CO-INFECTIONS AND COMORBIDITY (D BHATTACHARYA, SECTION EDITOR)

Epidemiology, Natural History, and Treatment of Hepatitis Delta Virus Infection in HIV/Hepatitis B Virus Coinfection

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Abstract

Purpose of Review Limited data exist on the prevalence, determinants, and outcomes of hepatitis delta virus (HDV) infection among HIV/hepatitis B virus (HBV)–coinfected persons. This review provides current evidence on the epidemiology, natural history, and treatment of HDV infection in patients with HIV/HBV coinfection and highlights future research needs.

Recent Findings Cross-sectional studies in Europe, Africa, South America, and Asia show that the prevalence of HDV among HIV/HBV-coinfected patients ranges from 1.2 to 25%. No studies have evaluated the prevalence of HDV infection among HIV/HBV-coinfected patients in the USA. HDV infection increases the risk of hepatic decompensation and hepatocellular carcinoma among HIV/HBV-coinfected patients. HDV treatment remains limited to pegylated interferon-alpha, which results in sustained virologic response in fewer than 25%.

Summary Data on the epidemiology, natural history, and treatment of HDV among HIV/HBV-coinfected persons remain limited. More research is needed to address these knowledge gaps in order to better manage HDV coinfection in HIV/HBV-coinfected patients.

Keywords Hepatitis delta infection · Hepatitis D virus · HDV · HIV/HBV coinfection · Hepatitis B infection

Introduction

Coinfection with hepatitis delta virus (HDV) is estimated to occur in approximately 5–10.6% of patients with chronic hepatitis B virus (HBV), affecting up to 72 million people worldwide [1–3, 4••]. The prevalence of HDV infection is thought to be rising in many parts of the world due to increased injection drug use, sexual transmission, and immigration of persons from areas of high endemicity [3, 5–8]. HDV coinfection is associated with more severe hepatitis and higher rates of hepatic decompensation, hepatocellular carcinoma, and death compared with infection with chronic HBV alone [2, 9••]. Despite being associated with worse outcomes, testing for HDV infection among chronic HBV-infected patients is often neglected in clinical practice [10]. Moreover, treatment options remain limited to pegylated interferon-alpha (PEG-IFN-α) therapy, which results in sustained virologic response in < 25% [11, 12•, 13, 14].

Few data exist on the prevalence, determinants, and outcomes of HDV infection among HIV/HBV-coinfected persons. The prevalence of HDV coinfection among HIV/HBV-coinfected patients has been estimated to range from 1.2 to 25% [9••, 15, 16]. HDV coinfection has been associated with an increased risk of liver complications, particularly hepatic decompensation and hepatocellular carcinoma, and death among HIV/HBV-coinfected patients [2, 6, 9••, 17–23]. Notably, no studies have examined the effectiveness of PEG-IFN-α or whether it reduces the risk of liver complications and mortality among HIV/HBV-coinfected patients.

In this article, we first provide a general overview of the virology, pathogenesis, natural history, and epidemiology of

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HDV infection. Next, we review current data on the epidemiology and clinical course of HDV infection among HIV/HBV-coinfected patients. We then discuss the efficacy of available treatment options and novel therapies being investigated for HDV infection. We conclude by highlighting the existing research needs for the field.

Virology and Pathogenesis of HDV

HDV is a small (35–37 nm in diameter) RNA virus that was discovered in 1977 [5, 24]. The HDV virion contains a circular negative single-stranded RNA genome and both small and large hepatitis delta antigen (HDAg) proteins [25]. The virion is defective, as it requires the hepatitis B surface antigen (HBsAg) for infection [25]. The HBsAg serves as an envelope protein, allowing HDV to enter hepatocytes [26]. Both HBV and HDV bind to heparan sulfate proteoglycans to adsorb onto hepatocytes [27] and utilize the sodium taurocholate cotransporting polypeptide receptor to enter the cells [26, 28]. Unlike conventional RNA viruses, HDV employs host RNA polymerases for viral replication [25, 29]. The small HDAg is important for the initiation of viral replication [25]. The large HDAg is essential for the assembly of new virion particles and undergoes several post-translational modifications, including prenylation (i.e., addition of hydrophobic molecules), which is being evaluated as a potential therapeutic target [25, 30, 31].

