment together with broad vaccination coverage are required. In this review, we summarize the current evidence on the treatment of viral hepatitis and detail future treatment options, and potential areas of research.

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## INTRODUCTION

Viral hepatitis is a major public health problem given that it can become chronic, and eventually lead to end-stage liver disease and/or hepatocellular carcinoma (HCC) development[1,2]. Consequently, viral hepatitis is one of the leading indications for liver transplantation and, thus, contributes to the discrepancy between donor organ supply and demand[3].

Whereas hepatitis A and E usually present with a self-limited course followed by complete recovery, hepatitis B and C often result in chronic infection and they are responsible for the most adverse consequences of this disease[4]. Worldwide, approximately 100 million people have the antibody against the hepatitis C virus (HCV) and 71 million present HCV viremia, according to the World Health Organization (WHO) [5]. In a multicentre international study, with the participation of 161 countries, the prevalence of the hepatitis B virus (HBV) surface antigen (HBsAg) was 3.61% [6]. Due to the high prevalence, WHO has set targets for eliminating hepatitis B and C by 2030. These targets include optimizing measures to prevent disease transmission and improving antiviral treatment offering[7]. In the last decade, rapid and significant advances in diagnosing and managing viral hepatitis have been made and have changed its treatment. Despite these advances, issues with screening, diagnosis, referral, and treatment of viral hepatitis still persist.

Therefore, due to the high prevalence of viral hepatitis and its serious consequences, research activity in this field has always been intense, and new and increasingly effective treatments have gradually emerged. This review aims to summarize the current evidence on the treatment of viral hepatitis, focusing on its clinical management. Also, future treatment options and areas of potential research interest are detailed.

## HEPATITIS A

Hepatitis A is caused by the hepatitis A virus (HAV), a ribonucleic acid (RNA) picornavirus. The virus is transmitted by the faecal-oral route and this is a major cause of acute viral hepatitis. Clinical manifestations range from asymptomatic infection to acute liver failure (ALF), occurring in less than 1% of cases, and there is no progression to chronic hepatitis[8]. Globally, an estimated 1.4 million cases of hepatitis A occur each year and 27731 deaths were registered in 2010[8]. This disease can occur sporadically or in an epidemic form and risk factors for transmission are mainly person-to-person contact related or *via* contaminated food or water[9,10].

Hepatic injury results from the host immune response to the HAV. Viral replication occurs in the hepatocyte cytoplasm and hepatocellular damage is caused by the destruction of infected cells mediated by human leukocyte antigen-restricted HAV-specific CD8<sup>+</sup> T lymphocytes and natural killer cells[8]. Exaggerated host response and marked reduction of circulation HAV RNA during acute infection are associated

with severe hepatitis. The development of symptomatic hepatitis is usually related to patient age as more than 70% of infected adults develop symptoms[8]. Full clinical and biochemical recovery is observed within two to three months in 85% of patients and complete recovery is observed by six months in nearly all patients[11]. The diagnosis is established by detection of serum immunoglobulin M antibody to HAV, which remains detectable for approximately three to six months. Serum immunoglobulin G antibodies appear early in the convalescent phase of the disease, remain detectable for decades, and are associated with lifelong protective immunity[8,11].

To date, there are no specific drugs against HAV infection available; thus, treatment consists mostly of supportive care[8,11]. Prevention of HAV infection includes vaccination, immune globulin, and attention to hygienic practices-handwashing, avoiding consumption of tap water and raw foods in areas with poor sanitation, and heating foods appropriately[12]. In summary, indications for vaccination include children aged 2-18 years who have not previously received hepatitis A vaccine, all persons aged more than one year infected with human immunodeficiency virus, and specific risk groups (individuals with chronic liver disease, travellers, men who have sex with men, *etc.*). Also, vaccination strategies may vary according to local public health policies in each country[8,12].

## HEPATITIS B

Although an effective preventive hepatitis B vaccine has existed for over 30 years, HBV infection is still a major cause of chronic liver disease worldwide[13]. HBV is a small deoxyribonucleic acid (DNA) virus of the Hepadnaviridae family. HBV infects hepatocytes and establishes its replication cycle *via* an RNA intermediate (through reverse transcription) and can integrate into the host genome, thus being able to persist in the nucleus of hepatocytes[13,14]. The viral envelope involves a nucleocapsid that contains a partially double-stranded and relaxed circular DNA genome (rcDNA)[15]. In the cytoplasm of infected hepatocytes, the nucleocapsid is transported to the nucleus and then the rcDNA is released and converted into a covalently closed circular DNA (cccDNA) by host factors, forming a stable minichromosome[15,16].

