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REVIEW

Diagnosis and Management of Hepatitis Delta Virus Infection

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Abstract

Hepatitis D virus (HDV) depends on hepatitis B virus (HBV) to enter and exit hepatocytes and to replicate. Despite this dependency, HDV can cause severe liver disease. HDV accelerates liver fibrosis, increases the risk of hepatocellular carcinoma, and hastens hepatic decompensation compared to chronic HBV monoinfection. The Chronic Liver Disease Foundation (CLDF) formed an expert panel to publish updated guidelines on the testing, diagnosis, and management of hepatitis delta virus. The panel group performed network data review on the transmission, epidemiology, natural history, and disease sequelae of acute and chronic HDV infection. Based on current available evidence, we provide recommendations for screening, testing, diagnosis, and treatment of hepatitis D infection and review upcoming novel agents that may expand treatment options. The CLDF recommends universal HDV screening for all patients who are Hepatitis B surface antigen-positive. Initial screening should be with an assay to detect antibodies generated against HDV (anti-HDV). Patients who are positive for anti-HDV IgG antibodies should then undergo quantitative HDV RNA testing. We also provide an algorithm that describes CLDF recommendations on the screening, diagnosis, testing, and initial management of Hepatitis D infection.

Keywords Hepatitis D virus · HDV Co-infection · HDV superinfection · HDV screening · Hepatitis delta virus

Introduction

Hepatitis D virus (HDV) is a hepatotropic virus that causes acute and chronic liver disease [1]. HDV is variously described as a "satellite virus," an "incomplete virus" or "defective virus" because it can only complete its life cycle with the aid of the hepatitis B virus (HBV) [2]. HDV

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depends on HBV for cell entry, and requires host enzymes for replication and, after it replicates, HBV is also required for the complete HDV virion to be released from the infected hepatocytes [3].

Despite being a "defective" virus, HDV can cause severe liver disease [3]. Chronic HDV infection causes more severe liver disease than chronic HBV monoinfection [4, 5], accelerates liver fibrosis [5, 6], increases the risk of hepatocellular carcinoma, and leads to earlier hepatic decompensation than in patients infected with HBV alone [1]. It our opinion that, unlike HBV and hepatitis C virus (HCV), there are very few extra hepatic manifestations that are clinically important.

Unfortunately, the clinical impact of HDV has often been overlooked. Referring to the epidemiology of HDV in the United States, the Hepatitis B Foundation has noted that "low awareness, testing, and the lack of inclusion on the notifiable diseases list contribute to the unclear picture of HDV prevalence in the U.S." [1] The lack of awareness of the significant burden of HDV has led to underestimation of the importance of testing for HDV among patients with HBV infection. Clinicians who wish to test for HDV may not be aware of the appropriate testing pathway and may find it difficult to access even antibody testing much less confirmatory polymerase chain reaction (PCR) testing or be aware of sensitivity thresholds for such testing. Furthermore, clinicians may have difficulty in selecting screening and confirming tests because of their complexity and limited availability, which further leads to underdiagnosis of HDV infection. Management of HDV remains challenging because patients typically present with advanced disease, current treatment options are currently limited with low rates of efficacy and significant toxicity, and, unlike treatment for hepatitis C virus (HCV), late relapse is possible even when virologic testing is negative 24 weeks following antiviral therapy [7, 8]. Moreover, no treatment is so far specifically approved by the FDA for the treatment of HDV infection [9]. However, several promising treatments are in late stages of development. Like HBV, there is no cure for HDV. The current guidelines from national and international associations have not been updated recently to incorporate new data on the diagnosis and management of HDV. For these reasons, we, as members of the Chronic Liver Disease Foundation (CLDF), have published these new guidelines on the testing, diagnosis and management of hepatitis delta virus.

The CLDF formed our expert panel and we had an initial planning meeting in March 2022 in Phoenix, Arizona. Subsequent meetings were held via web conference. We performed network data review on the transmission, epidemiology, natural history, and disease sequelae of acute and chronic HDV infection. Based on current available evidence, we provide recommendations for screening, testing, diagnosis, and treatment of Hepatitis D infection, including upcoming novel agents that may expand treatment options. We believe the current review and expert consensus will raise disease awareness among healthcare providers and improve the care for HDV infected individuals. We will emphasize the expert opinions of this group in this manuscript as well as review the facts and data supporting these thoughts.

