Hepatitis Delta Infection: A Clinical Review
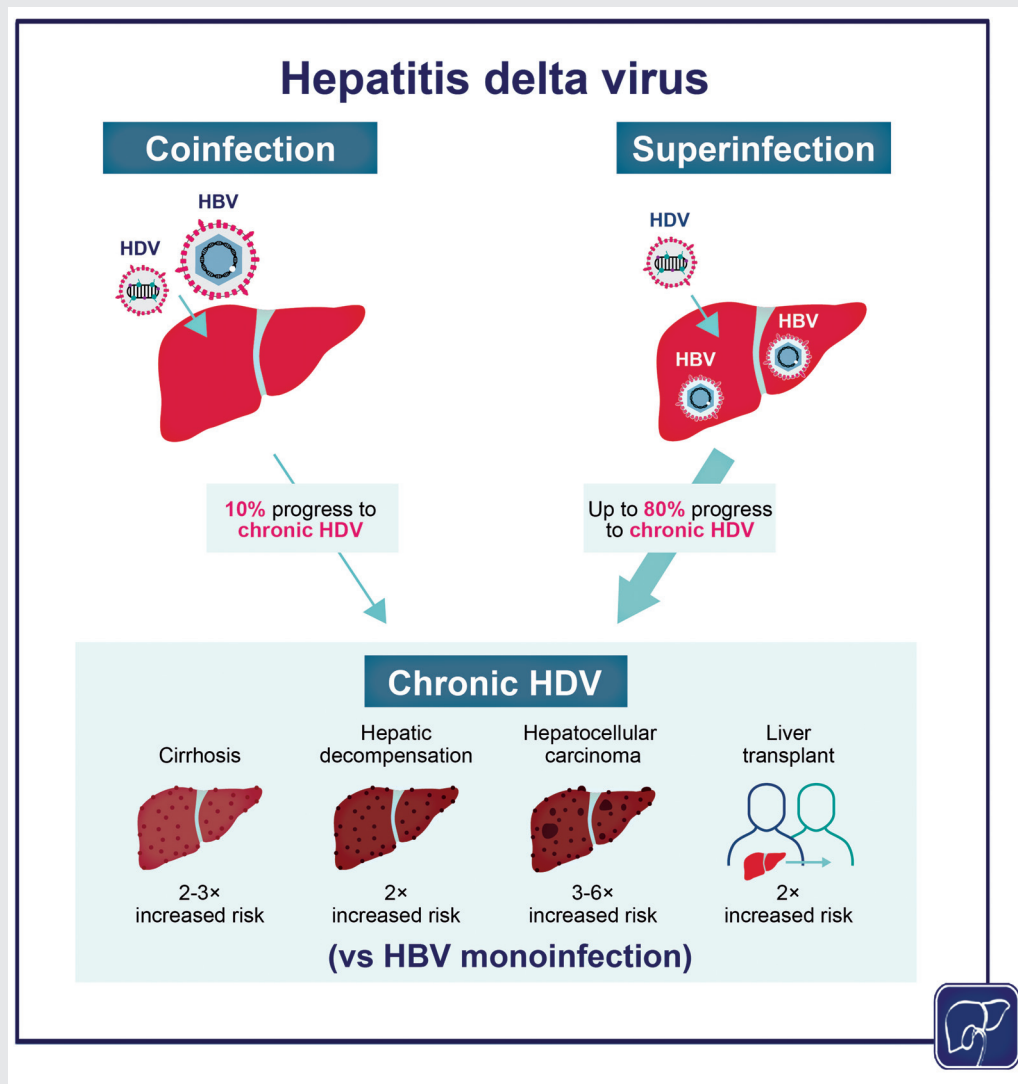
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Graphical Abstract

Abstract

First discovered over 40 years ago, the hepatitis delta virus (HDV) is a unique RNA virus, requiring hepatitis B virus (HBV) antigens for its assembly, replication, and transmission. HBV and HDV can be acquired at the same time (coinfection) or HDV infection can occur in persons with chronic HBV (superinfection). Screening guidelines for HDV are inconsistent. While some guidelines recommend universal screening for all people with HBV, others recommend risk-based screening. Estimates of the global HDV prevalence range from 4.5 to 14.6% among persons with HBV; thus, there may be up to 72 million individuals with HDV worldwide. HDV is the most severe form of viral hepatitis. Compared to HBV monoinfection, HDV coinfection increases the risk of cirrhosis, hepatocellular carcinoma, hepatic decompensation, mortality, and necessity for liver transplant. Despite the severity of HDV, there are few treatment options. Pegylated interferon (off-label use) has long been the only available treatment, although bulevirtide is conditionally approved in some European countries. There are many potential treatments in development, but as yet, there are few effective and safe therapies for HDV infection. In conclusion, given the severity of HDV disease and the paucity of treatments, there is a great unmet need for HDV therapies.

Keywords
► HDV
► hepatitis
► HBV
► bulevirtide
► delta

Lay Summary

First discovered over 40 years ago, the hepatitis delta virus (HDV) is unique, requiring the presence of the hepatitis B virus (HBV). HDV can be acquired at the same time as HBV (coinfection) or by individuals who already have HBV (superinfection). The number of individuals with HDV globally is uncertain; however, some estimates are as high as 72 million individuals with HDV worldwide. HDV is the most severe form of viral hepatitis. Compared to HBV alone, HDV increases the risk of cirrhosis, liver cancer, mortality, and the necessity for liver transplant. Despite the severity of HDV, there are few treatment options. This review discusses the structure, replication, transmission, prevalence, and treatment options in the development for HDV.

