Received: 28 September 2021 | Accepted: 20 June 2022

DOI: 10.1111/liv.15345

Liver INTERNATIONAL WILEY

REVIEW

Treatment of hepatitis delta and HIV infection

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Handling Editor: Luca Velenti

Abstract

Hepatitis delta virus (HDV) is a defective agent that only infects individuals with hepatitis B virus (HBV). Around 5–10% of chronic hepatitis B patients worldwide are superinfected with HDV, which means 15–25 million people. Hepatitis delta is the most severe of all chronic viral hepatitis, leading to cirrhosis, liver cancer and/or transplantation in most patients. Despite it, many HDV patients remain undiagnosed. The only treatment available until recently was peginterferon alfa, with poor results and significant side effects. The recent approval of bulevirtide, a lipopeptide that blocks HBV/HDV entry, has revolutionized the field. Another drug, lonafarnib, already approved to treat progeria, is expected to be available soon as HDV therapy. Since there is no cell reservoir for the HDV RNA genome, hypothetically viral clearance could be achieved if complete blocking of viral replication occurs for a minimum time frame. This is what happens in hepatitis C using direct-acting antivirals, with the achievement of cure in nearly all treated patients. We envision the cure of hepatitis delta using combination antiviral therapy. Given that sexual and parenteral transmission routes are the most frequent for the acquisition of HBV and HDV, shared with HIV infection and HBV/HDV and HIV coinfection. The clinical outcome of hepatitis delta is worst in the HIV setting, with more frequent liver complications. Since most persons infected with HIV are on regular health care follow-up, we propose that HIV-HDV patients should be prioritized for moving forward new and potentially curative treatments for hepatitis delta.

KEYWORDS
bulevirtide, coinfection, combination therapy, cure, hepatitis delta, HIV, lonafarnib, ultra-long acting antivirals

1 | THE GLOBAL BURDEN OF CHRONIC VIRAL HEPATITIS AND HIV INFECTION

Viral hepatitis is among the top four global causes of mortality because of infectious diseases alongside tuberculosis, malaria and HIV. However, whereas annual deaths are declining for the latest conditions, mortality is on the rise for viral hepatitis.[1,2]

Chronic viral hepatitis is the leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation worldwide.[2,3] Three viruses are largely responsible, named B, C and D. Chronic hepatitis B virus (HBV) infection occurs in over 290 million people.[4] Current estimates for chronic hepatitis C virus (HCV) infection are of 58 million people.[5] Finally, global figures for chronic hepatitis delta virus (HDV) infection range from 12 to 60 million.[6]

In comparison, the number of persons living with HIV worldwide is of 40 million people.[7] Of note, given the shared transmission routes -mainly sexual and parenteral-, coinfection between all these viruses is common[8] (Figure 1). In Europe, roughly 15% of serum HBsAg+

individuals with HIV infection are anti-HDV-positive.[9] Interestingly, the largest population groups with HDV infection have changed during the last decades. Injection drug users predominated in the 80s, immigrants/refugees from HDV endemic regions became more prevalent later, and nowadays hepatitis delta is frequently diagnosed in persons engaged in sex with drugs ('slamming').[10]

Medical interventions for viral hepatitis rely on vaccines and antivirals. The advent of direct-acting antivirals that cure hepatitis C has revolutionized the field.[5] However, the situation is different for hepatitis B and D, which together represent the 7th cause of mortality worldwide.[1–3] Whereas a vaccine has existed to prevent HBV infection for over 25 years, and several antivirals (tenofovir, entecavir, etc.) suppress HBV replication in most chronic carriers, HBV eradication is not feasible with these medications and therefore HBV treatment needs to be lifelong.[11]

No effective treatment has been available for hepatitis delta until now, despite HDV causing the most severe form of viral hepatitis, with progression to cirrhosis and liver cancer in more than half of infected patients.[6] Only recently, a viral entry inhibitor, bulevirtide, was approved as HDV therapy.[6] Another promising medication is lonafarnib, a drug already marketed for progeria, a rare human genetic disease. Lonafarnib is expected to be approved soon as HDV therapy.[6,12,13]