Chronic hepatitis B is a dynamic infectious disease with a pattern of progression strongly dependent on the interaction between the host immune response and the virus. Over two-thirds of patients with chronic hepatitis B are inactive carriers. They present a low viral replication rate and minimal or no liver necroinflammation, secondary to weak activation of the innate immunity and HBV-specific immunological response[17].

The definition of goals for HBV treatment is essential. A virological response during nucleos(t)ide analogue (NA) therapy is defined as a decrease in serum HBV DNA to undetectable levels by tests with a lower limit of detection of 10–20 IU/mL. If interferon (IFN) alpha is used for treatment, the virological response is defined as a serum level of HBV DNA below 2000 IU/mL, assessed at 6 mo after the start of treatment and at the end of the therapy[14]. The biochemical response is defined as the normalization of serum alanine aminotransferase. Biochemical response allied to a reduction in HBV viral load is an important goal to be achieved because they are both associated with a decreased risk of progression to cirrhosis and HCC[14,18].

Current key targets of HBV treatment are a functional cure and a complete or “sterilizing” cure[19,20]. A functional or partial cure is defined as a sustained loss of HBsAg with or without anti-HBs seroconversion, based on assays with a lower limit of HBsAg detection of 0.05 IU/mL. Complete cure is defined as the elimination of cccDNA together with sustained loss of HBsAg and undetectable serum HBV DNA[19,20]. Whilst liver biopsy is currently necessary to measure the intrahepatic activity of cccDNA, serum biomarkers that reflect this indicator have been examined for this purpose[21].

The persistence of cccDNA in the hepatocyte nucleus is the greatest therapeutic challenge in hepatitis B patient care. Even among patients who recover from acute infection, presenting HBsAg loss with HBsAg seroconversion, HBV may persist in a latent state. These patients are potentially at risk of reactivation if exposed to either cancer chemotherapy or immunosuppressive therapies (after transplantation, for example)[22,23].

Although lamivudine was used for many decades to treat chronic hepatitis B-due to its safety and low cost, the low genetic barrier and the risk of developing drug resistance resulted in this being a less effective therapy compared to other treatment agents. Currently, lamivudine therapy is reserved for specific situations, for example,

the unavailability of entecavir or tenofovir[24]. In addition, this treatment may still play a role in HIV-coinfected patients when used as part of an antiretroviral regimen [24].

The two formulations of IFN (conventional and pegylated) and five NAs [telbivudine, entecavir, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and besifovir dipivoxil] are antiviral agents used for chronic hepatitis B treatment. Albeit these drugs strongly suppress HBV replication, reduce the risk of cirrhosis, and prevent further disease progression, they are not curative and have no proved positive impact on the existing viral hepatocyte reservoir[24]. According to major hepatology societies, entecavir, TDF, TAF, and pegylated (Peg) IFN alpha are currently the first-line anti-HBV agents recommended for chronic hepatitis B treatment [25-27].

Over the last few years, TAF was developed as a safer alternative to TDF because the latter is associated with both proximal renal tubular dysfunction and low bone mineral density. Due to the pharmacological properties of TAF, far more active drug is delivered to target cells while much less is measurable in the bloodstream, reducing systemic toxicity[28,29]. These properties are especially beneficial for elderly patients, patients with renal dysfunction, or osteoporosis[26,28-30].

NAs and IFN have different modes of action as well as particular advantages and disadvantages. On the one hand, compared to NA, IFN has the advantages of being a treatment with a finite duration, absence of resistance, and a higher chance of off-treatment sustained virological response (SVR); as well as potentially offering a greater opportunity for sustained loss of HBsAg/anti-HBs seroconversion. Yet, IFN has the disadvantage of moderate antiviral effects, low tolerability, and an increased risk of adverse events[24,31]. On the other hand, compared to IFN, NA therapy has higher rates of undetectable serum HBV DNA and transaminase normalization after treatment, whilst requiring long-term therapy-hardly envisioning withdrawal-due to the high rate of disease recurrence after discontinuing the medication[19,20].