The hepatitis delta virus (HDV) is an RNA virus and the smallest hepatitis virus known to infect humans.[1–3] Importantly, HDV is incomplete and considered a satellite virus, which is dependent on hepatitis B virus (HBV) envelope proteins for its assembly and on host cellular proteins to facilitate its replication.[4]

The HDV antigen was discovered in 1977 in patients with what appeared to be a more severe form of HBV infection.[5] Since then, studies have shown that chronic HDV infection is the most severe form of viral hepatitis.[2] Patients with HBV/HDV have a higher risk of developing progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) compared with patients with HBV monoinfection.[6–10] HDV is an important contributor to the burden of liver disease; it is estimated to be responsible for 18% of cirrhosis and 20% of HCC among those with HBV infection.[11]

This review provides an overview of the epidemiology of and screening for HDV infection, viral replication and natural history of infection, and diagnostic and therapeutic options available now and in development.

Epidemiology and Screening

The World Health Organization (WHO) estimates the global prevalence of HBV at 296 million, and of those, an estimated 5%, or over 14 million, are infected with HDV.[12] Published estimates of HDV global prevalence vary widely.[9,11,13] One estimate, based on a meta-analysis of 95 WHO-member countries, was approximately 0.16% (0.11–0.25) or 12 million people.[11] Another meta-analysis of published data in English and Chinese languages estimated the global prevalence at 0.80% (95% CI, 0.63–1.00) or 48 to 60 million people.[13] A third meta-analysis, also examining data published in English and Chinese languages, showed a prevalence of 0.98% (95% CI, 0.61–1.42) or approximately 72 million people.[9]

Interestingly, countries that are highly endemic for HBV are not necessarily highly endemic for HDV. Greenland and the Amazon Basin have high HDV prevalence but are not highly endemic for HBV.[13,14] In persons positive for HBV surface antigen (HBsAg), the global estimate of HDV prevalence ranges from 4.5 to 14.6%.[9,11] A recent population-adjusted study reported HDV prevalence of 2.2% among the HBsAg-positive population after adjusting for geographic distribution, disease stage, and special populations.[15] HDV prevalence among individuals positive for HBsAg is highest in Mongolia, the Republic of Moldova, and countries in Western and Central Africa.[11] Countries with the highest disease burden include China, Pakistan, and Brazil.[9]

In the United States, screening rates for HDV are low, and prevalence is likely underestimated. A meta-analysis estimated the HDV prevalence in the United States to be 5.9%

(95% CI, 3.0–9.8), but the data were sparse.[11] In a 2015 retrospective analysis, 8.5% of U.S. military veterans with HBV were tested for HDV; 3.4% tested positive.[16] In the 2011 to 2016 National Health and Nutrition Examination Survey, HDV prevalence was 42% among HBsAg-positive carriers,[17] much higher than previous estimates.[18] In that survey, Asian Americans were oversampled, possibly inflating the estimate. In the United States, HDV prevalence is higher among several subpopulations, including people who inject drugs,[9,11,13,19] those infected with hepatitis C virus (HCV) or HIV,[11,13] and those who immigrated from areas of high HDV endemicity (►Table 1).[19,20]

Accurately assessing HDV global epidemiology is challenging, in part due to insufficient screening, variable estimates from individual countries, and inaccurate and outdated information.[21,22] Among the main challenges in describing HDV epidemiology is insufficient screening/testing, particularly in primary care settings.[23] Reports show that only 8.5 to 12% of HBsAg-positive patients were tested for HDV in the United States; the majority of such tests were ordered by gastroenterologists/hepatologists.[16,24] Similar percentages of patients positive for HBsAg are tested in Europe (8.2%).[23] Inconsistent screening recommendations also contribute to the lack of testing (►Table 2). The

Table 1 Areas of high HDV endemicity by estimated prevalence

	Estimated prevalence, % (95% CI)		
	Chen et al[9]	Miao et al[13]	Stockdale et al[11]
Africa			
Benin	3.74 (2.44–5.29)	1.77 (0.56–3.63)	1.7 (0.6–3.4)
Cameroon			1.0 (0.9–1.2)
Cote d'Ivoire			1.2 (0.5–2.3)
Djibouti		1.68 (0.84–2.80)	
Gabon	3.03 (0.51–7.43)	1.87 (1.50–2.27)	2.0 (1.5–2.8)
Guinea-Bissau			3.9 (2.4–5.9)
Mauritania	2.40 (1.76–3.13)	2.59 (1.68–3.70)	2.9 (2.7–3.5)
Niger	5.04 (2.91–8.60)	5.04 (2.63–8.18)	
Nigeria		2.09 (0.10–6.56)	1.6 (0.7–3.1)
Senegal		1.42 (0.12–4.09)	0.2 (0.1–0.5)
Somalia		3.19 (2.29–4.23)	
Togo			1.1 (0.2–2.6)
Tunisia		15.33 (12.85–18.00)	0.2 (0.1–0.4)
Uganda		3.07 (1.54–5.11)	0.2 (0.1–0.4)
Asia			
Mongolia	8.03 (5.26–12.08)	8.31 (4.15–13.73)	4.0 (3.2–4.8)
Pakistan	2.43 (1.63–3.62)	1.31 (0.11–3.81)	0.6 (0.1–1.7)
Vietnam			1.4 (0.7–2.3)
Europe			
Greenland		1.88 (0.61–3.85)	
Republic of Moldova		1.40 (0.71–2.32)	1.3 (0.8–1.9)
Oceania			
Australia	4.75 (3.96–5.70)		0.01 (0.0–0.02)
Micronesia		4.40 (2.53–6.47)	
Nauru	4.01 (3.51–4.59)	4.01 (3.49–4.57)	
South America			
Brazil	2.09 (0.37–5.10)	1.13 (0.24–2.66)	0.05 (0.01–0.2)
Columbia	1.22 (0.72–1.84)	1.94 (0.72–3.72)	
Venezuela	0.92 (0.28–1.86)	1.72 (0.84–2.90)	

Abbreviations: CI, confidence interval; HDV, hepatitis delta virus.