Spurred by the recent development of curative new antivirals for hepatitis C and expanding access to hepatitis B vaccination, the WHO has committed to eliminating viral hepatitis as a public health threat by 2030.[14] At this time, hepatitis delta is the largest unmet need in the viral hepatitis field.[15] Its unique biological dependence of hepatitis B explains that many researchers are reluctant to consider a cure for hepatitis delta without achieving at least a 'functional' cure for hepatitis B.[12]

In this review, we defend that new therapies for hepatitis delta should prioritize the HIV population. There are three major reasons for it. First, hepatitis delta is a neglected disease that often runs undiagnosed, since the exclusion of HDV superinfection is often forgotten in HBsAg+ patients. However, HDV misdiagnosis is less frequent in the HIV population and HDV testing can easily be ruled out in patients periodically attending HIV clinics. Second, the progression of liver disease occurs more rapidly in the HIV setting and therefore coinfected individuals are in more urgent need for HDV therapy. Third, good drug adherence to medications is crucial for drawing the maximal benefit of antiviral therapy, and HIV patients are already well trained with antiretroviral drugs.

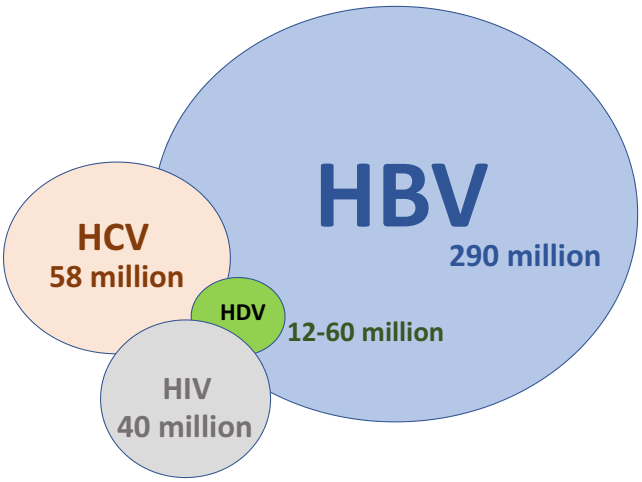


FIGURE 1 Global population with chronic viral hepatitis and HIV infection.

Keypoints

- Hepatitis delta is the most severe form of chronic viral hepatitis, frequently leading to cirrhosis and liver cancer. Clinical outcomes are worst in HIV-coinfected patients.
- The advent of new antivirals has revolutionized the HDV field. Given the lack of integration of the HDV genome into infected hepatocytes, the combination of HDV drugs might cure hepatitis delta.
- Treatment of hepatitis delta in HIV patients should be prioritized. This population is already well trained in good drug adherence and periodic attendance to clinics.
- The widespread use of tenofovir as anti-HIV agent has reduced HDV transmissions. However, the increased use of mono and dual antiretroviral regimens sparing tenofovir might revert this protective benefit.

Lay Summary

The hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis. In the absence of treatment, these patients will go to develop liver cirrhosis and liver cancer. In contrast with hepatitis B and C, no good therapy exists for hepatitis delta patients. Herein, we describe advances in antivirals against HDV and strategies to achieve a curative treatment using a combination of antivirals and modified drugs with prolonged activity.

2 | HEPATITIS B DESPITE VACCINES AND ANTIVIRALS

HBV is a DNA virus that primarily infects human hepatocytes. The sodium taurocholate cotransporting polypeptide (NTCP) is the cell receptor that binds to the HBV surface antigen (HBsAg). Following acute HBV exposure in adults, immunity generally controls virus replication and expression, clearing the virus from the bloodstream, and evoking markers of an immune response (anti-HBc and anti-HBs). However, the virus is not eliminated and the HBV genome universally remains in a small proportion of hepatocytes, as a sign of past infection. It reactivates occasionally causing hepatitis B flare-ups.

Since the human population is ageing, with increasing rates of cancers and the use of immunosuppressive therapies, HBV reactivation is emerging as a global medical threat.[16,17]

Globally, two billion people have been exposed to HBV and exhibit serological markers of past infection.[3] Around 290 million suffer from chronic hepatitis B, defined as the persistence of serum HBsAg+ for longer than 6 months (Figure 2).[3,4,11] All individuals chronically infected with HBV are at increased risk for developing cirrhosis and liver cancer.[11] The advent of safer and more efficacious HBV antivirals has expanded the indication for treating almost all chronic HBV carriers.[18,19] A major challenge, however, is keeping patients on good daily drug adherence for years.