Importantly, proper patient selection for better clinical efficacy in HBV treatment with Peg-IFN alpha is essential. Female gender, young age, high level of transaminases, lower level of HBV DNA, high rate of liver inflammation on biopsy samples (at least METAVIR A2), HBV genotype A or B, and low viral load increase the chance of a more favourable response to treatment[19,20,24,31]. For patients treated with NA for a longer time without serum hepatitis B e antigen (HBeAg) seroconversion or loss of HBsAg, add-on or switch to Peg-IFN therapy is an option to enhance patient response, although a protocol for this has not been determined. Large randomized controlled trials are awaited to provide definitive evidence of these strategies[32-34].

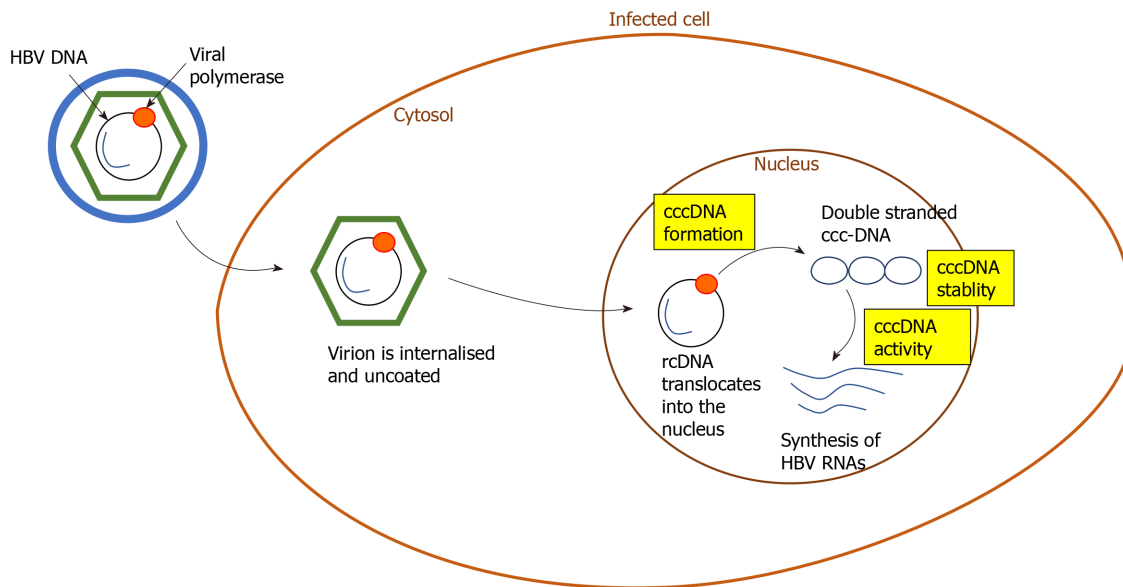
Elimination or inactivation of HBV cccDNA is the central focus of HBV research nowadays. Figure 1 illustrates treatment options that target cccDNA to attack HBV persistence, and these include interventions aiming to prevent cccDNA formation, affect its stability or even its activity. Although mechanistically these therapies would potentially offer a cure for the infection, further basic research and more detailed molecular studies are needed to evaluate the translational potential of novel antiviral strategies. New drugs that target HBV are required and immunomodulatory therapies and gene silencing technologies are the most promising approaches to eradicate HBV without killing the infected hepatocytes[17,21,35]. The advent of curative therapies for hepatitis C has renewed enthusiasm for also curing hepatitis B, going beyond viral suppression. Currently, there are numerous drugs under investigation to enable the cure of HBV infection[36]. In addition, efforts to increase hepatitis B vaccination coverage must be a priority.

## HEPATITIS C

The Nobel Prize in Physiology or Medicine in 2020 was awarded to three scientists, Harvey Alter, Michael Houghton, and Charles Rice, for their efforts on the identification of HCV[37]. The discovery of HCV was a remarkable achievement, which saved millions of lives. It enabled the development of highly sensitive diagnostic blood tests and the rapid expansion of the pool of antiviral drugs directed at hepatitis C. Approximately 71 million people worldwide live with HCV and nearly half of them are currently unaware due to suboptimal screening programmes[5].