HDV Prevalence Is Underestimated

As HBV immunization has increased, rates of both HBV and HDV infection have diminished globally and in specific countries. For example, HDV prevalence among patients infected with HBV in Italy decreased from 25% in 1983 [10] to 8.3% in 1997 [11]. However, a distinct minority of individuals with HBV are HDV coinfected. According to the World Health Organization (WHO), at least 5% of persons chronically infected with HBV are also infected with HDV [1] Based on estimates from 1980s, this equates to 15 to 20 million persons with chronic HDV infections worldwide. Geographical regions with lower socioeconomic status fare worse especially where HBV infection remains more common [12]. Areas in which HDV still remains endemic include the former Soviet republics, Western Pacific islands, Mongolia, Pakistan, Afghanistan, countries of sub-Saharan Africa, Mediterranean and Eastern European countries such as Turkey, Romania and Albania, and areas close to the Amazon River in South America [12, 13].

Despite being a resource-rich country, the true prevalence of HDV in the United States may be severely underestimated due to lack of testing and subsequent diagnosis [14] and prevalence estimates vary widely depending on the study. We recommend that HDV is a reportable disease. Currently, the testing rates are low overall; HDV reporting is voluntary and the infection is only reportable in only 23 states. Using International Classification of Diseases (ICD) 9 and 10 codes for patients with HDV/HBV infection from two longitudinal patient databases, researchers estimate more than 11.8% of patients with chronic HBV may also be infected with HDV [15]. However, only 4.7% of chronic HBV patients have been tested for HDV in one study [15]. Pooled data from the 2011–2016 NHANES identified 43 anti-HDV-positive adults all of whom were HBsAg positive (n = 43). Among HBsAg-positive adults (n = 113), 42% were anti-HDV-positive, with a prevalence of 33% and 46% in HBsAg-positive US-born and foreign-born adults, respectively [16]. Analyzing data from a total of 40 million individuals, approximately 10.58% of HBsAg carriers were also infected with HDV even without acknowledged intravenous drug users or high-risk sexual behavior, which is twofold greater than what had been previously estimated [3]. Almost 4% of over 2,000 US veterans who were HBsAg-positive also had HDV infection in a 2015 retrospective chart review [17]. Another chart review of chronic hepatitis B

patients in California identified an 8% HDV infection rate [7]. Lastly, a review of National Health and Nutrition Examination Survey (NHANES) data from 2011–2016 indicated that approximately 357,000 Americans either had or have HDV infection [16].

Transmission, Natural History, and Clinical Sequelae

Transmission

HDV is mainly transmitted percutaneously and, to a lesser extent, through mucosal contact with infectious blood, saliva, or semen. HDV is spread by sharing needles with an infected individual, and through sexual exposure. HDV can also be passed from blood or saliva of infected individuals to others via contact with mucosal membranes or through the shared use of personal hygiene objects such as razors or toothbrushes. While exceedingly rare, HDV can be transmitted with HBV from an infected mother to fetus in utero *or birth*, though HDV does not appear to accumulate in breast milk in sufficient quantities to infect newborns during breast feeding [18].

Virology

The HDV RNA genome is single-stranded, circular, of negative polarity and comprised of approximately 1700 nucleotides [19]. HDV is a defective or "satellite" RNA virus that lacks an outer protein coat and replicates only in hepatocytes. A functional HDV virion contains a ribonucleoprotein complex, HDV RNA complexed with the hepatitis D antigen (HDAg), which exists in two forms, the small (S-HDVAg) and large (L-HDAg) antigens, encapsulated by an HBsAg envelope. HDV does not encode its own polymerase but instead uses the RNA polymerase II of the host hepatocyte [20]. HDV also contains an antigenomic RNA, which is a complimentary copy of the genomic RNA [2]. The antigenomic RNA is less abundant and not assembled into virions, but does encode HDAg, which is produced in large (214 aa) and small (195 aa) forms. L-HDAg is critical for proper assembly of the HDV subvirion prior to release from the hepatocyte.

HDV virions bind to and enter hepatocytes in the same manner as HBV. Once inside the hepatocyte, the HDV genome is replicated. Two HDV antigens are produced, and a ribonucleoprotein complex is formed. Replication can proceed completely without HBV, though HBV must provide a glycoprotein envelope, consisting of HBsAg, for complete HDV assembly, release, and transmission [21]. Farnesylation of L-HDAg with an isoprenoid 15-C lipid moiety (a form of a process referred to as "prenylation") facilitates the interaction of the riboprotein with HBsAg on the viral surface. Without the HBV glycoprotein envelope, the ribonucleoprotein complex cannot exit the cell and infect other hepatocytes [7, 22]; however, replication-competent HDV RNA can be transferred between cells during hepatocellular mitosis [23].