The current antiviral treatment of chronic hepatitis B uses either **tenofovir** or entecavir, administered each as one oral pill once daily. Both drugs are highly efficacious and depict high barrier to resistance, although persons who had been exposed to lamivudine may fail more frequently on **entecavir**.[11] New antiviral drugs are in development,[20] with the aim of achieving the loss of serum HBsAg+ ('functional cure').[12] At this time, a definitive HBV cure, as a result of clearance of the HBV genome reservoir, the HBV cccDNA, remains unachievable.

3 | HEPATITIS DELTA – HARMFUL BUT CURABLE

HDV is a **defective (satellite) subviral agent** with a circular RNA coated by an external lipid layer in which the HBsAg from HBV is the envelope protein. In contrast with the HBV replication cycle, there is no chromosomal integration nor episomal reservoir for the HDV genome within infected hepatocytes.[6,21] In this way, HDV resembles more HCV and stopping replication with drugs for a minimum time frame could hypothetically be followed by viral extinction within the infected cells.[22]

Chronic hepatitis delta may progress to liver cirrhosis in half of the patients within 5 years on average. This is faster than what is seen with chronic hepatitis B or C. Accordingly, hepatitis D is associated with a higher incidence of decompensated liver disease, hepatocellular carcinoma and liver-related death.[23] Globally, HDV contributes to 1 in 6 cases of cirrhosis and 1 in 5 cases of **liver cancer** among patients with chronic hepatitis B.[23] There is a 6-fold increased risk of liver cancer in HDV/HBV infection than in HBV monoinfection.[24] Indeed, hepatitis delta has become a leading cause of **liver transplantation** in Europe.[25]

Recent estimates for global hepatitis delta are in the range of 15–25 million people, with large geographical differences.[6] Until recently, injection drug users and migrants from highly endemic regions accounted for most cases of hepatitis D in industrialized countries.[25–27] However, hepatitis delta is on the rise among men having sex with men, often as a result of using drugs during sex ('*slamming*')[10] (Figure 3). In this regard, coinfection with HIV leads to more rapid HDV-associated liver disease progression.[28–30]

HDV is highly dependent on host factors for the completion of its replication cycle. It encodes only one structural protein, the HDV antigen and lacks any polymerase that could be targeted by direct antiviral therapy. **Interferon-alpha** was the only drug used to treat hepatitis delta until recently, with poor efficacy.[6,12] The shortage of highly effective HDV therapies highlights the urgent need for new treatments.[15] **Bulevirtide** is a peptide that blocks the NTCP receptor for entry of HBV/HDV within hepatocytes (Figure 4). It was recently approved in Europe as the first HDV treatment. The report of several cases of hepatitis delta cured with bulevirtide has revitalized the field.[31] The drug is relatively well tolerated although it needs to be administered subcutaneously. Moreover, it is unclear for how long it should be prescribed.

Lonafarnib is a farnesyl transferase inhibitor that alters the maturation of the viral particle. Developed initially as an anti-cancer drug that interferes with cell cycle regulation, it also blocks the secretion of HDV virions. The drug has already been approved as a treatment for progeria, a rare genetic disorder. Clinical trials testing lonafarnib as HDV therapy are being completed.[6,32]

4 | THE HIV PARADIGM WITH ANTIRETROVIRALS

It has been 40 years since the first reports of AIDS. Around 80 million people have been infected since then, of whom half are dead.

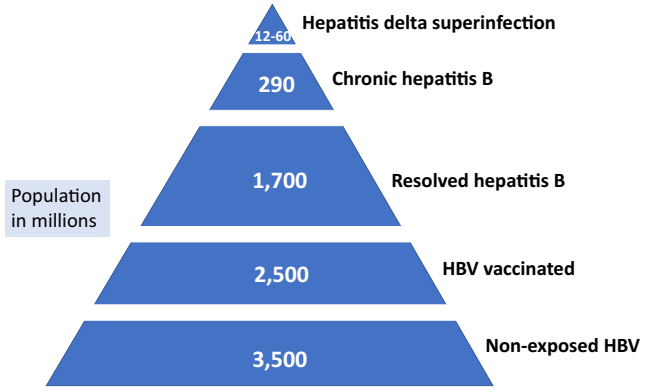


FIGURE 2 Distribution of the human population according to HBV status.

