**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 62614

**Manuscript Type:** MINIREVIEWS

**Update on the management and treatment of viral hepatitis**

Almeida PH *et al*. Update on viral hepatitis management

Patricia Holanda Almeida, Celso E L Matielo, Lilian A Curvelo, Rodrigo A Rocco, Guilherme Felga, Bianca Della Guardia, Yuri L Boteon

**Patricia Holanda Almeida, Celso E L Matielo, Lilian A Curvelo, Rodrigo A Rocco, Guilherme Felga, Bianca Della Guardia, Yuri L Boteon,** Liver Unit, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil

**Yuri L Boteon,** Instituto Israelita de Ensino e Pesquisa Albert Einstein, Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo 05652-900, Brazil

**Author contributions:** Boteon YL designed the study; Almeida PH, Matielo CEL, Curvelo LA, Felga G, Rocco RA, and Della Guardia B performed the literature review and analysis; Boteon YL, Almeida PH, Matielo CEL, and Curvelo LA drafted the manuscript; Boteon YL reviewed the manuscript critically; all authors contributed to editing and approved the final version of the manuscript.

**Corresponding author: Yuri L Boteon, MD, PhD, Doctor, Professor, Surgeon,** Liver Unit, Hospital Israelita Albert Einstein, Jardim Leonor, São Paulo 05652-900, Brazil. yurimed43@yahoo.com.br

**Received:** January 18, 2021

**Revised:** March 11, 2021

**Accepted:** April 21, 2021

**Published online:**

**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

Almeida PH, Matielo CEL, Curvelo LA, Rocco RA, Felga G, Della Guardia B, Boteon YL. Update on the management and treatment of viral hepatitis. *World J Gastroenterol* 2021; In press

**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.

**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+ 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 waited 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 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 coinfected 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 coinfected 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.

**ACKNOWLEDGEMENTS**

This paper presents independent research supported by the Brazilian Ministry of Health *via* the Support Program for Organizational Development of the SUS at the Hospital Israelita Albert Einstein. The views expressed are those of the author(s) and not necessarily those of the Ministry of Health, the PROADI-SUS, or the Hospital Israelita Albert Einstein. We are extremely grateful to the staff from the Hospital Israelita Albert Einstein and Hospital Municipal Vila Santa Catarina, whose continued support provides resources and intellectual input that is shaping the thoughts and future strategies for the continuing development of our research.

**REFERENCES**

1 **Ringelhan M**, McKeating JA, Protzer U. Viral hepatitis and liver cancer. *Philos Trans R Soc Lond B Biol Sci* 2017; **372**: 20160274 [PMID: 28893941 DOI: 10.1098/rstb.2016.0274]

2 **Ben Ari Z**, Weitzman E, Safran M. Oncogenic viruses and hepatocellular carcinoma. *Clin Liver Dis* 2015; **19**: 341-360 [PMID: 25921667 DOI: 10.1016/j.cld.2015.01.006]

3 **Santopaolo F**, Lenci I, Milana M, Manzia TM, Baiocchi L. Liver transplantation for hepatocellular carcinoma: Where do we stand? *World J Gastroenterol* 2019; **25**: 2591-2602 [PMID: 31210712 DOI: 10.3748/wjg.v25.i21.2591]

4 **Summerfield JA**. Virus hepatitis update. *J R Coll Physicians Lond* 2000; **34**: 381-385 [PMID: 11005078]

5 **World Health Organization.** WHO estimates of the prevalence and incidence of hepatitis C virus infection by WHO region, 2015. In: Global hepatitis report 2017 [cited 16 March 2021]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

6 **Schweitzer A**, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/S0140-6736(15)61412-X]

7 **World Health Organization.** Combating Hepatitis B and C to Reach Elimination by 2030: Advocacy Brief. WHO 2016 [cited 16 March 2021]. Available from: WHO\_HIV\_2016.04\_eng.pdf.