Table 2 HDV screening recommendations

EASL[25]	• Patients with chronic HBV infection should be screened for coinfection with HDV • Long-term follow-up HDV RNA monitoring for all treated patients with HBV–HDV coinfection as long as HBsAg is present in serum
APASL[26]	• Coinfection with HDV should be assessed in patients with chronic HBV infection • In patients with HBV-HDV coinfection, it is important to determine which virus is dominant, and the patient should be treated accordingly • Patients should be monitored for 6 months posttreatment and beyond

AASLD[20]	• HBsAg-positive persons at high risk of HDV should be screened
	 ○ Persons from regions with high HDV endemicity
	   ▪ Africa (West Africa, horn of Africa)
	   ▪ Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
	   ▪ Pacific Islands (Kiribati, Nauru)
	   ▪ Middle East (all countries)
	   ▪ Eastern Europe (Eastern Mediterranean regions, Turkey)
	   ▪ South America (Amazon basin)
	   ▪ Other (Greenland)
	 ○ Persons who have injected drugs
	 ○ Men who have sex with men
	 ○ Individuals infected with HCV or HIV
	 ○ Persons with multiple sexual partners or history of sexually transmitted disease
	 ○ Individuals with elevated ALT or AST with low or undetectable HBV DNA
	• If there is any uncertainty regarding the need to test, an initial anti-HDV test is recommended
	• For those at risk for HDV acquisition, periodic retesting is recommended

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine transaminase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate transaminase; EASL, European Association for the Study of the Liver; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus.

European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) recommend universal HDV screening for patients with HBV,[25,26] whereas the American Association for the Study of Liver Diseases (AASLD) recommends only risk-based screening.[20] Since EASL updated its HDV guideline in 2018 and recommended universal screening, testing increased from 7.5% (2015–2017) to 9.4% (2018–2021) in Spain.[23] The continued low levels of testing—despite the universal screening recommendation—highlight additional barriers to HDV screening, which can be grouped into educational and diagnostic challenges. Educational challenges include limited/conflicting guidance on HDV screening, limited healthcare provider education/awareness of HDV,[21] and lack of motivation to screen owing to the paucity of approved therapeutic options. Diagnostic challenges to screening include limited availability of HDV tests[24,26] and lack of standardization of HDV RNA tests, though commercial HDV RNA assays with better standardization are now available.[26–28]

Another major challenge in assessing HDV global epidemiology is the variability of estimates from individual countries. HDV prevalence continues to be a subject of debate, with most recent studies suggesting prevalence has been underestimated.[22,29,30] Estimates of HDV prevalence reported for the same country can vary depending on geographic regions surveyed and populations studied. A meta-analysis in Turkey revealed that even within a single country, prevalence estimates can vary widely.[31] Estimates in west Turkey from six studies showed an HDV prevalence of 4.8%, while estimates in central Turkey were 12% from two studies (> 1,995), and estimates in southeast Turkey, from two studies, were as high as 27.7% (> 1,995).[31] In the United States, a studied cohort of persons in Southern California from Mongolia showed 34% of individuals positive for HBsAg were also HDV positive,[32] which is much higher than the estimate for the general population in the United States of 5.9% and reflective of the high HDV prevalence within Mongolia.[11]

HDV has eight distinct genotypes, each with two to four subtypes, with approximately 35% sequence disparity among genotypes.[33] The predominant genotype in a geographic region varies (►Fig. 1) with genetic diversity among genotypes and within genotypes.[33] Genotype 1 is the most prevalent and is predominant in Europe and North America.[9] Genotype 2 is most common in Asia and the Middle East.[9] In comparison to Genotype 2, Genotype 1 has a higher risk of adverse outcomes and lower rates of remission.[34] Genotype 3, associated with the most pathogenic/severe liver disease and known locally as Labrea fever/hepatitis,[35,36] is found in the Amazon Basin[9] and is the most divergent from other genotypes.[37] Infection with HDV Genotype 3 may have been mistaken for yellow fever in the past because of clinical similarities.[38] Genotype 4 is found in Taiwan and China.[9] Genotypes 5, 6, 7, and 8 are found in Africa,[9,33] although Genotypes 5, 6, and 7 are now also found in Europe.[9]