Eight HDV genotypes have been identified [5, 24]. HDV genotype 1 is the most common worldwide and predominates in North America, Europe, and the Middle East. Knowledge regarding the clinical course based on HDV genotype remains limited, though HDV genotype 3 infection has been associated with fulminant hepatitis and severe liver disease in cohort studies of HBV-infected persons in South America [32–34].

The pathogenesis of HDV is poorly understood, especially in the setting of HIV/HBV coinfection. Observational studies suggest that HDV infection induces liver injury primarily by generating a host-mediated immune response that results in hepatic inflammation, similar to chronic HBV and hepatitis C virus (HCV) infections [35, 36]. An immune-mediated process is suggested by the prominent necroinflammatory pattern observed on liver histology among patients with either chronic HDV coinfection or superinfection [36, 37]. In addition, one study found that HDV infection was associated with the generation of HDAg-specific CD4+ T lymphocyte responses in the peripheral blood of patients with HDV infection [38]. In this study, the CD4+ T lymphocytes generated high levels of inflammatory cytokines, particularly interferon-gamma [38]. Whether or not the HDAg-specific T lymphocyte response and cytokine production plays a role in defense against HDV infection, immunopathogenesis, or both remains unknown. In the setting of HIV coinfection, HIV-induced reductions in CD4+ T lymphocyte count have been shown to

increase HDV viremia, suggesting that cell-mediated immunity may contribute to the control of HDV infection in HIV [39]. Whether or not HDV has cytopathic activity remains controversial. One study supports HDV cytotoxicity during acute HDV infection [40], whereas other studies do not support this [35, 41]. A study performed among transgenic mice expressing HDAg did not result in hepatocyte injury [35]. Similarly, a cohort study of liver transplant recipients who expressed HDAg after liver transplantation demonstrated that HDAg persistence did not manifest hepatocyte injury [41].

The interactions between hepatitis B, C, and D remain poorly understood. A well-described phenomenon with viral hepatitis coinfection is reciprocal interference, where one hepatitis virus suppresses the replication of other hepatitis viruses [42]. Several studies have found HDV to dominate HBV and HCV, suppressing replication of both viruses and resulting in lower levels of HBV and HCV viremia, regardless of HIV status [43–47].

Diagnosis and Clinical Course of HDV Infection

Diagnostic tests for HDV infection can assess the presence of immunoglobulin M (IgM) or immunoglobulin G (IgG) antibody to HDAg (anti-HDV) in serum or plasma, HDV RNA in serum or plasma, and HDAg in serum or within tissue specimens by direct immunohistochemical staining. Initial diagnosis of HDV infection typically involves testing for total anti-HDV antibodies (IgM and IgG), which usually are present after 4 weeks of acute infection, by using an enzyme immunoassay or radioimmunoassay. Anti-HDV IgM appears in serum 2–4 weeks after the time of initial infection, can persist with chronic infection, and may correlate with disease activity [48–52]. Anti-HDV IgG develops several weeks after anti-HDV IgM and persists with chronic HDV infection [52, 53].

In those who are HDV antibody-positive, HDV RNA should be used to confirm active HDV infection. The detection of HDV RNA by reverse transcriptase PCR amplification can be qualitative or quantitative [54]. Although assays for the detection of anti-HDV have been standardized and are now commercially available, assays for HDV RNA have not been standardized and have varying sensitivity [54, 55]. Levels of HDV viremia may be transient and fluctuate over time [56]. HDV RNA levels have not been shown to correlate with the severity of liver disease [57]. HDV RNA testing is also used to assess virologic response to antiviral treatment.