HBV-infected cells produce about 10,000-fold more HBsAg than that required for assembly of HBV virions [24]. The empty envelopes are present in substantial quantities in the circulation and re-enter hepatocytes. Additionally, HDV can be packaged and transmitted via truncated HBsAg from naturally integrated HBV [25]. Thus, even when HBV replication is undetectable, there are still sufficient amounts of empty glycoprotein envelopes to coat HDV ribonucleoprotein complexes and subsequently permit release of virions and infect other hepatocytes [24].

Clinical Manifestations and Outcomes of HDV Infection

Symptoms of acute hepatitis D typically first appear 3–7 weeks after initial HDV infection [26]. Initial signs and symptoms of acute hepatitis D are nonspecific and include fever, fatigue, loss of appetite, nausea, and vomiting. Serum levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase dramatically as HDV replication is at its most active. Initial symptoms are often followed by an icteric phase. Nausea and fatigue persist and may worsen in the icteric phase, but abate in the third phase of acute infection, the convalescent phase.

While the clinical manifestations of acute HDV infection are largely indistinguishable from those of other etiologies of acute viral hepatitis, patients with HDV tend to have more severe disease and therefore worse outcomes (Table 1 [17, 27–31]). Nearly half of patients with HDV infection have cirrhosis at the time of diagnosis [6]. Of patients with chronic HDV superinfection, cirrhosis, and liver failure occur in 70%–80% within 5–10 years and in 15% within 1–2 years, respectively [32–34]. A 28-year follow-up study of patients with chronic HDV infection in Italy found that liver failure was the cause of death in 59% of patients [30]. The estimated, adjusted five-year probability for hepatic

Table 1 Risks associated with chronic hepatitis delta infection

Clinical sequela	Increased relative risk vs. HBV monoinfection
Cirrhosis [28, 31]	2.3 to 2.58
Hepatocellular carcinoma [17, 27, 29, 30]	1.43 to 9.3
Liver decompensation [29, 30]	2.2 to 3.17
Liver transplantation [28]	1.93
Mortality [29, 30]	2.0 to 7.88

decompensation in compensated cirrhosis type B patients is 18%, 8%, and 14% for anti-HDV positive/HBeAg negative, anti-HDV negative/HBeAg negative, and anti-HDV negative/HBeAg positive patients, respectively [35]. Positive HDV serology is also associated with a nearly twofold increased risk of liver transplantation [28].

In addition to having higher rates of cirrhosis, patients with HDV infection are also at increased risk of HCC and mortality than patients with HBV monoinfection or HCV infection [5, 6]. Patients develop hepatocellular carcinoma (HCC) at an annual rate of 2.8% [32]. The study found that HDV infection increased the risk for HCC threefold and for mortality twofold in patients with cirrhosis type B [35]. This expert group does not recommend any increase in surveillance that is different from standard HCC imaging and biomarkers. In a retrospective cohort of 200 Western Europeans with compensated HBV cirrhosis, the risk for HCC increased 3.2-fold (95% CI, 1.0–10), decompensation increased 2.2-fold (95% CI, 0.8–5.7), and mortality increased 2.0-fold (95% CI, 0.7–5.7) in anti-HDV positive vs. HDV-negative cirrhotic patients after adjusting for clinical and serological differences [35].

HDV Co-infection vs. Superinfection

Patients can either acquire HDV through co-infection or superinfection [32]. Co-infection occurs when a person simultaneously becomes infected with HBV and HDV. Superinfection, on the other hand, occurs when a person who is already chronically infected with HBV subsequently acquires HDV.

The distinction between co-infection vs. superinfection has important clinical implications. More than 95% of patients co-infected with HBV and HDV completely clear both viruses within six months [36]. Nonetheless, acute HBV-HDV co-infection may cause severe acute hepatitis with evolution to acute liver failure [27, 28]. Likewise, fulminant hepatitis is more common in people with HBV/HDV co-infection than those with HBV monoinfection [8, 37].

In contrast to acute HBV/HDV co-infection that rapidly resolves, more than 80% of patients who acquire acute HDV superinfection will develop chronic HDV infection. HDV superinfection exacerbates and accelerates the progression of chronic HBV infection [37], despite interfering with HBV replication [31]. Progression to cirrhosis occurs up to a decade earlier in HDV-superinfected persons compared to those infected with HBV alone [38]. Persistence of HDV replication appears to predict the development of cirrhosis [39]. Another study compared impact of HDV coinfection in those with HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) coinfection. In this Spanish cohort, 66% of patients coinfected with HBV/HCV/HDV/HIV, but only 6% of patients coinfected with HBV/HCV/HIV, presented with cirrhosis [40].

Screening Recommendations

The Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the National Institutes of Health (NIH) have published guidelines to help clinicians select patients who should be screened for HDV (Table 2 [8, 41–44]).