8 **Shin EC**, Jeong SH. Natural History, Clinical Manifestations, and Pathogenesis of Hepatitis A. *Cold Spring Harb Perspect Med* 2018; **8** [PMID: 29440324 DOI: 10.1101/cshperspect.a031708]

9 **Daniels D**, Grytdal S, Wasley A; Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ* 2009; **58**: 1-27 [PMID: 19478727]

10 **Foster MA**, Hofmeister MG, Kupronis BA, Lin Y, Xia GL, Yin S, Teshale E. Increase in Hepatitis A Virus Infections - United States, 2013-2018. *MMWR Morb Mortal Wkly Rep* 2019; **68**: 413-415 [PMID: 31071072 DOI: 10.15585/mmwr.mm6818a2]

11 **Matheny SC**, Kingery JE. Hepatitis A. *Am Fam Physician* 2012; **86**: 1027-34; quiz 1010-2 [PMID: 23198670]

12 **Nelson NP**, Weng MK, Hofmeister MG, Moore KL, Doshani M, Kamili S, Koneru A, Haber P, Hagan L, Romero JR, Schillie S, Harris AM. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep* 2020; **69**: 1-38 [PMID: 32614811 DOI: 10.15585/mmwr.rr6905a1]

13 **Nelson NP**, Easterbrook PJ, McMahon BJ. Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. *Clin Liver Dis* 2016; **20**: 607-628 [PMID: 27742003 DOI: 10.1016/j.cld.2016.06.006]

14 **Trépo C**, Chan HL, Lok A. Hepatitis B virus infection. *Lancet* 2014; **384**: 2053-2063 [PMID: 24954675 DOI: 10.1016/S0140-6736(14)60220-8]

15 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]

16 **Seeger C**, Mason WS. Molecular biology of hepatitis B virus infection. *Virology* 2015; **479-480**: 672-686 [PMID: 25759099 DOI: 10.1016/j.virol.2015.02.031]

17 **Shire NJ**. Cure Strategies for Hepatitis B Virus: The Promise of Immunotherapy. *Clin Pharmacol Drug Dev* 2017; **6**: 186-194 [PMID: 28263466 DOI: 10.1002/cpdd.317]

18 **Mendy ME**, Welzel T, Lesi OA, Hainaut P, Hall AJ, Kuniholm MH, McConkey S, Goedert JJ, Kaye S, Rowland-Jones S, Whittle H, Kirk GD. Hepatitis B viral load and risk for liver cirrhosis and hepatocellular carcinoma in The Gambia, West Africa. *J Viral Hepat* 2010; **17**: 115-122 [PMID: 19874478 DOI: 10.1111/j.1365-2893.2009.01168.x]

19 **Liaw YF**, Jia JD, Chan HL, Han KH, Tanwandee T, Chuang WL, Tan DM, Chen XY, Gane E, Piratvisuth T, Chen L, Xie Q, Sung JJ, Wat C, Bernaards C, Cui Y, Marcellin P. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. *Hepatology* 2011; **54**: 1591-1599 [PMID: 22045673 DOI: 10.1002/hep.24555]

20 **Wang YC**, Yang SS, Su CW, Wang YJ, Lee KC, Huo TI, Lin HC, Huang YH. Predictors of response to pegylated interferon in chronic hepatitis B: a real-world hospital-based analysis. *Sci Rep* 2016; **6**: 29605 [PMID: 27405043 DOI: 10.1038/srep29605]

21 **Yang HC**, Kao JH. Viral hepatitis. HBV cure--can we pin our hopes on immunotherapy? *Nat Rev Gastroenterol Hepatol* 2015; **12**: 129-131 [PMID: 25623202 DOI: 10.1038/nrgastro.2015.8]

22 **Voican CS**, Mir O, Loulergue P, Dhooge M, Brezault C, Dréanic J, Chaussade S, Pol S, Coriat R. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann Oncol* 2016; **27**: 2172-2184 [PMID: 27803003 DOI: 10.1093/annonc/mdw414]