Structure, Replication, and Natural History

HDV is 35 to 37 nm in diameter,[1–3] with an outer lipoprotein envelope, typically composed of HBV-derived lipoproteins surrounding a single-stranded circular RNA genome, composed of almost 1,700 nucleotides (genotype dependent; ►Fig. 2).[39–41] The RNA genome encodes for only two proteins, the small and
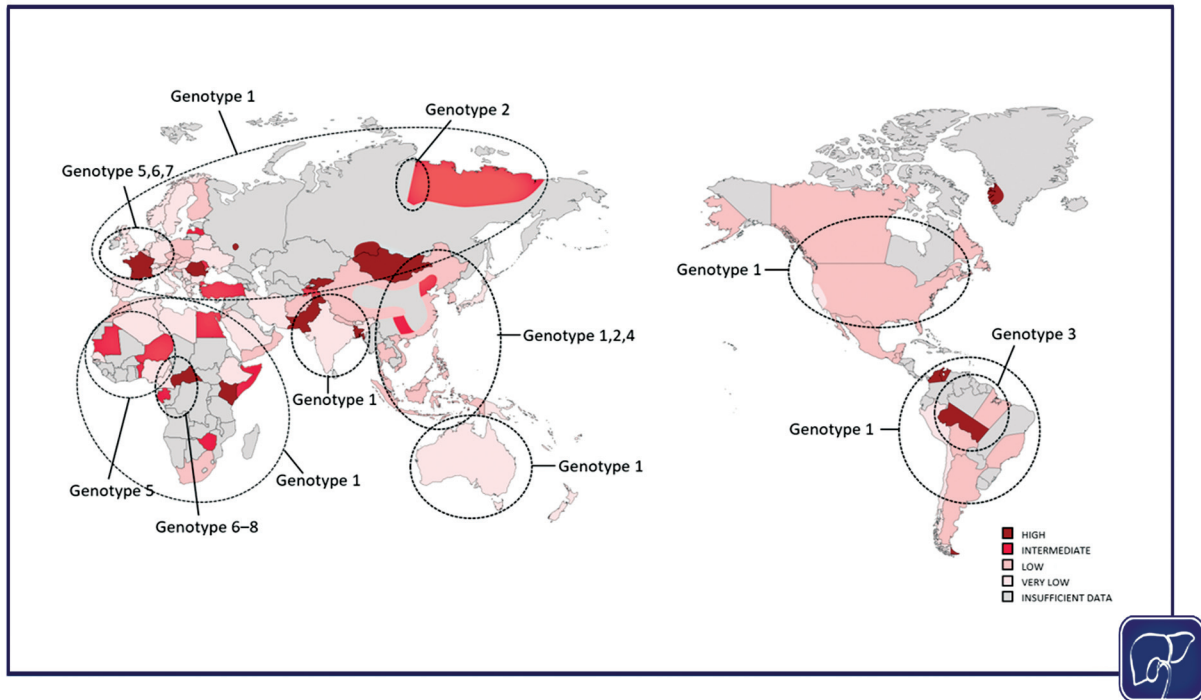
Fig. 1 Global epidemiology of hepatitis delta virus and viral genotype.[27]
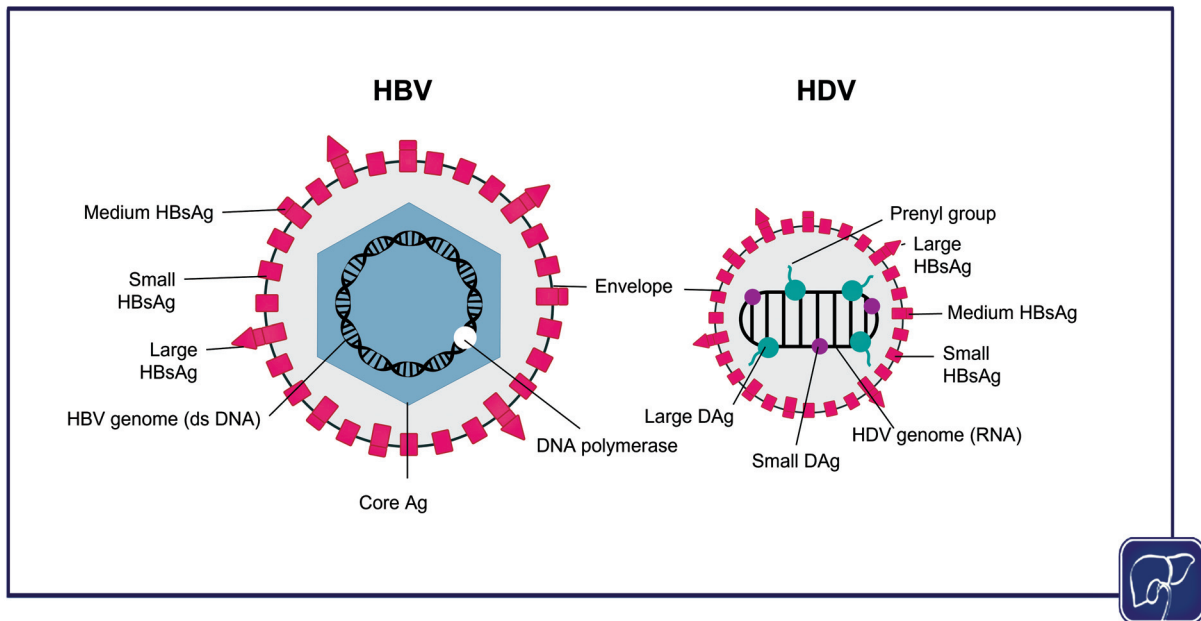

Fig. 2 Structures of HBV and HDV. HDV is composed of an outer lipoprotein envelope, typically made of the three HBsAg subtypes (large, medium, and small). Inside is an inner ribonucleoprotein structure containing the single-stranded circular RNA HDV genome. The HDV genome encodes the DAg, which exists in two forms: small (S-DAg; 24 kDa, 195 amino acids) and large (L-DAg; 27 kDa, 214 amino acids). Ag, antigen; DAg, HDV antigen; ds, double stranded; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus.

large HDV antigen (S- and L-DAg, respectively).[42,43] The S-DAg is required for replication and is produced via transcription of the open reading frame using the host cell's RNA polymerase II.[42,44–46] During transcription, the L-DAg is formed by adenosine deaminase-1,[47–51] converting a stop codon to one encoding tryptophan, thus extending the sequence by 19 amino acids.[42]

Within the extended region of L-DAg, a prenylation site allows the antigen to become farnesylated (posttranslational modification of proteins involved in signal transduction, which facilitates their membrane association), a requirement of the HDV assembly process.[52,53] Disruption at this site prevents L-DAg's ability to either interact with or form secreted particles with the HBsAg.

HDV replication occurs solely within hepatocytes[42] and spreads through the liver via extracellular or cell division–mediated pathways. The most established route is extracellular—sodium taurocholate cotransporting polypeptides (NTCP) receptor-HDV virions are released from infected hepatocytes to infect neighboring cells (►Fig. 3).[54] In the alternative route, HDV survives cell division, replication is established in both daughter cells, and HDV spread is amplified.[54] Once HBV and HDV have entered hepatocytes via NTCP, the viruses have different replication cycles,[4] which explains why HBV nucleotide analogs (NAs) are ineffective against HDV infection.[55]