Hepatitis C infection is a silent systemic disease secondary to a hepatotropic and lymphotropic virus with a high chronicity rate. It promotes chronic systemic inflammation due to direct and indirect viral activities, characterised by increased levels of pro-inflammatory cytokines and chemokines. Chronic systemic inflammation is a well-known risk factor for insulin resistance; thus, it increases the risk for type 2 diabetes





**Figure 1 Diagrammatic summary of the therapeutic options targeting covalently closed circular deoxyribonucleic acid to prevent hepatitis B virus persistence.** After entering the cell, the virion is uncoated and the relaxed circular deoxyribonucleic acid (DNA) genome (rcDNA) translocates into the cell nucleus. Once there, the covalently closed circular DNA (cccDNA) formed resides in the nucleus of infected cells as a minichromosome and originate the new viruses. Drugs that prevent cccDNA formation, that affect its stability, or even cccDNA activity must stop hepatitis B virus persistence. cccDNA: covalently closed circular deoxyribonucleic acid; HBV: Hepatitis B virus; RNA: Ribonucleic acid.

mellitus and, for cardiovascular events[38].

Hepatic manifestations include steatosis, fibrosis, and, finally, cirrhosis. The complications of cirrhosis and the occurrence of HCC compose the indications for liver transplantation in this disease[39]. Due to its lymphotropic property, HCV is able to multiply inside B lymphocytes and cause chronic stimulation of these cells by the viral infection. This stimulation possibly triggers autoimmune disorders, such as cryoglobulinemia vasculitis, purpura or necrotizing acrodermatitis, membranoproliferative glomerulonephritis, peripheral neuropathies, and polyarthritis[39,40]. Ultimately, B lymphocyte infection or chronic antigenic stimulation may be associated with lymphoma, mainly non-Hodgkin, splenic lymphoma type, or diffuse lymphomas[39, 40]. Thus, chronic hepatitis C can enter the consulting rooms of several medical specialties because it is a systemic disease with manifestations affecting different organs and systems.

In the last decades, there have been significant advances in the treatment of hepatitis C, which motivated the WHO in 2017 to set targets to eradicate HCV by 2030 [7]. For more than 20 years, IFN has been used to treat chronic HCV infection. Pegylation (Peg-IFN) allowed a reduction in the frequency of subcutaneous injections from three to once a week[41]. Whereas the combination of Peg-IFN with ribavirin significantly increased the effectiveness of the treatment, it was poorly tolerated and resulted in a cure rate of at most 50% in 24 to 48 wk[41,42].

In 2011, the first protease inhibitors (telaprevir and boceprevir) demonstrated significant benefits, but they were not well tolerated and resulted in a suboptimal cure rate. Later, the development of the first polymerase inhibitor (sofosbuvir) and the first inhibitor of nonstructural protein (NS) 5A (daclatasvir) changed hepatitis C history due to the excellent tolerance and a cure rate of approximately 95%[43].

Direct-acting antivirals (DAAs) are highly effective agents, regardless of genotype and high barrier to resistance, which revolutionized HCV treatment[44]. Multiple combinations of DAAs with high pangenotypic efficacy result in high SVR rates, excellent safety, and good tolerance, even for patients with advanced fibrosis and cirrhosis[44]. The strong antiviral potency of these pangenotypic treatments has withdrawn the factors of poor response and developed a 'simplified route', which allowed general practitioners to treat patients without hepatic comorbidity and liver dysfunction[45]. This HCV treatment decentralization strategy was shown to be effective and safe for most patients. For example, multiple combinations of drugs with high pangenotypic efficacy, easy to use (one to three capsules per day) for 8 to 12 wk provide a cure for the vast majority of patients; these include the combinations glecaprevir/pibrentasvir, sofosbuvir/velpatasvir with or without voxilaprevir[45,46].

Combinations of DAAs are also available for specific genotypes. For example, ledipasvir/sofosbuvir (Harvoni™, Gilead Sciences) is approved for genotypes 1, 4, 5, and 6; and elbasvir/grazoprevir (Zepatier™, Merck Sharp and Dohme) for genotypes 1 and 4[44,47-49].

Therapeutic failures occur in approximately 3%-5% of cases, secondary to non-adherence to treatment or drug resistance. Resistance-associated variants of HCV have been identified and they are mainly a consequence of mutations in the nonstructural proteins NS3 and especially NS5. Only in cases of therapeutic failure in the first regimen is it advisable to perform resistance genotyping[50].