23 **Seto WK**, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lau EHY, Cheung KS, Lie AKW, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in occult viral carriers undergoing hematopoietic stem cell transplantation: A prospective study. *Hepatology* 2017; **65**: 1451-1461 [PMID: 28027590 DOI: 10.1002/hep.29022]

24 **Yeh ML**, Huang JF, Dai CY, Yu ML, Chuang WL. Pharmacokinetics and pharmacodynamics of pegylated interferon for the treatment of hepatitis B. *Expert Opin Drug Metab Toxicol* 2019; **15**: 779-785 [PMID: 31593639 DOI: 10.1080/17425255.2019.1678584]

25 **Vittal A**, Ghany MG. WHO Guidelines for Prevention, Care and Treatment of Individuals Infected with HBV: A US Perspective. *Clin Liver Dis* 2019; **23**: 417-432 [PMID: 31266617 DOI: 10.1016/j.cld.2019.04.008]

26 **Terrault NA**, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; **63**: 261-283 [PMID: 26566064 DOI: 10.1002/hep.28156]

27 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

28 **Labarga P**, Barreiro P, Martin-Carbonero L, Rodriguez-Novoa S, Solera C, Medrano J, Rivas P, Albalater M, Blanco F, Moreno V, Vispo E, Soriano V. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. *AIDS* 2009; **23**: 689-696 [PMID: 19262355 DOI: 10.1097/QAD.0b013e3283262a64]

29 **Bedimo R**, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; **26**: 825-831 [PMID: 22301411 DOI: 10.1097/QAD.0b013e32835192ae]

30 **De Clercq E**. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). *Biochem Pharmacol* 2016; **119**: 1-7 [PMID: 27133890 DOI: 10.1016/j.bcp.2016.04.015]

31 **Buster EH**, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, Janssen HL. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology* 2009; **137**: 2002-2009 [PMID: 19737568 DOI: 10.1053/j.gastro.2009.08.061]

32 **Lampertico P**, Brunetto MR, Craxì A, Gaeta GB, Rizzetto M, Rozzi A, Colombo M; HERMES Study Group. Add-on peginterferon alfa-2a to nucleos(t)ide analogue therapy for Caucasian patients with hepatitis B 'e' antigen-negative chronic hepatitis B genotype D. *J Viral Hepat* 2019; **26**: 118-125 [PMID: 30187599 DOI: 10.1111/jvh.12999]

33 **Ning Q**, Han M, Sun Y, Jiang J, Tan D, Hou J, Tang H, Sheng J, Zhao M. Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: a randomised open-label trial (OSST trial). *J Hepatol* 2014; **61**: 777-784 [PMID: 24915612 DOI: 10.1016/j.jhep.2014.05.044]

34 **Matsumoto A**, Nishiguchi S, Enomoto H, Kang JH, Tanaka Y, Shinkai N, Kurosaki M, Enomoto M, Kanda T, Yokosuka O, Yatsuhashi H, Nagaoka S, Okuse C, Kagawa T, Mine T, Takaguchi K, Saito S, Hino K, Ikeda F, Sakisaka S, Morihara D, Miyase S, Tsuge M, Chayama K, Hiramatsu N, Suzuki Y, Murata K, Tanaka E. Combinational use of hepatitis B viral antigens predicts responses to nucleos(t)ide analogue/peg-interferon sequential therapy. *J Gastroenterol* 2018; **53**: 247-257 [PMID: 28634723 DOI: 10.1007/s00535-017-1360-z]