Current guidelines on HDV testing vary by region. The American Association for the Study of Liver Diseases recommends HDV antibody testing only in select patients, specifically HIV-infected individuals, persons who inject drugs, men who have sex with men, those at risk for sexually transmitted infections, immigrants from areas of high HDV endemicity, and

patients identified with low HBV DNA levels but elevated liver aminotransferases [12•]. Despite these recommendations, HDV screening is low in the USA. One study evaluating HDV testing in the Veterans Health Administration found that only 8.5% of HBsAg-positive patients ever underwent anti-HDV antibody screening [10]. In contrast, the European Association for the Study of Liver Diseases and the Asian-Pacific Association for the Study of the Liver recommend testing for HDV infection in all HBsAg-positive patients [13, 14]. Even with these recommendations, HDV screening remains suboptimal and occurs only in up to 46% of HBsAg-positive individuals [58].

The clinical course of HDV infection varies and typically depends on the mode of infection, defined as coinfection or superinfection. Simultaneous HBV/HDV coinfection is usually self-limited, though may cause an acute or fulminant hepatitis that is associated with higher mortality than that of acute HBV infection alone [3, 25]. HBV/HDV coinfection results in HDV viral clearance in more than 90% of cases as a result of resolution of HBV infection [3, 17, 25]. In contrast, HDV superinfection of HBV carriers is frequently associated with acute hepatitis and more likely results in persistent HDV replication [3, 25], with up to 90% of cases progressing to chronic HDV infection [17, 46, 59].

Regardless of the mode of infection, once chronic HDV infection occurs, it is associated with more severe hepatitis and accelerated progression of liver fibrosis to cirrhosis. Chronic HDV infection is also associated with a higher risk of hepatic decompensation, hepatocellular carcinoma, and all-cause mortality among chronic HBV-infected persons [2, 6, 9••, 17–23, 60, 61]. In one cohort study of 299 chronic HDV/HBV-coinfected patients in Italy (13 of whom had HIV coinfection), the annual incidence of hepatocellular carcinoma was 2.8% per year over a mean follow-up of 19 years [18]. In a cohort study of 200 chronic HBV-infected patients with compensated cirrhosis, HDV infection was associated with a 3-fold increased risk of hepatocellular carcinoma over a median of 6.6 years [21]. The incidence of hepatocellular carcinoma was not compared by HIV status in either study.

Epidemiology of HDV Infection

HDV infection is a significant source of healthcare and economic burden. Globally, it is estimated that 5–10.6% of individuals with chronic HBV are coinfected with HDV, representing up to 72 million people worldwide [2, 3, 4••, 62]. The prevalence of HDV/HBV coinfection varies geographically. HDV coinfection is highly endemic in the Mediterranean basin, Vietnam, Pakistan, Iran, Mongolia, Romania, Central Africa, West Africa, and the Amazon Basin, with estimates of prevalence exceeding 20% in these regions [63]. The prevalence of HDV coinfection has been reported to be as high as 42% in the Brazilian Amazon [64], and 75% among HIV-infected injection drug users in Taiwan [65].

In the USA, HDV/HBV coinfection is associated with higher healthcare utilization and costs than HBV monoinfection [66••].

As a result of HBV vaccination, the prevalence of HDV infection has declined since the 1990s in certain parts of Europe, particularly Italy [67, 68], Spain [69], and Turkey [70], where the prevalence has stabilized around 8–11% [8, 67, 71]. However, a resurgence of HDV infection has been observed in some countries due to increases in injection drug use, unprotected sex, and immigration of persons from highly endemic regions [3, 6–8].

In the USA, studies have found the prevalence of HDV infection to range widely. A cross-sectional study in the mid-1980s reported the prevalence of HDV infection to be 3.8% in HBsAg-positive blood donors [72]. Some recent cross-sectional studies in the USA have found the prevalence of HDV to be similarly low among HBsAg-positive individuals, with estimates of 2.2% in the US Midwest [73], 3.4% in the US Veterans Health Administration [10], and 8% in northern California [74]. However, one cross-sectional analysis from the 2011–2016 National Health and Nutrition Examination Survey found that 42% of HBsAg-positive individuals were HDV antibody-positive [75••]. Among HBsAg-positive injection drug users, the frequency of HDV infection is high, with studies reporting the prevalence to range from 42 to 67% [76–78].