AASLD guidelines suggest screening for all HBsAg-positive individuals in or from certain endemic countries [8]; however, this guidance is limited by two issues. First, many countries lack high-quality epidemiological studies to definitively show the presence or absence of HDV endemicity. Second, all healthcare providers may not know country-specific HDV prevalence. In these cases, the AASLD suggests screening when endemicity is "uncertain." Given these practical limitations, the lead author of the 2018 AASLD guidelines, Dr. Norah A. Terrault, recommends universal screening of all HBsAg-positive persons [45]. Indeed, the American Hepatitis B Foundation has recently suggested HDV antibody testing for all HBsAg-positive individuals with a reflexive quantitative HDV RNA assay for all positive screening results similar to EASL recommendations [41].

Universal testing is reasonable in light of the improvements in HDV diagnostics, a lack of awareness of guideline recommendations and the consequences of chronic HDV infection [46]. We recommend universal HDV screening for all patients who are HBsAg-positive (Table 2). We agree with the AASLD guidelines that suggest starting with an assay to detect antibodies generated against HDV (anti-HDV) [8, 43]. Patients who are positive for anti-HDV IgG antibodies should then undergo HDV RNA testing. Those at ongoing risk of acquiring HDV should be re-screened periodically. In patients who are anti-HDV–positive, HDV RNA and HBV DNA levels should also be re-assessed periodically (Fig. 1).

It is also important to distinguish coinfection from superinfection. As IgM HDV can persist in chronic infection, HBV serologies can help distinguish confection from superinfection. The presence of IgM anti-HBc, indicative of acute HBV infection suggests confection, whereas its absence indicates superinfection.

Prevention of HDV Infection

The mainstay of HDV prevention is HBV vaccination alongside harm reduction, including safe sexual practices. Immunity to HBV infection prevents HDV infection [7,

Table 2 HDV Screening Recommendations in Patients with Hepatitis B

Organization	Year	Screening Recommendation
APASL [41, 42]	2015	In patients with HBV infection, *"Other causes of chronic liver disease should be systematically looked for, including coinfections with HDV, HCV and/or HIV. Comorbidities, including alcoholic, autoimmune, and metabolic liver disease with steatosis or steatohepatitis should be assessed."*
EASL [41]	2017	In patients with HBV infection, *"Co-morbidities, including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis and other causes of chronic liver disease should be systematically excluded including co-infections with HDV, HCV and HIV."*
AASLD [8, 43]	2016/2018	HBsAg-positive persons at particular risk for HDV should be tested for HDV • Persons with HIV and/or HCV infection, • Persons who have ever injected drugs, • Men who have sex with men, • Persons with multiple sexual partners or any history of sexually transmitted disease, and • Immigrants from areas of high HDV endemicity HBsAg-positive patients with elevated ALT or AST but with low or undetectable HBV DNA should be considered for HDV screening
NIH [44]	2021	HBsAg-positive individuals with HBV-DNA < 2,000 IU/mL and/or alanine aminotransferase > 40 U/L, those born in an HDV endemic country, and intravenous drug users
CLDF	2022	Universal screening of all HBsAg-positive persons