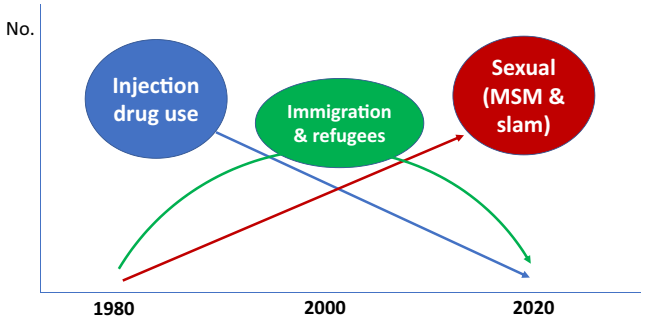
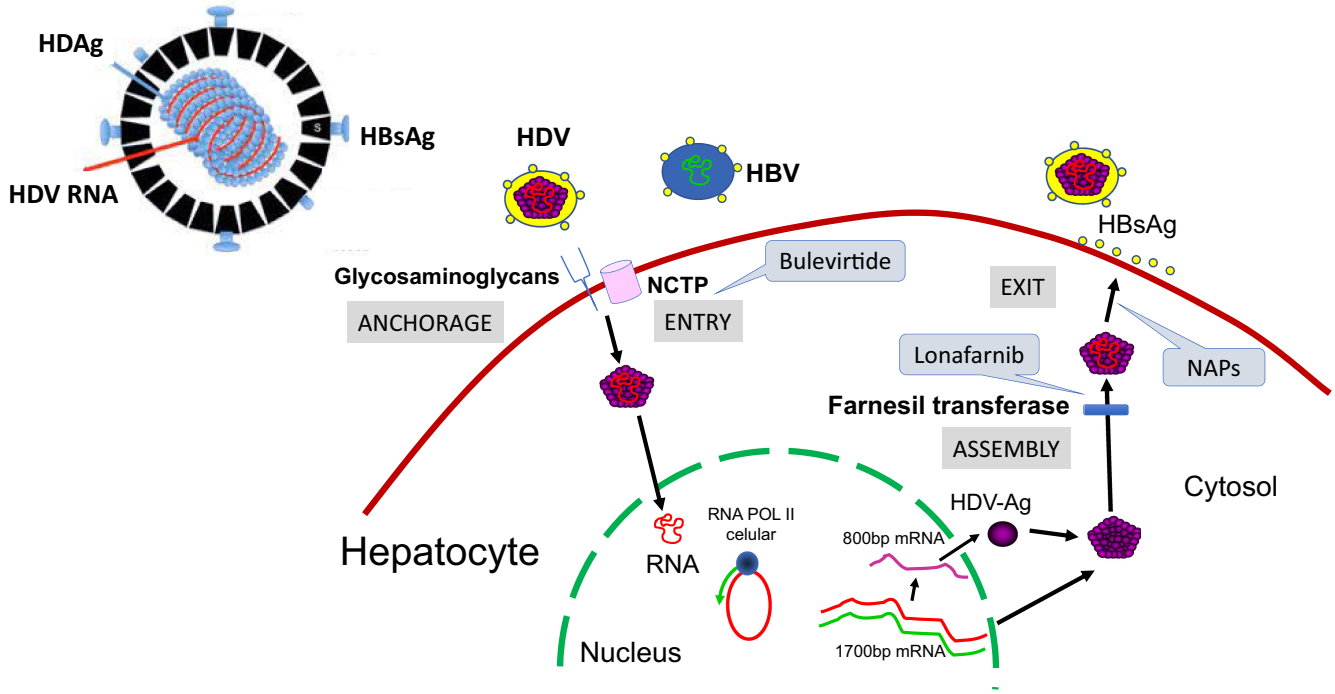


FIGURE 3 Evolution of major populations with HIV and hepatitis delta coinfection in Europe.