Similar to HBV, HDV is spread via parenteral exposure. However, HDV transmission from mother to offspring, or through sexual contact, has rarely been reported.[56,57] HDV can be transmitted via two major patterns: coinfection or superinfection.[58] HBV/HDV coinfection occurs as simultaneous infection with both HBV and HDV.[58] Coinfection typically leads to acute hepatitis. In more than 90% of cases, HBV/HDV coinfection ends in complete viral clearance and is self-limiting; as HDV is dependent on HBV, the rate of HDV chronicity cannot be any higher than the rate of HBV chronicity from that acute infection of HBV.[21,27,58] In rare cases, coinfection may cause severe acute hepatitis with the potential for a fulminant disease course.[59] With an acute HDV infection, patients may present with nonspecific flu-like symptoms, including nausea, fatigue, anorexia, and lethargy with high levels of aminotransferases following an incubation period of 3 to 7 weeks.[21,58,60]

With the transmission pattern of superinfection, HDV infection occurs in an individual who has chronic HBV.[21,58] This pattern of infection causes severe acute hepatitis. HDV is cleared spontaneously in only a minority of patients with chronic inactive HBV (HBsAg carriers) with HDV superinfection.[59]
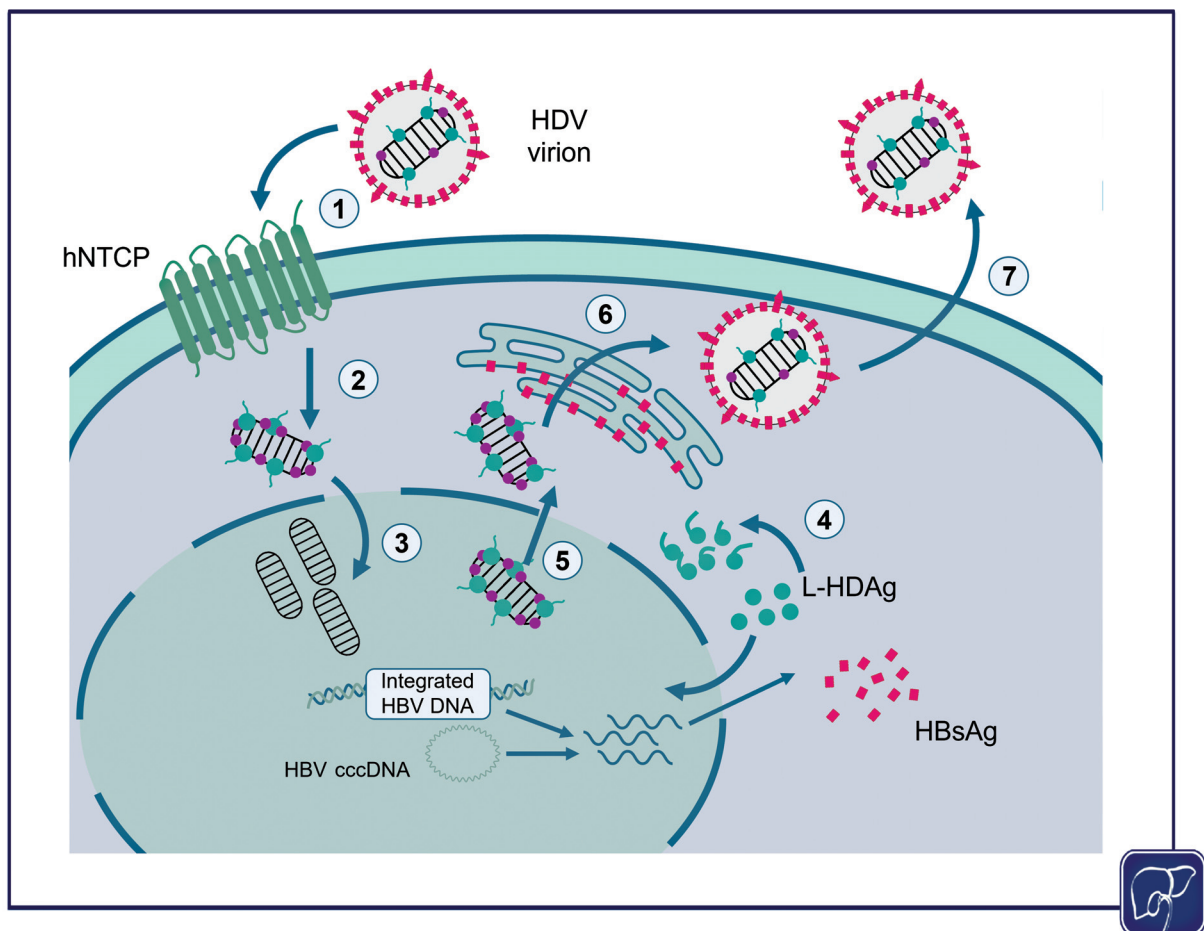

Fig. 3. Life cycle of HDV. (**1**) The HBsAg envelope of the HDV virion binds to the extracellular loop(s) of the sodium taurocholate cotransporting polypeptides (NTCP) receptor. This receptor, a transmembrane protein and the same receptor HBV uses for entry, mediates the transport of bile acids, removing them from circulation. (**2**) The binding with NTCP leads to endocytosis and thus the ribonucleoprotein (RNP) complex enters the hepatocyte cytoplasm. (**3**) This allows the HDV RNP complex to enter the nuclei of hepatocytes, where HDAg mRNA transcription and replication of HDV RNA occur. (**4**) L-HDAg is farnesylated by a cellular farnesyltransferase before being retranslocated to the nucleus. (**5**) S- and L-HDAg interact with the newly synthesized genomic RNA to form viral RNP that is exported to the cytoplasm. (**6**) Viral RNPs interact with the cytosolic part of HBsAg at the endoplasmic reticulum surface inducing their envelopment. (**7**) HDV virions are then secreted (modified from Sandmann and Cornberg, 2021[98]). cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; hNTCP, human sodium taurocholate cotransporting polypeptide; L-HDAg, large hepatitis D antigen; S-HDAg, small HDAg.