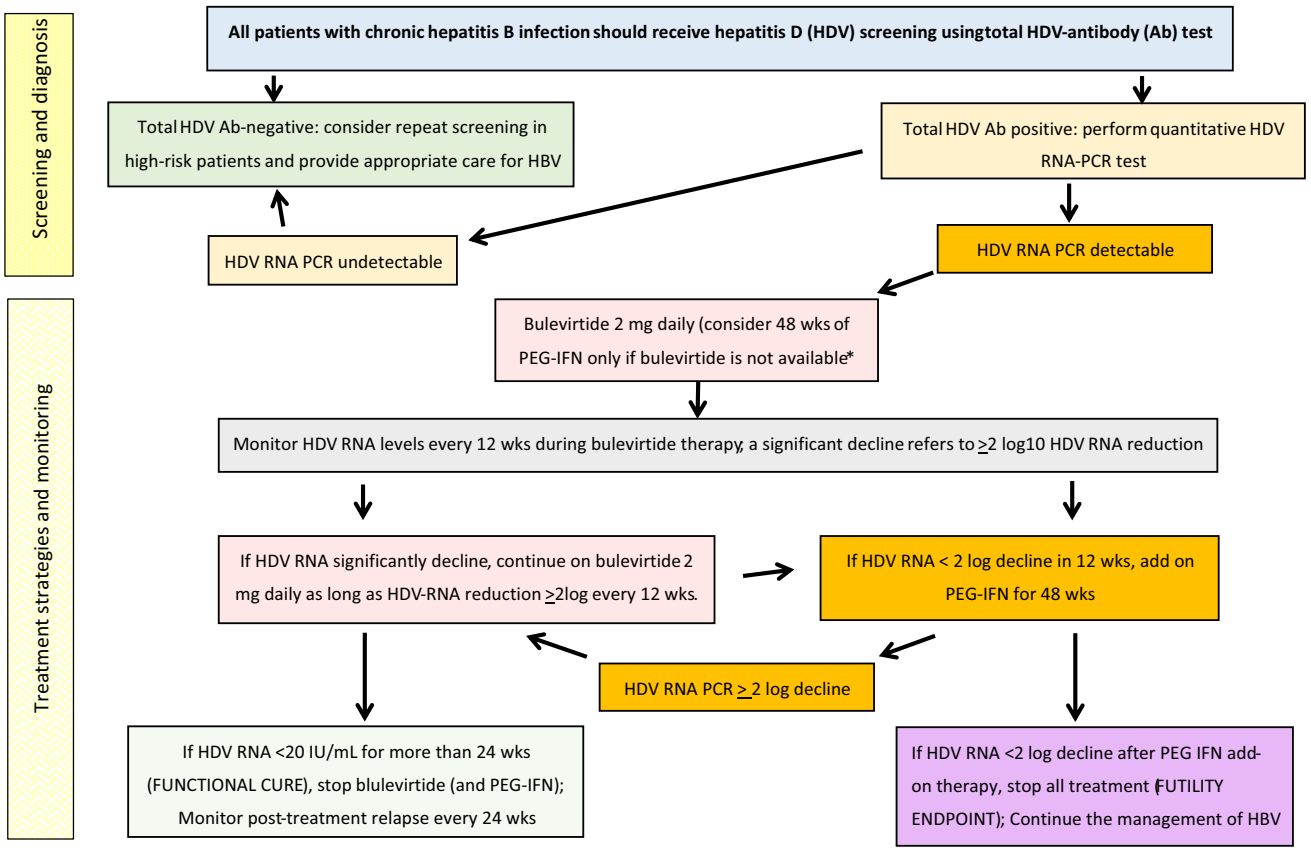

Fig. 1 Algorithm for the Screening, Diagnosis, and Treatment of Patients with Chronic Hepatitis D Infection

47]. We endorse the recently updated recommendations from the Advisory Committee on Immunization Practices that all adults aged 19 to 59 should be immunized against HBV along with adults 60 years of age or older if they have an additional risk factor or other indication [48]. The recommendations from the CDC to test all adults for HBV with the HBV triple panel allows for HDV prevention and treatment.

Two recombinant vaccines, Recombivax (Merck) and Engerix-B (GSK), both produced from yeast cells, are given in identical schedules at 0, 1, and 6 months at doses of 10 µg or 20 µg per dose in adults. Both vaccines are approved for use in patients from birth through adulthood and in people on dialysis [49, 50]. Heplisav-B (formerly HBsAg-108; Dynavax) was introduced in 2018. The vaccine combines 20 µg of recombinant HBsAg with a toll-like receptor 9 (TLR9) agonist adjuvant. The rationale for the TLR9 agonist is to stimulate plasmacytoid dendritic cells and B cells to augment both humoral and cellular immune responses. Heplisav-B is administered intramuscularly at 0 and 1 month and is approved for use in adults 18 years of age or older [51]. In late 2021, PreHevbrio (VBI Vaccines) became available for the prevention of hepatitis B in adults age 18 or older. The recombinant vaccine contains 10 mcg of hepatitis B surface antigens (S, pre-S1 and pre-S2) and is administered in 3 doses at 0, 1, and 6 months.

Treatment of HDV Infection

The treatment of chronic HDV had not evolved significantly since the 1980s until recently. Patients with chronic HDV infection have been treated with either interferon-alpha (IFNα) or pegylated interferon-alfa (PEG-IFNα) without regulatory approval. The ideal goals of antiviral treatment in chronic HDV are to eradicate both HDV and HBV and to prevent the long-term sequelae of infection. The optimal treatment endpoint would be to achieve HBsAg clearance or seroconversion, which seldom occurs with present treatments. At present, the attainable goal of HDV therapy is to suppress HDV replication. If this is successful, ALT levels tend to normalize and liver inflammation and necrosis subside [52]. Unfortunately, HDV RNA undetectability is attainable in 23% to 57% of patients on IFN-α treatment [51, 53, 54] and the benefit is often not sustained, even when HDV RNA is still undetectable 24 weeks after completion of treatment [51, 54, 55].