Epidemiology of HDV in HIV/HBV Coinfection

Coinfection with HBV occurs in 6–14% of HIV-infected individuals in North America and Europe [79, 80] and 10–20% in Asia and Africa [81–83], resulting in 3–6 million persons with HIV/HBV coinfection worldwide [84]. Despite the prevalence of HIV/HBV coinfection and clinical impact of HDV infection, few studies have evaluated the epidemiology of HDV infection among HIV/HBV-coinfected patients. The prevalence in these studies varies by geographic location.

A cross-sectional study of 422 HIV/HBV-coinfected patients with stored serum samples in the EuroSIDA cohort found the prevalence of HDV infection to be 14.5%, of whom 87% had HDV viremia. In this study, HDV-infected patients were more likely to have used injection drugs or have HCV coinfection. A cross-sectional analysis within the Swiss HIV Cohort Study determined that the HDV prevalence was 15.4% among a sample of 771 HIV/HBV-coinfected patients, of whom 63% had HDV viremia. Injection drug use and HCV coinfection were also risk factors for HDV infection in this study. Additionally, the prevalence of HDV infection was 20% in a cross-sectional analysis of 85 HIV/HBV-coinfected patients from Spain [85], 22.2% in a sample of 162 HIV/HBV-coinfected patients from Taiwan [86], and 25% among 72 HIV/HBV-coinfected patients from Guinea-Bissau in Africa [16]. Three cross-sectional studies of HIV/HBV-coinfected injection drug users in Taiwan reported the prevalence of HDV infection to range from 75 to 84% [65,

Table 1 Studies examining the prevalence and risk factors of hepatitis delta virus infection among HIV/hepatitis B virus-coinfected persons

Reference (year)	Setting	No. anti-HDV antibody-positive among HBsAg-positive	Anti-HDV antibody prevalence (%)	Significant risk factors for HDV infection in HIV/HBV coinfection
Beguelin et al. (2017) [9••]	Swiss HIV Cohort Study	119/771	15.4	• Injection drug use • MSM • Hepatitis C infection
Coffie et al. (2017) [89]	IeDEA West Africa Cohort	10/67	14.9	Not reported
Hsieh et al. (2016) [87]	Taiwan (injection drug users)	48/57	84.2	Not reported
Katwesigye et al. (2016) [90]	Uganda	6/198	3.2	Not reported
Lin et al. (2015) [65]	Taiwan (injection drug users)	197/263	74.9	Not reported
Lee et al. (2015) [91]	Taiwan	7/64	10.9	Not reported
Honge et al. (2014) [16]	Guinea-Bissau	18/72	25	Not reported
Hung et al. (2014) [92]	Taiwan	38/375	10.1	Not reported
Fernandez et al. (2014) [85]	Spain	17/85	20	• Injection drug use • Significant alcohol use*
Thio et al. (2013) [93]	Multi-national study	15/113	13.3	Not reported
Soriano et al. (2011) [15]	Eurosida	61/422	14.5	• Injection drug use • Hepatitis C infection
Chang et al. (2011) [88]	Taiwan (injection drug users)	135/179	75.4	• Younger age
Mendes-Correa et al. (2011) [94]	Brazil	1/86	1.2	Not reported
Sheng et al. (2007) [86]	Taiwan	36/162	22.2	• Injection drug use

HBV hepatitis B virus, *HBsAg* hepatitis B surface antigen, *HDV* hepatitis delta virus, *MSM* men who have sex with men

* Significant alcohol use defined as > 60 g/day of alcohol intake

87, 88]. One possible explanation for the high prevalence of HDV infection among HIV/HBV-coinfected persons is the shared route of transmission through injection drug use. Table 1 summarizes the existing studies that have examined the prevalence and risk factors of HDV infection in HIV/HBV coinfection. Notably, no studies have determined the prevalence of HDV infection among HIV/HBV-coinfected patients in the USA, limiting our understanding of the epidemiology of HDV coinfection in US settings.