35 **Gane EJ**, Lim YS, Gordon SC, Visvanathan K, Sicard E, Fedorak RN, Roberts S, Massetto B, Ye Z, Pflanz S, Garrison KL, Gaggar A, Mani Subramanian G, McHutchison JG, Kottilil S, Freilich B, Coffin CS, Cheng W, Kim YJ. The oral toll-like receptor-7 agonist GS-9620 in patients with chronic hepatitis B virus infection. *J Hepatol* 2015; **63**: 320-328 [PMID: 25733157 DOI: 10.1016/j.jhep.2015.02.037]

36 **Binder B,** Hofmann M, Thimme R. Role of Immunomodulators in Functional Cure Strategies for HBV. *Curr Hepatology Rep* 2020; **19**: 337-44 [DOI: 10.1007/s11901-020-00538-6]

37 **Afdhal NH**. The natural history of hepatitis C. *Semin Liver Dis* 2004; **24** Suppl 2: 3-8 [PMID: 15346240 DOI: 10.1055/s-2004-832922]

38 **El-Serag HB**, Christie IC, Puenpatom A, Castillo D, Kanwal F, Kramer JR. The effects of sustained virological response to direct-acting anti-viral therapy on the risk of extrahepatic manifestations of hepatitis C infection. *Aliment Pharmacol Ther* 2019; **49**: 1442-1447 [PMID: 30932218 DOI: 10.1111/apt.15240]

39 **Pol S**, Vallet-Pichard A, Hermine O. Extrahepatic cancers and chronic HCV infection. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 283-290 [PMID: 29339810 DOI: 10.1038/nrgastro.2017.172]

40 **Cacoub P**, Desbois AC, Comarmond C, Saadoun D. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. *Gut* 2018; **67**: 2025-2034 [PMID: 29703790 DOI: 10.1136/gutjnl-2018-316234]

41 **McHutchison JG**, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**: 580-593 [PMID: 19625712 DOI: 10.1056/NEJMoa0808010]

42 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749 DOI: 10.1016/s0140-6736(01)06102-5]

43 **Gitto S**, Gamal N, Andreone P. NS5A inhibitors for the treatment of hepatitis C infection. *J Viral Hepat* 2017; **24**: 180-186 [PMID: 27925362 DOI: 10.1111/jvh.12657]

44 **Asselah T**, Boyer N, Saadoun D, Martinot-Peignoux M, Marcellin P. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. *Liver Int* 2016; **36** Suppl 1: 47-57 [PMID: 26725897 DOI: 10.1111/Liv.13027]

45 **Zeuzem S**, Foster GR, Wang S, Asatryan A, Gane E, Feld JJ, Asselah T, Bourlière M, Ruane PJ, Wedemeyer H, Pol S, Flisiak R, Poordad F, Chuang WL, Stedman CA, Flamm S, Kwo P, Dore GJ, Sepulveda-Arzola G, Roberts SK, Soto-Malave R, Kaita K, Puoti M, Vierling J, Tam E, Vargas HE, Bruck R, Fuster F, Paik SW, Felizarta F, Kort J, Fu B, Liu R, Ng TI, Pilot-Matias T, Lin CW, Trinh R, Mensa FJ. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *N Engl J Med* 2018; **378**: 354-369 [PMID: 29365309 DOI: 10.1056/NEJMoa1702417]

46 **Gane E**, Lawitz E, Pugatch D, Papatheodoridis G, Bräu N, Brown A, Pol S, Leroy V, Persico M, Moreno C, Colombo M, Yoshida EM, Nelson DR, Collins C, Lei Y, Kosloski M, Mensa FJ. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. *N Engl J Med* 2017; **377**: 1448-1455 [PMID: 29020583 DOI: 10.1056/NEJMoa1704053]

47 **Karaoui LR**, Mansour H, Chahine EB. Elbasvir-grazoprevir: A new direct-acting antiviral combination for hepatitis C. *Am J Health Syst Pharm* 2017; **74**: 1533-1540 [PMID: 28947524 DOI: 10.2146/ajhp160558]