HDV replication is periodically monitored by assessing serum HDV RNA. If HBV DNA is also detectable, antiviral therapy with a nucleoside analogue should be considered although interferon also has modest efficacy against HBV. In contrast, nucleos(t)ide analogues have no efficacy against HDV infection. The AASLD guidance endorses entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide to suppress concomitant HBV replication and thus treat patients with chronic hepatitis D who have elevated HBV DNA levels [8]. We recommend treating all patients who are HBV DNA positive at any level.

Type and Timing of Interferon Treatment

Guidelines recommend PEG-IFNα rather than non-pegylated formulations [8, 41, 42] largely due to more convenient dosing and higher response rates with the former [56, 57]. Treatment success with PEG-IFNα is modest. Only 23% to 57% of patients achieve undetectable levels of HDV RNA, 24 weeks after treatment completion (HIDIT-I) [51, 53, 54]. Moreover, late relapse, i.e., a new increase in HDV RNA levels, occurs in patients who are followed for longer periods post-treatment. For example, only 40% of patients achieve undetectable HDV RNA level 24 weeks after completing 48 weeks PEG-IFNα treatment with or without adefovir [54], which decreased to 12% within 4.3 years on average [58]. In a separate study, 14 of 60 patients achieved undetectable HDV RNA at follow-up week 24, though only 6 maintained a virological response at later timepoints [59]. In the remaining 8 patients, late-HDV RNA relapse occurred between post-treatment years 2 and 9. Five of these 8 patients were re-treated with PEG-IFNα, but only one achieved undetectable HDV RNA levels.

Extending the duration of PEG-IFNα treatment beyond one year does not appear to improve outcomes (HIDIT-II) [60–64]. Six months after completing therapy, HDV RNA and ALT levels were not significantly different in patients with hepatitis D who had received PEG-IFNα-2b therapy for 24 months compared to 12 months [63]. In one study of longer treatment, 6 years on average, 54% (7/13) of patients had undetectable HDV RNA levels at follow-up and only 15% (2/13) of patients benefited from treatment beyond 5 years [64]. Notably, patients who responded to PEG-IFNα treatment had less mortality and liver-related events than non-responders. Interferon therapy for HDV, therefore, can suppress replication and disease activity in some patients but may not eradicate infection [51, 55].

The Future of HDV Treatment—New and Emerging Therapies

Pegylated Interferon Gamma

PEG-IFNα has no effect in vitro on HDV replication in hepatocyte cell lines [65–67], but it does appear to block viral entry into hepatocytes [68]. Efforts to improve the efficacy and/or tolerability of PEG-IFNα led previously to the development of a novel, first-in-class, Type III IFN receptor agonist called PEG-IFN-lambda (λ). Type III IFN receptors are highly expressed on hepatocytes with relatively little expression on hematopoietic cells or cells

within the central nervous system. The downstream effects of both type I and type III receptor activation in cells are similar. More specific hepatocyte targeting but similar post-receptor effects likely explain the better tolerability of PEG-IFN-λ in patients with hepatitis B and/or C compared to PEG-IFNα [69–71].

The Interferon Monotherapy Study in HDV (LIMT) is a Phase 2 open-label study of PEG-IFN-λ 120 and 180 µg SC weekly injections for 48 weeks in patients with chronic HDV infection [72, 73]. At the end of treatment and after 24 weeks follow-up, 36% of patients in the high dose and 16% of patients in the low dose group had a virologic response below the level of quantification [72]. For responders, viral response treatment was durable at 24 weeks after the 48-week PEG-IFNα treatment period. ALT levels improved between the end of treatment and the 24-week follow-up. The Phase 3 LIMT-2 study is currently underway (NCT05070364).

Bulevirtide (Formerly Myrcludex B)

Bulevirtide is a subcutaneously administered synthetic lipopeptide derived from the pre-S1 domain of the HBV envelope protein, which binds to the hepatocyte NTCP receptor to permit viral entry. By binding to the NTCP receptor itself, the drug prevents HBV attachment and entry.

In a Phase 1b/2a study, 24 patients with chronic HDV infection were randomized (1:1:1) to receive bulevirtide, PEG-IFNα-2a, or both [74]. HDV RNA significantly declined at week 24 in all cohorts and was undetectable in 2 patients who received each monotherapy and in 5 patients who received both treatments. Virus kinetic modeling suggested a strong synergistic effect of bulevirtide and PEG-IFNα-2a on both HDV and HBV. ALT also normalized under monotherapy. The drug was well tolerated. While elevations in glycine-conjugated and taurine-conjugated bile salts were reported, no clinical consequences from these elevations were noted [74, 75].