Up to 80% of cases progress to CHD infection (infection that has not cleared within 6 months).[58] Clinically, these patients may have nonspecific symptoms or be asymptomatic. Three patterns of CHD have been described: (1) predominant HDV occurs in the majority of patients; HDV replication dominates and suppresses HBV replication; (2) similar viral loads, in which replication of HDV and HBV is comparable; and (3) more rarely predominant HBV, in which HBV replication dominates HDV replication.[21] Multiple studies have reported no impact on HDV outcomes associated with HBV viral load, possibly because HDV suppresses HBV replication in the majority of cases.[21]

CHD clinical outcomes are typically worse than HBV mono-infection,[21] increasing the risk of cirrhosis by two- to threefold, HCC by three- to sixfold,[6,10] and hepatic decompensation by twofold.[21] CHD more often requires liver transplantation,[61] increasing risk twofold compared to HBV monoinfection. CHD also doubles the risk of mortality.[21] Additionally, CHD is associated with rapid progression of liver disease. Patients with CHD develop cirrhosis in approximately 5 years and HCC within 10 years, far faster than those with HBV monoinfection. Male gender, chronic infection/liver disease at the time of presentation, and lack of antiviral therapy are associated with disease progression and advanced fibrosis/cirrhosis in HDV patients.[62] Low albumin, older age, high gamma-glutamyl transferase, and low cholinesterases are likewise associated with advanced fibrosis/cirrhosis in HDV patients.[63]

Using variables associated with the development of worse clinical outcomes (age, sex, regions of origin, cirrhosis, bilirubin, platelets, and international normalized ratio [INR]), a baseline-event-anticipation score for HDV was developed.[64] Based on this score, it is possible to predict outcomes—from as low as 6% to as high as an 80% chance of future clinical events.[65] Patients with persistent HDV viremia have worse prognoses based on this scoring model[65]; however, one study showed about a quarter of untreated, chronically HDV-infected patients had a 2 or more log decrement in HDV RNA levels, and roughly 20% reach undetectability when followed up for approximately 5 years.[66] About 30 to 50% of HDV-infected patients have cirrhosis at diagnosis[67]; while the long-term prognosis is poor even for those without cirrhosis at baseline, there is a growing awareness of a substantial group of patients with a more indolent disease course.[68] Taken together, these data suggest some variability in the outcomes of individuals with CHD, perhaps due to differences in patient characteristics

Diagnosis, Testing, Staging, and Surveillance

Since HDV is a satellite virus of HBV, every HBsAg-positive patient at risk should be tested for HDV infection via serum-based testing.[69] Often, the first step in screening is antibody testing (total HDV antibody) to determine the presence of the HDV antigen.[70,71] The WHO diagnostic criteria for HDV infection are high levels of anti-HDV immunoglobulin M (IgM) and immunoglobulin G (IgG) with confirmation by HDV RNA detection in the serum.[12] IgM antibody serum

levels for HDV are detectable approximately 2 to 4 weeks after symptom onset and often disappear 2 months after acute infection.[60,70] However, IgM levels can be elevated in patients with CHD during flares; thus, anti-HDV IgM levels cannot be used to differentiate between acute and CHD infection.[70] Assessing serologic patterns of HDV and HBV antibody markers can differentiate superinfection from co-infection, which is important for prognosis and management.[71] Superinfection is characterized by a serologic pattern of anti-HDV IgM antibodies (followed by detection of anti-HDV IgG antibodies) and anti-HBc IgG antibodies in the serum, the latter representing more established HBV infection, typically in chronic inactive HBV infection (carrier). The serologic pattern for coinfection is the detection of anti-HDV IgM antibodies (with seroconversion to IgG), high levels of HDV RNA in the serum, and detection of anti-HBc IgM antibodies, the last of which is associated with recent HBV infection.[60] Anti-HDV IgM antibody serum levels are associated with HDV inflammatory and biochemical disease activity.[72] However, there is no correlation between the stage of liver disease and levels of HDV RNA.[73]

Staging of liver disease (fibrosis) is an important part of the HDV diagnostic workup, as HDV infection is often severe.[27] Stages of liver disease (METAVIR staging system) range from no scarring (fibrosis [F]0) to cirrhosis (advanced scarring, F4).[74] Liver biopsies are traditionally used to assess fibrosis.[27,63] However, biopsies are invasive and can have complications.[75] Noninvasive tests include serum markers or liver stiffness measurements through vibration-controlled transient elastography (VCTE; FibroScan, Echosens, Baarn, the Netherlands).[63,76–78] Serum fibrosis markers have lower performance accuracy in patients with CHD Genotype 1 versus those with HBV only or HCV.[78] However, in HDV Genotype 3, there is evidence suggesting aspartate transferase-to-platelet ratio index and F4 scores may identify significant fibrosis.[76] Use of VCTE was validated for HBV and HCV and is the preferred noninvasive test with superior performance compared to serum markers of liver fibrosis and cirrhosis.[77,79] In HDV, VCTE testing performance was comparable to that seen for HBV and HCV, suggesting it is a useful noninvasive test for determining fibrosis in HDV.[77] However, serum markers and VCTE may overestimate fibrosis scores because of the increased severity of hepatic inflammation in HBV/HDV.[78]

In addition to the HDV diagnostic workup, most guidelines recommend HCC screening due to the increased HCC risk associated with HDV. Globally, liver cancer is the second most common cause of cancer-related death among men.[80] Increased risk for progression to HCC in HDV may be due to HDV-inducing oncogenic mechanisms; HDV enhances HBV oncogenic properties, such as enhanced transforming growth factor-beta signaling.[81] Similar to screening for HDV, guidelines differ in their recommendations for HCC screening. AASLD guidelines recommend patients positive with HBsAg be screened for HCC independent of cirrhosis, whereas EASL and APASL suggest a more individualized approach to HCC screening dependent on risk factors.[20,25,26]

Therapy

The goal of HDV treatment is sustained HDV virologic response (negative HDV RNA 6 months after stopping treatment), although ideally therapy would lead to a clearance of HBsAg.[82] The U.S. Food and Drug Administration (FDA) has proposed a combined response endpoint for clinical trials: more than 2 $\log_{10}$ IU/mL decrement in HDV RNA coupled with normalization of alanine transaminase (ALT) level.[83] NA, despite suppressing serum HBV DNA, are ineffective for HDV treatment, since HDV has no reverse transcriptase enzyme. Treating HDV is challenging due to its unique nature and severity.[82] To date, there are no therapies approved by the U.S. FDA for the treatment of HDV. However, there are several therapies in development (▶Fig. 4).