48 **Keating GM**. Ombitasvir/Paritaprevir/Ritonavir: A Review in Chronic HCV Genotype 4 Infection. *Drugs* 2016; **76**: 1203-1211 [PMID: 27401997 DOI: 10.1007/s40265-016-0612-1]

49 **Sandmann L**, Schulte B, Manns MP, Maasoumy B. Treatment of Chronic Hepatitis C: Efficacy, Side Effects and Complications. *Visc Med* 2019; **35**: 161-170 [PMID: 31367613 DOI: 10.1159/000500963]

50 **Liang TJ**, Ghany MG. Therapy of hepatitis C--back to the future. *N Engl J Med* 2014; **370**: 2043-2047 [PMID: 24795199 DOI: 10.1056/NEJMe1403619]

51 **Thursz M**, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 28-35 [PMID: 24080775 DOI: 10.1038/nrgastro.2013.179]

52 **Huang CF**, Chiu YW, Yu ML. Patient-centered outreach treatment toward micro-elimination of hepatitis C virus infection in hemodialysis patients. *Kidney Int* 2020; **97**: 421 [PMID: 31980077 DOI: 10.1016/j.kint.2019.10.030]

53 **Yang TH**, Fang YJ, Hsu SJ, Lee JY, Chiu MC, Yu JJ, Kuo CC, Chen CH. Microelimination of Chronic Hepatitis C by Universal Screening Plus Direct-Acting Antivirals for Incarcerated Persons in Taiwan. *Open Forum Infect Dis* 2020; **7**: ofaa301 [PMID: 32818142 DOI: 10.1093/ofid/ofaa301]

54 **Volpicelli L**, Biliotti E, Milito C, Cruciata A, Spaziante M, Rivano Capparuccia M, Taliani G, Mezzaroma I. Glecaprevir/pibrentasvir ultra-short treatment to cure HCV infection: case report and literature review. *Infez Med* 2020; **28**: 616-620 [PMID: 33257639]

55 **Huang CF**, Dai CY, Yeh ML, Huang CI, Lee HC, Lai WT, Liang PC, Lin YH, Hsieh MY, Hou NJ, Lin ZY, Chen SC, Huang JF, Chuang WL, Yu ML. Cure or curd: Modification of lipid profiles and cardio-cerebrovascular events after hepatitis C virus eradication. *Kaohsiung J Med Sci* 2020; **36**: 920-928 [PMID: 32643842 DOI: 10.1002/kjm2.12275]

56 **Muzica CM**, Stanciu C, Huiban L, Singeap AM, Sfarti C, Zenovia S, Cojocariu C, Trifan A. Hepatocellular carcinoma after direct-acting antiviral hepatitis C virus therapy: A debate near the end. *World J Gastroenterol* 2020; **26**: 6770-6781 [PMID: 33268960 DOI: 10.3748/wjg.v26.i43.6770]

57 **Hensel N**, Gu Z, Sagar, Wieland D, Jechow K, Kemming J, Llewellyn-Lacey S, Gostick E, Sogukpinar O, Emmerich F, Price DA, Bengsch B, Boettler T, Neumann-Haefelin C, Eils R, Conrad C, Bartenschlager R, Grün D, Ishaque N, Thimme R, Hofmann M. Memory-like HCV-specific CD8+ T cells retain a molecular scar after cure of chronic HCV infection. *Nat Immunol* 2021; **22**: 229-239 [PMID: 33398179 DOI: 10.1038/s41590-020-00817-w]

58 **Rizzetto M**, Hoyer B, Canese MG, Shih JW, Purcell RH, Gerin JL. delta Agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees. *Proc Natl Acad Sci U S A* 1980; **77**: 6124-6128 [PMID: 6934539 DOI: 10.1073/pnas.77.10.6124]

59 **Bonino F**, Hoyer B, Shih JW, Rizzetto M, Purcell RH, Gerin JL. Delta hepatitis agent: structural and antigenic properties of the delta-associated particle. *Infect Immun* 1984; **43**: 1000-1005 [PMID: 6698598 DOI: 10.1128/IAI.43.3.1000-1005.1984]