Despite the existence of effective treatments, HCV still remains a threat to public health. Albeit differences between the effectiveness of the medicines in clinical trials and real-life being a contributing factor, the main challenges are the low awareness of the disease, lack of screening programs, loss of follow-up in health services, and high rate of reinfection in certain populations[51].

Extensive efforts are being made to create efficient HCV care programmes around the world, respecting the particularities of each country. Macro-elimination based on mass testing and treatment has started in several American and European countries. Other countries, aiming to improve the efficiency of the therapy and considering cost-effectiveness, have chosen to adopt micro-elimination, targeting smaller population groups at high risk of infection, such as those in hyper-endemic areas, prisons, and haemodialysis centres[52,53].

In the DAA era, optimisation of their use must be a top priority. Identifying factors predicting a high chance of SVR with an ultra-short DAA regimen could be of great value in the global goal of HCV eradication[54]. Also, specific care needs to be taken in the post-RVS phase: (1) surveillance every six months for both HCC and hepatic decompensation remains imperative in patients with advanced fibrosis, especially in those with comorbidities that increase the risk of fibrosis progression, such as obesity, diabetes mellitus, and alcohol abuse; (2) close monitoring of extrahepatic complications, such as cardiovascular diseases, diabetes, lymphoma, and cryoglobulinemia, the once beneficial effects of HCV elimination on these complications are not clear; and (3) annual screening for HCV reinfection, mainly for those at high risk, such as people who inject drugs and those in prisons[55,56]. Recent analyses investigated the effects of eliminating a long-term persistent infection on the immune system. Persistent HCV infection is known to cause profound changes in the immune system, which do not appear to be fully reversible after viral elimination[57].

It is expected that the efforts of several countries in extensive testing for HCV and the availability of oral treatments of acceptable cost and with few side effects will result in the successful elimination of HCV. Hopes for an eventual preventive HCV vaccine remain.

## HEPATITIS D

The hepatitis D virus (HDV) is a single-stranded circular RNA virus, first reported in 1977[58]. This is a defective virus, so HDV does not produce an envelope or capsid, requiring the use of HBV envelopes. Therefore, HBV infection is necessary for productive HDV infection in humans[58,59]. Although HDV infection is chronic in less than 5% of coinfecting patients in adulthood, chronic infection is more common in the neonatal period[60].

An estimated 15-20 million people are infected worldwide[60]. Due to the dependence of HDV on HBV, the presence of HBsAg is necessary for the diagnosis of HDV infection. Serum HDV RNA and the presence of serum delta antigen are useful for diagnosis[61,62]. HDV infection can be acute or chronic[60].

Acute HDV infection can occur through HBV coinfection (simultaneous infection with both viruses during the same exposure) or superinfection (HDV infection in an HBsAg-positive individual). The clinical course of an acute HDV/HBV coinfection resembles an acute HBV infection, but with an increased risk of ALF[60]. Characteristically, there is a biphasic course with two peaks of alanine aminotransferase, sometimes separated by weeks, since HBV infection must be established first to allow for subsequent HDV infection. Whereas acute HDV superinfection can be mistaken for an HBV flare in patients with previous HBV infection, in undiagnosed patients it can be misinterpreted as acute HBV infection[60,63]. Therefore, high suspicion of HDV infection is required in patients with identified risk factors, such as a history of intravenous drug use, high-risk sexual behaviour, first-degree relative infection, and immigration from HDV-endemic regions[63].

Chronic HDV/HBV coinfection commonly results in the most rapidly progressive form of hepatitis, with a higher likelihood of cirrhosis and its complications. Compared to HBV monoinfected patients, HDV/HBV coinfecting patients have a risk of HCC up to 3 times higher and that of liver decompensation up to 2 times higher[63, 64].

Although the guidelines recommend Peg-IFN alpha for the treatment of chronic HDV infection, this therapy is limited by poor tolerance. Also, it is usually avoided in patients with cirrhosis, active autoimmune disease, or certain psychiatric disorders[27, 63, 64].

Novel therapeutic options targeting HDV life cycle are currently under clinical investigation. HDV cell entry, replication, and viral assembly and release are targets for medications such as bulevirtide, telafarnibe, and REP3702139, respectively[65]. Among all the agents studied, bulevirtide (formerly known as Myrcludex-B) received conditional marketing authorization under the trade name Hepcludex® by the European Medicines Agency in 2020. The agency warns that administration should continue 'as long as the patient benefits' and until future clinical trial data indicate different therapeutic actions. Hepcludex® blocks the entry of viruses into hepatocytes and should be administered at a dose of 2 mg once daily by subcutaneous injection as monotherapy or co-administered with a nucleoside/nucleotide analogue for the treatment of underlying HBV infection. The ideal duration of treatment is unknown. Hepcludex® has also been tested in combination therapy with Peg-IFN[66].