Immune Modulators/Interferon

Interferon is the only therapy recommended for use (off-label) as treatment of HDV. The most recent AASLD guidance on HBV recommends a 12-month course of peginterferon alfa (PegIFN-2a) for elevated HDV RNA and ALT levels.[20] However, treatment success is low. In a study assessing PegIFN-2a monotherapy versus PegIFN-2a in combination with ribavirin, monotherapy resulted in only 20% of patients achieving sustained HDV clearance.[84] Adverse events (AE) were common on therapy, with dose modifications required for 50% of patients on PegIFN-2a monotherapy.[84] Likewise, relapses are frequent; in a 5-year follow-up of a trial of PegIFN-2a with or without adefovir dipivoxil, 56% of patients with HDV infection who had achieved sustained virologic response had a virologic relapse after therapy was discontinued.[85]
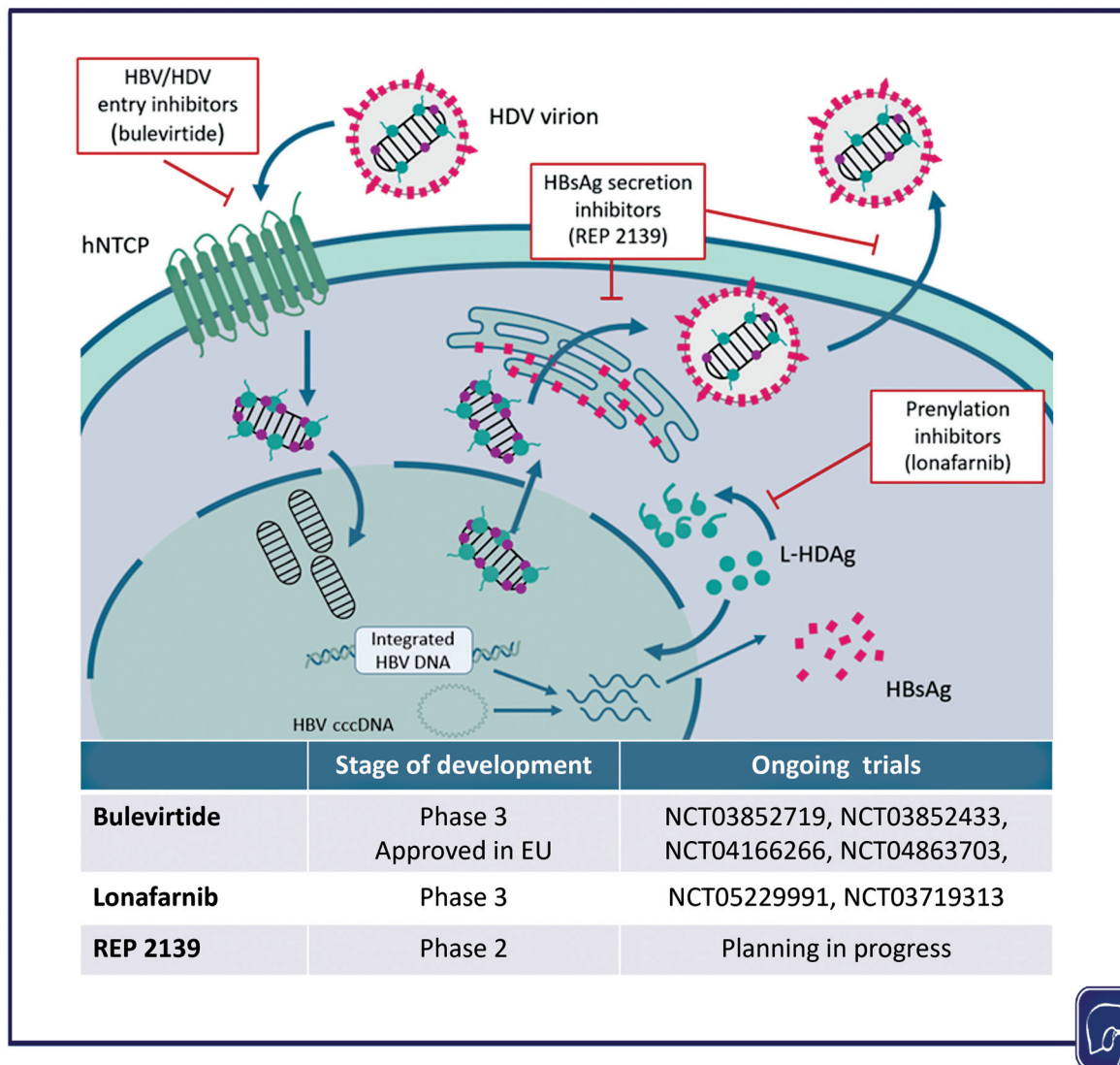

	Stage of development	Ongoing trials
Bulevirtide	Phase 3 Approved in EU	NCT03852719, NCT03852433, NCT04166266, NCT04863703,
Lonafarnib	Phase 3	NCT05229991, NCT03719313
REP 2139	Phase 2	Planning in progress

Fig. 4 HDV therapies in development (modified from Sandmann and Cornberg, 2021[98]). cccDNA, covalently closed circular DNA; EU, European Union; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; hNTCP, human sodium taurocholate cotransporting polypeptide; L-HDAg, large hepatitis D antigen.