HBV, hepatitis B virus; HDV, hepatitis delta virus; NTCP, sodium taurocholate cotransporting polypeptide; HDAg, HDV antigen; HBsAg, HBV surface antigen; NAPs, nucleic acid polymers

FIGURE 4 HDV replication cycle.

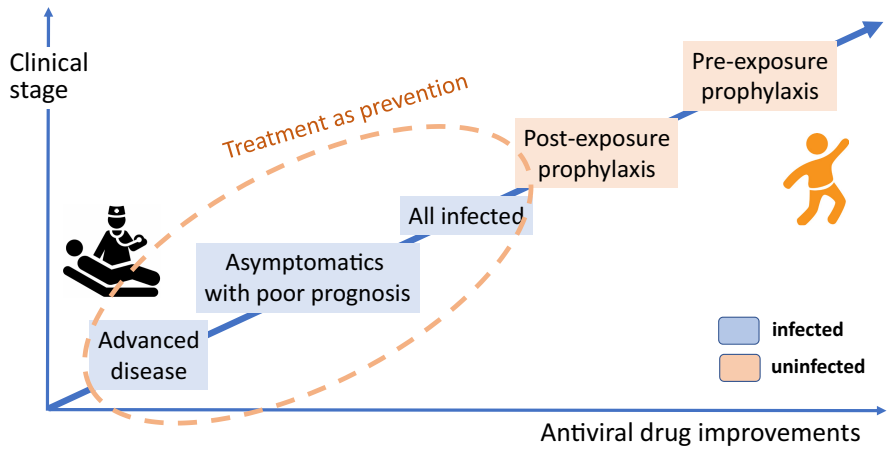


FIGURE 5 Expanding considerations for using antivirals alongside improvements in drug efficacy, safety and convenience.

The advent of potent antiretroviral therapy (ART) in the 90s dramatically improved the prognosis of HIV infection. Indeed, under good adherence to medications, immunological damage no longer occurs, and the life expectancy of treated HIV-seropositive individuals approaches that seen in the general population.[7]

Improvements in ART during the last two decades have been significant, in terms of potency, safety and easy-to-take drug regimens.[7,33] Current HIV medications depict unique appealing profiles, often in the form of one single multi-drug pill given once daily. Furthermore, ART is highly efficacious virologically, well-tolerated and safe, generally with few and manageable drug interactions, and high barrier to resistance. As a result, ART is nowadays recommended for all HIV-positives, including those asymptomatic and with normal CD4 counts. Indeed, ***'rapid initiation of ART'*** is recommended right after HIV diagnosis (Figure 5).[33]

Following the widespread use of ART has been the recognition of its power to halt HIV transmission. Infected persons treated with ART with undetectable viremia do not transmit the virus. This effect is known as ***'treatment-as-prevention'***[34] and globally has fostered the use of ART.

Finally, a breakthrough step in the widespread use of ART came from the recognition that HIV-seronegative persons at risk for viral acquisition could prevent infection by taking antiretrovirals.[35] HIV ***'pre-exposure prophylaxis'*** (PrEP) is currently recommended for uninfected individuals engaged in risky behaviours, such as men having sex with men with multiple partners, sex workers or injection drug

users who share needles. PrEP is prescribed as single pills taken either daily, two to three times per week or at demand. These pills combine tenofovir and emtricitabine. They prevent HIV acquisition in more than 90% of users with good drug adherence.[35–37]

Efforts to make easier daily oral ART have resulted in the recent development of **long-acting antiretrovirals**, such as cabotegravir and rilpivirine, that are administered monthly intramuscularly.[38] In the clinic, these formulations are considered for HIV patients as an alternative to daily medications in persons that complain of poor drug adherence. However, these injectable medications may produce local injection site reactions and require monthly visits to clinics. As result, long-term adherence to treatment goes down.