In a multicenter, open-label Phase 2b clinical trial that assessed the assess safety and efficacy of bulevirtide plus tenofovir in patients with chronic HBV/HDV co-infection, 120 patients who had taken tenofovir for at least 12 weeks were randomized into one of four arms; three groups received 2, 5, or 10 mg of received bulevirtide plus tenofovir and the fourth group received tenofovir only. At end of the 24-week treatment period, 46.4%, 46.8%, 76.6%, and 3.3% of patients reached the primary endpoint, which was defined as ≥ 2 log HDV RNA reduction or negativity. Median HDV RNA declined by -1.75 log, -1.60 log, -2.70 log, and -0.18 log. ALT normalized in 42.8%, 50%, 40%, and 6.6% of patients. At 12 weeks after bulevirtide cessation, HDV RNA relapse occurred in 60%, 80%, and 83% of HDV RNA responders. These results indicate bulevirtide substantially and dose-dependently suppresses HDV replication, but that 24 weeks treatment appears to be insufficient to exert induce a durable response. Longer treatment times or even long-term maintenance therapy may be needed [76].

A study of 30 patients with chronic HBV/HDV co-infection examined the efficacy of 10 mg bulevirtide once daily or in two divided doses for 48 weeks [77]. Patients were also administered 180 µg PEG-IFNα once weekly and tenofovir for hepatitis B infection. The primary endpoint was defined as undetectable HDV RNA 24 weeks off therapy (week 72). HDV RNA was undetectable in 86.7% and 40% of patients at week 48 in the daily and BID arms, respectively. ALT levels declined during treatment in both groups. HBsAg was undetectable in one patient treated with BLV/PEG-IFNα. No serious adverse events were reported.

Lonafarnib

Lonafarnib is a farnesyltransferase inhibitor that reduces the farnesylation of numerous cellular proteins including the large delta antigen (L-HDAg) [78]. Farnesylation, a form of prenylation, is critical for anchoring the HDV ribonucleoprotein to HBsAg, which is in turn essential for HDV virion formation.

In a Phase 2a double-blind, randomized, placebo-controlled study, adults with chronic HDV received either 100 (Group 1) or 200 mg of lonafarnib (Group 2) twice daily for 28 days and were followed for 6 months [79]. Between January 2012, and April 2014, 14 patients were enrolled, of whom eight were assigned to group 1 and six were assigned to group 2. Lonafarnib dose-dependently reduced HDV RNA compared to baseline, and serum concentrations of lonafarnib correlated with the degree of HDV RNA change ($r^2 = 0.78$, $p < 0.0001$). No participants discontinued treatment.

Four clinical trials, Lonafarnib With or Without Ritonavir (LOWR) HDV, were conducted to study the safety and efficacy of lonafarnib in various doses and durations. LOWR HDV-1 was a dose-finding, treatment optimization study in which 15 patients divided into 5 groups received various doses of lonafarnib with or without PEG-IFNα or ritonavir [80]. Lonafarnib monotherapy appeared to decrease HDV viral load in a dose-dependent manner; however, gastrointestinal adverse events increased at higher doses. Ritonavir, a cytochrome P450 3A4 inhibitor, increased the antiviral effect of lonafarnib 100 mg BID beyond the 300 mg BID monotherapy but with fewer adverse effects.

In LOWR HDV-2, a dose-ranging clinical trial was conducted to identify effective and tolerable combinations of lonafarnib plus ritonavir with or without PEG-IFNα [81, 82]. All-oral lonafarnib plus ritonavir doses suppress HDV-RNA to undetectable levels. Adding PEG-IFNα to low dose

lonafarnib plus ritonavir maximized the viral response while avoiding lonafarnib-related serious adverse events.

The LOWR HDV-3 study was a phase 2a double-blinded, randomized, placebo-controlled, dose-finding study of lonafarnib [79]. Twenty-one patients chronically infected with HDV on hepatitis B nucleos(t)ide analogue therapy were enrolled into one of six groups to receive 50, 75, or 100 mg daily doses of lonafarnib plus 100 mg of ritonavir. Three of the six groups received placebo for the first 12 of 24 weeks of therapy. Follow-up extended 24 weeks after the end of treatment. Serum HDV RNA levels significantly declined during 12 and 24 weeks of therapy at all three doses of lonafarnib compared to placebo. Also, the all-oral combination of once-daily ritonavir boosted lonafarnib was safe and tolerable in patients for up to 6 months of therapy.

The LOWR HDV-4 dose escalation study showed that at the end of 24 weeks of treatment, one-third of patients reached and maintained the highest tested dose 100 mg of lonafarnib plus ritonavir and 53% of patients had normalized ALT levels [83]. At week 48 (24 weeks after treatment cessation), increases in HDV RNA were noted, though 4 out of 15 patients had levels that were below the lower limits of quantification.