Clinical Course of HDV Infection in HIV/HBV Coinfection

There is limited information about the natural history of HDV infection in HIV/HBV-coinfected patients. Existing studies suggest that HIV/HBV/HDV triple infection is associated with worse outcomes compared with HIV/HBV coinfection [9••, 15, 44, 85, 86]. In the 2011 EuroSIDA study, HDV antibody-positivity was associated with a more than 4-fold increased risk of liver-related death and more than 2-fold increased risk of all-cause mortality over a median follow-up of 7.5 years [15]. Similarly, in the 2017 Swiss HIV Cohort Study, HDV coinfection increased the risk of hepatocellular carcinoma 9-fold and the risk of liver-related death 8-fold over a median follow-up of 8.7 years [9••]. Moreover, a 2014 Spanish study found that HIV/HBV/HDV infection increased the risk of hepatic

decompensation or death 7-fold over a median 81 months of follow-up [85]. Finally, a 2007 cohort study from Taiwan found that HDV infection was associated with an increased incidence of cirrhosis, hepatic decompensation, and death over a median of 54.7 months, though this study only included 29 HIV/HBV/HDV-infected patients, all of whom were non-cirrhotic at start of follow-up [86]. Taken together, these data suggest that HDV coinfection increases the risk of liver complications, such as hepatic decompensation or hepatocellular carcinoma, and mortality among HIV/HBV-coinfected patients.

Factors associated with liver complications remain unknown among HIV/HBV/HDV-infected patients. HIV-related immune dysfunction has been shown to enhance HBV replication and accelerate HBV-related liver disease [95]. Thus, the level of HIV-related immune function may be an important determinant of HDV-induced liver disease. The independent effects of HDV, HIV, and HBV viremia, as well as other traditional liver disease risk factors (e.g., body mass index, alcohol consumption, tobacco use, diabetes mellitus, and HCV coinfection), have not been evaluated among triply infected persons and are in need of study in this population.

Treatment of HDV Infection

All patients with HIV/HBV coinfection should initiate an antiretroviral therapy (ART) regimen that contains tenofovir

alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), emtricitabine or lamivudine, and a third antiretroviral drug, regardless of the CD4+ cell count [96••]. Tenofovir is preferred as the anti-HBV backbone because virologic efficacy is high [97–99], and the risk of HBV resistance has been shown to be low among both HBV-monoinfected [100, 101] and HIV/HBV-coinfected patients [102–104]. If tenofovir cannot be safely used, the nucleoside analogue entecavir is an alternative, but it should only be used when added to an ART regimen that has resulted in HIV suppression [105]. Entecavir's activity can be limited in patients with prior lamivudine treatment or resistance [106], which is common in HIV/HBV-coinfected patients [107, 108]. The main goal of HBV-active ART is sustained suppression of HBV DNA to an undetectable level and clearance of HBsAg to reduce the likelihood of liver-related complications and HBV person-to-person transmission [109–112, 113•]. Given the high likelihood of HBV reactivation upon discontinuation of HBV-active nucleos(t)ide analogues [114], HBV-active ART is typically continued indefinitely in HIV/HBV-coinfected patients to achieve persistent HBV control.

Nucleos(t)ide analogues have been shown to be generally ineffective in achieving HDV suppression. Lamivudine, adefovir, and entecavir do not affect HDV RNA levels when used alone or in combination with interferon-alpha (IFN-α) [11, 115, 116]. Whether or not tenofovir contributes to reducing HDV RNA remains unclear, with studies reporting mixed results. In a Spanish study of 19 HIV/HBV-coinfected patients treated with TDF for a median of 58 months, 53% of patients had undetectable HDV RNA [117]. In contrast, a French cohort study did not find significant declines in HDV RNA level among either 4 HIV/HBV-coinfected patients treated with TDF-based ART plus IFN-α or 13 coinfected individuals treated with TDF-based ART alone [118]. Similarly, a recent study of 21 HIV/HBV-coinfected patients in the Swiss HIV Cohort Study who received TDF-containing ART demonstrated no significant reductions in HDV RNA levels after a median of 5 years of therapy [119••].