60 **Noureddin M**, Gish R. Hepatitis delta: epidemiology, diagnosis and management 36 years after discovery. *Curr Gastroenterol Rep* 2014; **16**: 365 [PMID: 24293018 DOI: 10.1007/s11894-013-0365-x]

61 **Safaie P**, Razeghi S, Rouster SD, Privitera I, Sherman KE. Hepatitis D diagnostics:Utilization and testing in the United States. *Virus Res* 2018; **250**: 114-117 [PMID: 29596839 DOI: 10.1016/j.virusres.2018.03.013]

62 **Kucirka LM**, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS, Kirk GD, Segev DL, Nelson KE, Marks M, Heller T, Golub ET. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. *J Infect Dis* 2010; **202**: 845-852 [PMID: 20701536 DOI: 10.1086/655808]

63 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu.**; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

64 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

65 **Mentha N**, Clément S, Negro F, Alfaiate D. A review on hepatitis D: From virology to new therapies. *J Adv Res* 2019; **17**: 3-15 [PMID: 31193285 DOI: 10.1016/j.jare.2019.03.009]

66 **Rizzetto M**, Hamid S, Negro F. The changing context of hepatitis D. *J Hepatol* 2021 [PMID: 33484770 DOI: 10.1016/j.jhep.2021.01.014]

67 **Chan HLY**, Ahn SH, Chang TT, Peng CY, Wong D, Coffin CS, Lim SG, Chen PJ, Janssen HLA, Marcellin P, Serfaty L, Zeuzem S, Cohen D, Critelli L, Xu D, Wind-Rotolo M, Cooney E; LIRA-B Study Team. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B). *J Hepatol* 2016; **64**: 1011-1019 [PMID: 26739688 DOI: 10.1016/j.jhep.2015.12.018]

68 **Kamar N**, Izopet J, Pavio N, Aggarwal R, Labrique A, Wedemeyer H, Dalton HR. Hepatitis E virus infection. *Nat Rev Dis Primers* 2017; **3**: 17086 [PMID: 29154369 DOI: 10.1038/nrdp.2017.86]

69 **Wedemeyer H**, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. *Gastroenterology* 2012; **142**: 1388-1397.e1 [PMID: 22537448 DOI: 10.1053/j.gastro.2012.02.014]

70 **Dalton HR**, Hazeldine S, Banks M, Ijaz S, Bendall R. Locally acquired hepatitis E in chronic liver disease. *Lancet* 2007; **369**: 1260 [PMID: 17434400 DOI: 10.1016/S0140-6736(07)60595-9]

71 **Zhang JZ**, Im SW, Lau SH, Chau TN, Lai ST, Ng SP, Peiris M, Tse C, Ng TK, Ng MH. Occurrence of hepatitis E virus IgM, low avidity IgG serum antibodies, and viremia in sporadic cases of non-A, -B, and -C acute hepatitis. *J Med Virol* 2002; **66**: 40-48 [PMID: 11748657 DOI: 10.1002/jmv.2109]

72 **Lhomme S**, Marion O, Abravanel F, Izopet J, Kamar N. Clinical Manifestations, Pathogenesis and Treatment of Hepatitis E Virus Infections. *J Clin Med* 2020; **9** [PMID: 31991629 DOI: 10.3390/jcm9020331]

73 **Krain LJ**, Nelson KE, Labrique AB. Host immune status and response to hepatitis E virus infection. *Clin Microbiol Rev* 2014; **27**: 139-165 [PMID: 24396140 DOI: 10.1128/CMR.00062-13]

74 **Péron JM**, Dalton H, Izopet J, Kamar N. Acute autochthonous hepatitis E in western patients with underlying chronic liver disease: a role for ribavirin? *J Hepatol* 2011; **54**: 1323-4; author reply 1324-5 [PMID: 21281681 DOI: 10.1016/j.jhep.2011.01.009]