PegIFN-lambda appears to be better tolerated than PegIFN-2a and has been assessed in several clinical trials. Patients receiving PegIFN-lambda showed durable virologic response after 24 weeks of follow-up subsequent to 48 weeks of therapy with better tolerability than seen previously with PegIFN-2a.[86] Patients with low viral load at baseline were more apt to achieve undetectable HDV viremia at the end of the study period.[86] PegIFN-lambda Phase 3 trials are ongoing. PegIFN-lambda is also being investigated in combination with lonafarnib, a prenylation inhibitor in development (see below). Compared to PegIFN-lambda monotherapy, the combination of PegIFN-lambda and lonafarnib showed greater HDV viral decline ($> 2 \log_{10}$ IU/mL decline).[87]

NTCP Antagonists

Bulevirtide (previously called myrcludex-B) is an HDV-entry inhibitor that acts on NTCP, blocking cell entry of HBV and HDV. In clinical trials, bulevirtide as monotherapy and in combination with PegIFN-2a through 24 weeks of therapy resulted in high rates of viral decline: HDV RNA decline was -2.32 and $-3.81 \log_{10}$ IU/mL, respectively.[88] Among patients receiving bulevirtide 2 mg as monotherapy for 24 weeks, 55% had a virologic response, 53% had a biochemical response, and 37% had a combined response.[88] No serious AEs related to bulevirtide and no AEs leading to discontinuation were reported.[88] A study of bulevirtide in combination with tenofovir disoproxil fumarate (TDF) showed 54, 50, and 77% of patients on 2, 5, and 10 mg of bulevirtide with TDF, respectively, achieved undetectable HDV RNA at 24 weeks.[89] At 48 weeks of bulevirtide monotherapy, the combined primary endpoint response ($> 2 \log_{10}$ decrease in HDV RNA *or* undetectable RNA *and* ALT normalization) rate was 45% for 2 mg and 48% for 10 mg, suggesting no advantage associated with the higher dose.[90] In a large, real-world cohort, bulevirtide was well tolerated up to 24 months, and strong antiviral responses were observed.[91] In July 2020, bulevirtide dosed at 2 mg/day received conditional marketing authorization in the European Union for the treatment of CHD infection in plasma (or serum) HDV RNA–positive adult patients with compensated liver disease.[92]

Prenylation Inhibitors

Lonafarnib is an orally administered farnesyltransferase inhibitor and prevents L-DAg prenylation, assembly, and release of HDV particles. Lonafarnib 200 mg, twice daily, significantly reduced virus levels compared to placebo, and the decline in virus replication was significantly correlated with serum drug levels.[93] Due to AEs with the 200-mg dosage, treatment with lonafarnib 100 mg twice daily, either with ritonavir or PegIFN-2a, was evaluated and resulted in a decrease in viremia, although it was still associated with significant AEs.[93] In another study, patients receiving lonafarnib 50 mg twice daily + ritonavir or combination regimens of lonafarnib (25 or 50 mg twice daily) + ritonavir + PegIFN-2a, 46 and 89%, respectively, achieved $2 \log_{10}$ or greater decline or less than lower limit of quantification of HDV RNA from baseline at the end of treatment.[94] These lesser dosed lonafarnib-containing combination combinations were

more tolerable than lonafarnib + ritonavir alone; most AEs were gastrointestinal symptoms. Given the antiviral efficacy and tolerability, these combinations hold promise as HDV treatments.

HBsAg Secretion Inhibitors

HBsAg secretion inhibitors can block the release of the HBsAg. In an uncontrolled Phase 2 study, REP 2139 (a nucleic acid polymer) led to HDV suppression rates greater than 80% during treatment and were maintained after treatment in greater than 50% of patients.[95] Evaluation of REP 2139-Ca (calcium chelate complex formulation) in combination with PegIFN showed that in 7 of 11 patients, HDV RNA was not detected at 24 weeks, and this was maintained through 3.5 years.[96] Although these results are promising, more data are necessary to better understand the efficacy and safety of REP 2139.

Future Potential Therapies

Small interfering RNA (siRNA) agents prevent synthesis of viral antigens. There are several such investigational compounds in Phase 1 or 2 studies, including GalNAc-siRNA, VIR-2218 (NCT05461170), DCR-HBVS (NCT03772249), and JNJ-3989 (NCT04535544). There are also three antisense nucleotides in Phase 2 studies, GSK3389404, RO7062931, and GSK3228836 (NCT04954859).

Therapeutic approaches with available and investigational compounds have been suggested. One proposed approach is finite-duration therapy using bulevirtide or lonafarnib (with ritonavir) in combination with either PegIFN-2a or PegIFN-lambda with the treatment goal of undetectable HDV RNA and HBsAg loss off treatment.[97] A second possible approach is long-term/indefinite maintenance therapy using bulevirtide or lonafarnib (with ritonavir), similar to NA therapy for HBV. The goal with such an approach would be to keep HDV RNA undetectable in the presence of HBsAg.[97]

Conclusion

CHD is a substantial public health problem, as it results in severe liver disease with increased risk of HCC and cirrhosis relative to that posed by HBV monoinfection. The global HDV prevalence is uncertain, with estimates ranging from 4.5 to 14.6% of persons positive for HBsAg.[9,11] The current risk-based approach to HDV screening in the US is likely inadequate, and universal screening for HDV infection among persons with known HBV infection may become the standard of care. Future studies are needed to develop cost-effective approaches to increase testing for HDV, especially in high-risk groups.

Given the severity of HDV disease and the paucity of treatments, there is a great unmet need for HDV therapies. Several mechanistic routes aimed at various viral and cellular targets are in development and hold the promise of improving patient outcomes. There are several unanswered questions in finding a cure for HDV. First, can current antiviral therapies in development engender a sustained virologic response/cure? If so, is interferon required as part of the regimen? Second, are there baseline or on-treatment predictors for sustained response?

Third, are new drugs targeting HBsAg loss effective in HBV/HDV coinfection? Finally, is HDV sustained virologic response possible without loss of HBsAg?

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