In an attempt to overcome this problem, **ultra-long acting (XLA) antivirals** are being developed.[39,40] In one example, when a single dose intramuscular injection of a cabotegravir prodrug formulation is administered, drug concentrations above the protein-adjusted 90% inhibitory concentration can be sustained for 1 year in animal studies.[39] The agent exhibits unique properties for prolonged drug release, reflecting a selective depot formation at the injection site and within the reticuloendothelial system. Macrophages are the primary cell depot for drug uptake and wide biodistribution across lymphoid, mucosal, gut and brain tissues.[41] Following intramuscular or subcutaneous administration, the drug is slowly absorbed into the blood and redistributed into peripheral tissues that serve as secondary drug storage sites. Therefore, unlike orally administered medicines for which clearance rates determine the drug half-life, the extended duration of activity for XLA-antivirals is dependent on the amount of drug absorbed/day from such injection site depots to collectively enable lower loading doses to last for months.[41] Given their nanocrystal formulation, volumes of less than 1 mL are needed for yearly administration in humans, reducing the likelihood of local injection site reactions.

In another example, this time with dolutegravir,[40] a palmitic acid conjugated prodrug was prepared by esterification of a hydroxyl group of dolutegravir with the carboxyl group of palmitic acid. Physicochemical properties of the prodrug were characterized and PK evaluation was performed in rabbits by subcutaneous injection. Microparticle formulation was prepared by emulsification evaporation method and characterized for particle size distribution, shape, drug loading and in vitro release. The shape of dolutegravir-palmitate crystals was fine-needle. Plasma half-life, area under the curve and mean-residence time were longer than for dolutegravir alone. Drug release was less than 85% in 6 months from dolutegravir-palmitate microparticles. The authors concluded that biodegradable microparticles of the prodrug had the potential for sustaining dolutegravir release for ultra-long periods.[40]

5 | XLA-ANTIVIRALS - A PATH FORWARD TO ELIMINATE HEPATITIS DELTA

There is growing interest in the development of XLA-antiviral formulations to manage chronic viral infections other than HIV. In the near future, we envision a groundbreaking opportunity for chronic hepatitis delta.[22] At first glance, special populations that would primarily benefit from once-a-year injectables are persons with particular drug adherence challenges. Such populations are infected persons in jail, children and adolescents, homeless, mentally ill and refugees for whom regular attendance of visits at health care sites might be particularly difficult. For similar reasons, infected people in some of the poorest regions would benefit from yearly instead of daily medications. Additional advantages would be in terms of lower risk for selection of drug resistance and increased efficacy ensuring sustained maximal viral suppression. With respect to hepatitis delta, a single shot could be curative, making it possible to move forward '*test*, *treat* & *cure*' strategies in one single visit.

A further consideration, like using ART in HIV patients, is that the clinical benefit as a result of suppressing viremia would run along with community benefit derived from treatment as prevention, as viral undetectability would be associated with untransmissibility (U=U).[7,34]

Besides the advantages of long-acting medications for life-long therapies, a second look at long-extended release drugs might envision more appealing goals, maximizing their activity at target sites and even opening opportunities for viral elimination. We postulate that this will be the case for hepatitis delta.[22] This is a unique condition, and hypothetically HDV could be eliminated from infected hepatocytes despite HBV persistence since there is no genomic HDV RNA reservoir (Figure 6). Indeed, experience drawn with interferon and bulevirtide shows that HDV elimination may be achieved occasionally.[31,42]

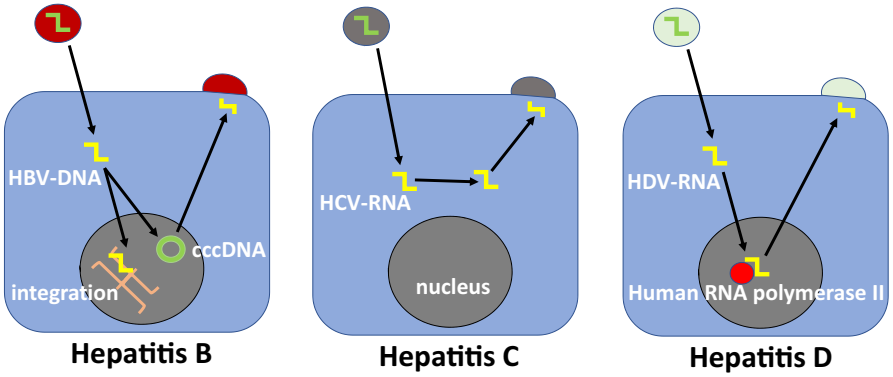


FIGURE 6 Major differences in replication for hepatitis viruses.