There is no approved therapy for the treatment of chronic HDV infection, but a 12–18-month course of PEG-IFN-α is often used [12•, 13, 14]. However, the rate of sustained virologic response (SVR), defined as absence of HDV viremia 6 or more months after completion of therapy, has been low with this treatment [113•]. The efficacy of IFN-α therapy was evaluated in a trial of 42 patients with chronic HDV infection who were randomly assigned to receive either 9 million or 3 million units of standard IFN-α-2a (three times a week for 48 weeks) compared with no treatment [120]. In approximately half of the patients who received either dosage of IFN-α-2a, serum alanine aminotransferase levels normalized, serum HDV RNA becomes undetectable, and histologic improvement occurred. However, HDV infection relapse was common after treatment was discontinued, and only 17% achieved SVR at 6 months after completion of therapy

[120]. In a prospective cohort study evaluating the effectiveness of a 48-week course of PEG-IFN-α administered to 104 chronic HDV-infected patients, SVR at 24 weeks post-treatment was observed in only 24 (23.1%) patients [121]. Failure to achieve SVR to PEG-IFN-α is more likely among patients with a < 3 log$_{10}$ decrease in HDV RNA over the initial 6 months of antiviral treatment [122]. Notably, patients with HIV infection were excluded from these studies.

New treatment options for HDV infection are currently being investigated in clinical trials and include myrcludex-B, lonafarnib, REP 2139-Ca, and pegylated interferon-lambda. Myrcludex-B (also known as bulevirtide) is a synthetic lipopeptide that inhibits the liver-specific sodium taurocholate co-transporting polypeptide receptor and can block entry of both HBV and HDV [123, 124]. In a phase 2 clinical trial, myrcludex-B was shown to reduce HDV RNA levels significantly at week 24 of treatment when used alone or in combination with PEG-IFN-α [125]. However, only 1/7 (14.3%) of patients achieved SVR [125]. Lonafarnib is a farnesyltransferase inhibitor that prevents prenylation of the large HDAg, which ultimately disrupts HDV virion assembly and release. Ritonavir acts as a booster, allowing the use of a lower dose of lonafarnib. Lonafarnib has been shown to reduce HDV RNA levels rapidly in a dose-dependent manner and has been more effective when used in combination with PEG-IFN-α [30, 31]. Phase 3 trials of myrcludex-B and lonafarnib are ongoing. REP 2139-Ca is a synthetic nucleic acid polymer that inhibits the attachment of HBV and HDV to heparan sulfate proteoglycans. In one clinical trial in which REP 2139-Ca was followed by PEG-IFN-α, significant reductions in HDV RNA, reductions in quantitative HBsAg levels, and the development of anti-HBs-positivity were reported [126, 127••]. Finally, pegylated interferon-lambda has been shown to reduce HDV RNA levels in 50% of treated patients [128••] and is currently being studied in combination with lonafarnib. Figure 1 illustrates current and potential future targets for HDV treatment.