Recently, Peg-IFN lambda has also been studied against HDV[65]. Despite having an antiviral effect equivalent to Peg-IFN alpha, patients had better tolerability to the drug[67]. The combination of Peg-IFN lambda and other drugs is also under clinical investigation[65].

## HEPATITIS E

Hepatitis E virus (HEV) is responsible for outbreaks in developing countries and zoonotic cases in both developing and developed countries, mainly transmitted enterically[68]. This virus is a member of the Hepeviridae family; within the genus Orthohepevirus, species Orthohepevirus A, which includes eight recognised HEV genotypes. Genotypes 1 and 2 HEV have only been detected in humans, and these infections frequently result in outbreaks of jaundice in areas traditionally considered endemic, which are resource-poor, where HEV is spread by the faecal-oral route often *via* contaminated water[68]. Other genotypes, including HEV3 and HEV4, have been detected in both humans and animals, with pigs being the main reservoir[68, 69].

Whilst most infections are acute and self-limiting or asymptomatic, there are situations wherein it can progress to ALF and even become chronic. Immunocompromised patients are at risk of developing chronic HEV infection, such as solid organ transplant recipients, patients with haematologic malignancy undergoing chemotherapy, and those with human immunodeficiency virus infection[68, 69]. Extrahepatic manifestations, mostly neurological and renal diseases, have also been described. Acute icteric hepatitis is a classic presentation that occurs in 5%–30% of infected patients. Pregnant women are particularly at risk and a large proportion of those in their second and third trimester of pregnancy can progress to ALF. Patients with underlying liver disease have a poor prognosis in developing and developed countries [68–70].

The mechanisms of pathogenesis appear to be substantially immune-mediated[71]. Several studies have suggested that the immune response, rather than viral damage to hepatocytes, may drive clinical manifestations of hepatitis E, including both self-limiting acute viral hepatitis and ALF. One of the reasons that pathogenesis may be mediated by the immune system rather than by the virus itself is that the onset of icteric symptoms typically coincides with a rise in antibodies and a decline in viral load[71]. Chronic HEV infections, which are rarely seen in otherwise healthy individuals, are increasingly being recognized in patients with impaired immune function[72].

Diagnostic assays with good sensitivity and specificity have only recently become commercially available. To facilitate global access to the tools necessary is vital to identify and respond to HEV infections, whether sporadic cases or nascent outbreaks. Clinical and field surveillance, coupled with laboratory investigations of viral strains isolated from human cases, will help advance our understanding of HEV genotypes' relative virulence, intergenotypic variation, and other features of the HEV global epidemiology[73].

There is no recommended treatment for acute HEV infections, which are usually self-limiting with spontaneous HEV clearance. Although a recent study suggested that ribavirin is effective in treating immunocompetent patients with severe hepatitis E, it is difficult to claim that the drug improved the course of the infection due to study limitations (*e.g.*, the absence of a control group)[74]. Sofosbuvir demonstrated antiviral activity against HEV *in vitro*, however, it had limited clinical efficacy. There are some studies on new anti-HEV drugs: NITD008, a broad-spectrum chain-terminating adenosine nucleoside analogue initially developed to treat the dengue virus; and GPC-N114, which binds to the RNA channels of picornavirus polymerases. These compounds are promising HEV antiviral candidates. Lastly, T cell therapy may be an alternative to conventional medicines[75,76].

Vaccines to combat HEV have been developed and tested, and one highly efficacious vaccine is now available to consumers in China[77]. Understanding the determinants of susceptibility and resistance to repeat infection and clinical disease is imperative. Identifying environmental factors, such as regional climatic patterns, water, and sanitation practices, farming, and food processing practices, which affect lifetime exposures to HEV may help both to explain regional differences in the age-specific incidence of the infection and the severity of the disease, which cannot be explained solely by genotypic variability. Identification of these determinants also may help to provide risk-based strategies for intervention.