To date, liver transplantation is the only treatment option for hepatitis delta patients with end-stage liver disease, hepatocellular carcinoma or fulminant hepatitis.[23,25] Given the unmet medical need,[15] new antivirals for HDV patients, such as bulevirtide and lonafarnib, are being developed under special programmes from both the FDA and EMA (breakthrough therapy designation, prime eligibility, orphan drug status).[6,13,31] Recent advances in nanoparticles and chemical prodrug design are providing the opportunity to develop nanoformulations combining bulevirtide, lonafarnib and tenofovir that will selectively target HDV-infected hepatocytes. The addition of tenofovir to the anti-HDV combination, relies on its potent suppression of HBV that ultimately providing the necessary envelope protein to the HDV particle. However, tenofovir on its own does not depict a direct anti-HDV activity.[43–45] The demonstration of HDV clearance with combination therapy and the use of XLA-antiviral formulations might transform the management of hepatitis delta. Ultimately, it could promote once and for all the implementation of '*test*, *treat & cure*' strategies for HDV infection.

6 | CURRENT CAVEATS & FUTURE PROSPECTS

The advent of antivirals to treat hepatitis delta has opened an unprecedented opportunity to explore whether combination therapy given for a minimum timeframe could achieve viral eradication. In other words, consider the cure of hepatitis delta.[22] This assumption has robust biological support based on the different replication of hepatitis viruses, with the establishment of indefinite cell reservoirs of integrated HBV DNA genomes, whereas for RNA genomes from HCV and HDV there is only a transient dynamic presence within infected hepatocytes.[21]

Although initial attempts combining bulevirtide and lonafarnib in humanized mice models failed to clear HDV, those studies did not optimize dosing or exposure time, as treatment was given for only 2 weeks.[46] Several XLA-antiviral forms active against HBV/HDV are moving from prodrug nanoformulations to the latest steps of animal testing and initial assessment in human volunteers.[47] Hopefully, they will overcome the limitations of current meds. Given the prolonged activity of nanoformulations with antiviral prodrugs, in an unprecedented step moving forward, a single subcutaneous shot could be curative for hepatitis delta. Moreover, this new goal for hepatitis delta therapeutics should be feasible without achieving serum HBsAg loss ('*functional HBV cure*').[22]

Enthusiasm unabated, lessons taken from the hepatitis C field should enlighten which should be the next steps for confronting hepatitis delta in the most efficient way. A major caveat is HDV underdiagnosis. Most infected people are unaware of their diagnosis. A major effort to unveil HDV will be testing all HBsAg+ carriers. A similar threat is nowadays hampering the benefit of using the new curative treatments for hepatitis C.[48]

Another potential caveat derives from the wide HDV heterogeneity. At least 8 distinct genotypes have been described, which vary in their genome sequence by 30%–50%.[49,50] No information exists about the susceptibility of distinct HDV genotypes to bulevirtide and/or lonafarnib, if any. Finally, serum HDV-RNA has become the best biomarker of HDV replication. The use of reliable viral load assays and validation across distinct HDV variants must be performed before full engagement in new curative HDV therapeutics.[51]

A final caveat refers to the indirect benefit of the widespread use of tenofovir as anti-HIV agent reducing HBV and HDV sexual transmissions. This protective effect has been well established in both HIV-infected individuals under antiretroviral therapy as well as in HIV-uninfected persons at risk under pre-exposure prophylaxis.[52,53] However, the increasing trend in HIV therapeutics using mono or dual regimens sparing tenofovir might revert this trend.[54]

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None for all authors.

DATA AVAILABILITY STATEMENT

Data sharing not available.

ETHICS APPROVAL STATEMENT

No need to review articles like this one, according to the Spanish law regulation.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM ANOTHER SOURCE

Not applicable.

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How to cite this article: Soriano V, de Mendoza C, Treviño A, et al. Treatment of hepatitis delta and HIV infection. *Liver Int*. 2022;00:1-8. doi: 10.1111/liv.15345