Research Needs

Many questions remain unanswered regarding HIV/HBV/HDV coinfection, and dedicated research in this area is needed. More basic research is needed to understand the pathogenesis of HDV infection among HIV/HBV-coinfected patients and to elucidate the complex interactions between HIV, HBV, and HDV. Understanding these viral interactions in the context of HIV infection may help identify targets for antiviral therapy. In addition, the epidemiology of HDV infection among HIV/HBV-coinfected patients has not been thoroughly studied, especially in the USA. More data on the prevalence and risk factors for HDV infection among HIV/HBV-coinfected persons are needed to identify high-risk subgroups that warrant HDV testing. Moreover, the effects of viral
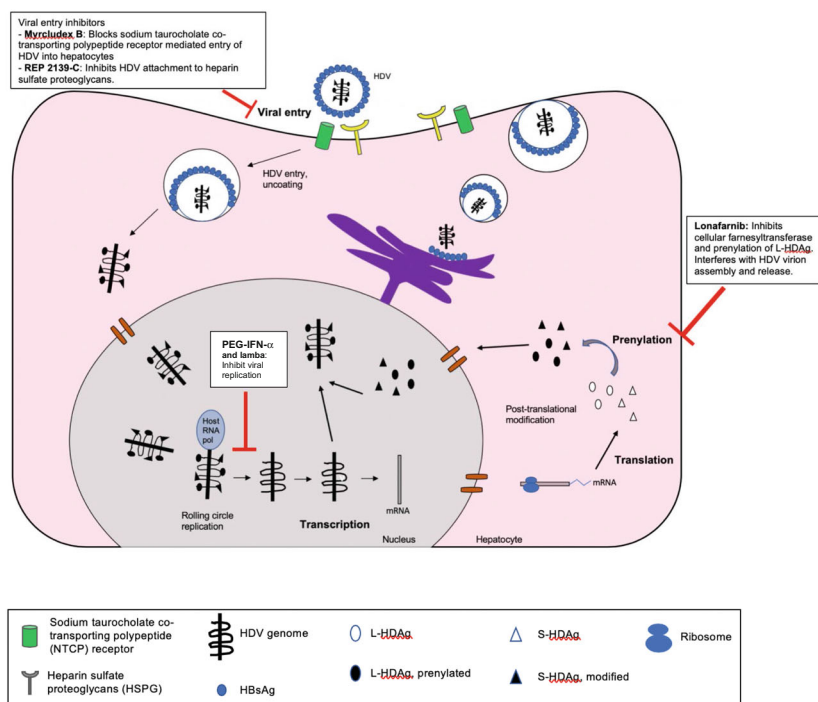
Fig. 1 Current and potential future targets for therapeutic interventions against chronic hepatitis delta virus infection. *HDAg* hepatitis delta antigen, *HDV* hepatitis delta virus, *Host RNA pol* host RNA polymerase, *HBsAg* hepatitis B surface antigen, *L-HDAg* large hepatitis delta antigen, *mRNA* messenger RNA, *PEG-IFN-α* pegylated interferon alpha, *S-HDAg* small hepatitis delta antigen

factors (e.g., HDV genotype and HDV, HIV, and HBV viremia), host factors (e.g., HIV-related immune function, antiretroviral therapy use), and traditional determinants of liver disease (e.g., obesity, alcohol consumption, tobacco use, diabetes mellitus, HCV coinfection) on outcomes such as hepatic decompensation and hepatocellular carcinoma remain incompletely understood among triply infected persons. Such studies are needed to identify the factors that might be modified to attenuate liver disease progression in this group. Finally, research is needed in novel therapies of HDV infection among HIV/HBV/HDV-infected patients to reduce the risk of adverse liver outcomes and prolong survival in these individuals.

Conclusion

HDV coinfection occurs in up to 25% of persons with HIV/HBV coinfection. HDV coinfection has been associated with an increased risk of hepatic decompensation, hepatocellular carcinoma, and death among HIV/HBV-coinfected patients. Despite the clinical impact of HDV coinfection, treatment options remain limited to PEG-IFN-α-based therapy, which results in SVR in fewer than 25% of treated patients, but the effectiveness of this treatment has not been evaluated in HIV/HBV/HDV-infected patients. More studies are needed to understand the interactions between HIV, HBV, and HDV infections; determine the epidemiology of HDV infection

among HIV/HBV-coinfected patients; and evaluate novel treatment strategies in triply infected persons to increase rates of SVR and reduce the risk of liver complications and mortality. These knowledge gaps must be overcome in order to appropriately understand and manage HDV coinfection in HIV/HBV-coinfected patients.

Compliance with Ethical Standards

Conflict of Interest   No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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