## HURDLES AND OPPORTUNITIES IN VIRAL HEPATITIS TREATMENT

In the last decade, rapid and significant advances in diagnosing and managing viral hepatitis were made and changed its treatment. These advances include the development of DAAs for the treatment of chronic hepatitis caused by HCV[78]-with SVR rates greater than 95%, the improvement of HBV vaccination as well as enhancement of the immunogenicity of HBV vaccines[79,80], and the identification of antiviral therapies with low rates of viral resistance[27]. Table 1 summarises the current clinical management of viral hepatitis and areas of development for future treatments.

Immunomodulators have been investigated to strengthen the immune system to fight HBV. Medications that stimulate both innate and adaptive immune systems, overcome CD8+ T cell exhaustion by checkpoint blockade, and transfer HBV-specific engineered CD8+ T cells are some of the therapies under investigation[36]. Immunomodulators may present a future treatment to cure hepatitis B infection, even though further research is necessary for this treatment.

Acute hepatitis A and E, frequently self-limiting or asymptomatic, still have no treatment recommendations, although the development and enhancement of vaccines improved its prevention. A vaccine to combat HEV is already available and consistent indications for HAV vaccination are now defined[12,77,81].

Despite these advances, issues with screening, diagnosis, referral, and treatment of viral hepatitis still persist. Problems in accessing treatment are reported in the published literature and reinforce the need to establish appropriate public policies for patient referral[82]. In addition, the identification of patients with viral resistance to the new treatment regimens and those with a satisfactory viral response and liver fibrosis, who might need close monitoring, deserve further investigation[83].

## CONCLUSION

The treatment of viral hepatitis has evolved rapidly over the last decade with the remarkable introduction of curative therapies for hepatitis C. The development and improvement of HAV and HEV vaccination also constitute substantial advances in this field. Despite these advances, drugs that also cure hepatitis B, going beyond viral suppression, are so far not available. Targeted antiviral drugs against HBV are encouraging future treatments and immunomodulatory therapies and gene silencing technologies are the most promising approaches to eradicate the virus. The increase in the frequency of HDV cases leads to the development of targeted antiviral agents against HDV, currently under clinical investigation. Finally, optimal screening *via* extensive testing allied to broad vaccination and treatment coverage are fundamental goals to eliminate viral hepatitis and reduce the public health burden of these infections.



**Table 1** Current clinical management of viral hepatitis and areas of development for future therapies

Type	Current management	Areas of development
Hepatitis A	No specific drugs against HAV infection are available so far; thus treatment consists of supportive care; Prevention of HAV infection includes vaccination, immune globulin, and attention to hygienic practices	Public health campaigns to promote the prevention of hepatitis A; Raise awareness of indications for hepatitis A vaccination
Hepatitis B	Entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, and pegylated interferon alpha are currently the first-line anti-HBV agents recommended for chronic hepatitis B treatment; Prevention of HBV infection is focused on vaccination;	Elimination or inactivation of HBV cccDNA is the major focus of HBV research; Targeted therapies to HBV (immunomodulatory therapies and gene silencing technologies are promising approaches); Need to increase hepatitis B vaccination coverage
Hepatitis C	Multiple combinations of direct-acting antivirals with high pangenotypic efficacy result in high sustained virological response rates, excellent safety, and good tolerance, even for patients with advanced fibrosis and cirrhosis;	Increase awareness of the disease, develop screening programmes; Optimization of direct-acting antivirals use; Attention to specific care needs to be taken in the post-treatment phase
Hepatitis D	There are no satisfactory drugs for this disease; Pegylated interferon alpha recommended for the treatment of chronic HDV infection, although limited by poor tolerance is usually avoided in patients with cirrhosis, active autoimmune disease, or certain psychiatric disorders	Further research on novel targeted HDV antiviral medications is necessary due to the lack of effective therapeutic options
Hepatitis E	There is no recommended treatment for acute HEV infections because it is usually self-limiting with spontaneous HEV clearance	Ribavirin is suggested to be an effective treatment for immunocompetent patients with severe hepatitis E; New anti-HEV drugs are under investigation; T cell therapy may be an alternative to conventional medicines; Vaccines to combat HEV have been developed and tested

HAV: Hepatitis A virus; HBV: Hepatitis B virus; cccDNA: Covalently closed circular deoxyribonucleic acid; HDV: Hepatitis D virus; HEV: Hepatitis E virus.

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