75 **Netzler NE**, Enosi Tuipulotu D, Vasudevan SG, Mackenzie JM, White PA. Antiviral Candidates for Treating Hepatitis E Virus Infection. *Antimicrob Agents Chemother* 2019; **63** [PMID: 30885901 DOI: 10.1128/AAC.00003-19]

76 **Nishiyama T**, Kobayashi T, Jirintai S, Kii I, Nagashima S, Prathiwi Primadharsini P, Nishizawa T, Okamoto H. Screening of novel drugs for inhibiting hepatitis E virus replication. *J Virol Methods* 2019; **270**: 1-11 [PMID: 31004661 DOI: 10.1016/j.jviromet.2019.04.017]

77 **Huang WJ**, Zhang HY, Harrison TJ, Lan HY, Huang GY, Wang YC. Immunogenicity and protective efficacy in rhesus monkeys of a recombinant ORF2 protein from hepatitis E virus genotype 4. *Arch Virol* 2009; **154**: 481-488 [PMID: 19240977 DOI: 10.1007/s00705-009-0335-7]

78 **AASLD/IDSA HCV Guidance Panel.**. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; **62**: 932-954 [PMID: 26111063 DOI: 10.1002/hep.27950]

79 **Chang MH**, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, Wu SF, Lee CM, Yang SS, Chu HC, Wang TE, Chen BW, Chuang WL, Soon MS, Lin CY, Chiou ST, Kuo HS, Chen DS; Taiwan Hepatoma Study Group. Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. *Gastroenterology* 2016; **151**: 472-480.e1 [PMID: 27269245 DOI: 10.1053/j.gastro.2016.05.048]

80 **Heyward WL**, Kyle M, Blumenau J, Davis M, Reisinger K, Kabongo ML, Bennett S, Janssen RS, Namini H, Martin JT. Immunogenicity and safety of an investigational hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40-70 years of age. *Vaccine* 2013; **31**: 5300-5305 [PMID: 23727002 DOI: 10.1016/j.vaccine.2013.05.068]

81 **Shrestha MP**, Scott RM, Joshi DM, Mammen MP Jr, Thapa GB, Thapa N, Myint KS, Fourneau M, Kuschner RA, Shrestha SK, David MP, Seriwatana J, Vaughn DW, Safary A, Endy TP, Innis BL. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007; **356**: 895-903 [PMID: 17329696 DOI: 10.1056/NEJMoa061847]

82 **Rege S,** Gonzalez YS, Marx S, Reau N. 964 Patient Flow Across Physician Specialties Over the Course of the Hepatitis C Care Cascade: A Real World Analysis From the United States. *Am J Gastroenterol* 2019; **114** [DOI: 10.14309/01.ajg.0000593392.14697.54]

83 **Farhang Zangneh H**, Wong WWL, Sander B, Bell CM, Mumtaz K, Kowgier M, van der Meer AJ, Cleary SP, Janssen HLA, Chan KKW, Feld JJ. Cost Effectiveness of Hepatocellular Carcinoma Surveillance After a Sustained Virologic Response to Therapy in Patients With Hepatitis C Virus Infection and Advanced Fibrosis. *Clin Gastroenterol Hepatol* 2019; **17**: 1840-1849.e16 [PMID: 30580095 DOI: 10.1016/j.cgh.2018.12.018]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to disclose.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** International Liver Transplantation Society; Associação Brasileira de Transplante de Órgãos; American College of Surgeons; and The Transplantation Society.

**Peer-review started:** January 18, 2021

**First decision:** February 23, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Brazil

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Akbulut S, Bader El Din NG, Niu ZS, Sporea I **S-Editor:** Zhang L **L-Editor:** Webster JR **P-Editor:**

**Figure Legends**



**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.

**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.