Nucleic Acid Polymers

The mechanism of action of phosphorothioate nucleic acid polymers (NAPs) remains to be elucidated, though evidence suggests they interfere with the cellular release of subviral HBsAg particles [84, 85]. Two NAPs, REP 2055 and REP 2139 were first clinically evaluated in HBV-infected, HBeAg-positive patients. When given as monotherapy, REP 2055 and REP 2139 each substantially reduced or cleared serum HBsAg and HBV DNA, with anti-HBs seroconversion reported in some patients [86] The treatments were well-tolerated causing grade 1–2 fever, shivering, chills, and headache that resolved 2–8 h after infusion.

REP 2139 was studied in an open label trial in treatment naive, HBeAg-negative, HDAg-positive, HDV RNA-positive patients with elevated serum HBsAg concentrations (REP 301 trial; NCT02233075) [87]. Participants received weekly 500 mg REP 2139 intravenously for 15 weeks, followed by 250 mg REP 2139 IV and 180 µg subcutaneous PEG-IFNα-2a once weekly for 15 weeks, then with weekly 180 µg PEG-IFNα-2a monotherapy for 33 weeks. All 12 patients experienced at least one adverse event during treatment including anemia, neutropenia, and thrombocytopenia. One-third of patients had a serious adverse event and 100% had lab abnormalities including ALT, AST, or bilirubin elevations. Despite this toxicity, 9 patients achieved HBV DNA suppression at the end of treatment. Nine patients achieved HDV RNA suppression at the end of treatment, which was durable at the 1-year follow-up visit in 7 of these patients. Nine of 12 patients had normal serum aminotransferases at 1 year. The same patients were followed for 3.5 years (NCT02876419) [88]. Aside from asymptomatic grade 1–2 ALT elevations in 2 participants who had viral rebound; no safety or tolerability issues were reported. All patients who had responded to treatment at the 1- year timepoint had durable results at 3.5 years including normal ALT, HBsAg response, and HDV RNA response. Seven of 11 participants had a durable HDV functional cure, 3 had persistent HBV virologic control, and 4 had a functional cure with HBsAg seroconversion [88].

Combination Regimens

Because PEG-IFN-λ, bulevirtide, lonafarnib, and NAPs act at different cellular locations and at different points in the HDV life cycle, a combination of these treatments may provide synergistic benefits. The Lambda InterFeron comboTherapy (LIFT) HDV study is a Phase 2a open-label study in which 26 adults with chronic HDV infection were treated with PEG-IFN-λ, lonafarnib, and ritonavir for 24 weeks. At the end of therapy, median HDV RNA declined by a median of 3.4 log IU/mL (IQR: 2.9–4.5, $p < 0.0001$), 11 patients (42%) achieved undetectable HDV RNA, and 3 patients (11%) had levels below the lower level of quantification. Almost all (25 of 26; 96%) patients achieved > 2 log decline of HDV RNA during 24 weeks of the triple treatment regimen. Adverse events were mostly mild to moderate and included GI related side effects, weight loss, hyperbilirubinemia, and anemia. The dose of therapy needed to be reduced in 3 patients and treatment was discontinued in 4 patients [89]. Most recently, topline 48 week data was released from the Phase 3 D-LIVR study (N = 407), evaluating lonafarnib boosted with ritonavir alone (all-oral) and in combination with peginterferon alfa (combination) in HDV patients. Responses rates were as follows: lonafarnib/ritonavir, 10.1% ($p = 0.0044$); lonafarnib/ritonavir in combination with peginterferon alfa, 19.2% ($p < 0.0001$); peginterferon alfa comparator arm, included for contribution of effect, 9.6%. The key secondary endpoint of proportion of patients with improvement in histological response rate demonstrated with statistical significance in combination arm vs placebo. Remaining secondary endpoints including virologic, biochemical, and composite responses at Week 72 (24-weeks post-treatment) are being collected and are expected to be reported mid-2023 [90].

Recommendations on Screening, Diagnosing, and Treating HDV Infection

We endorse universal screening of adults for HBV. Testing should include hepatitis B surface antigen, antibody to hepatitis B core antigen, and antibody to hepatitis B surface antigen.

Given the severity of HDV and the possibility to positively affect outcomes, the authors recommend that all patients who are positive for HBsAg be screened for anti-HDV IgG antibodies (Fig. 1). Likewise, all newly diagnosed HBsAg-positive patients should be reflexively screened for anti-HDV total by ELISA and reflex to qHDV RNA by PCR. Anti-HDV testing with quantitative microarray antibody capture or Western blot are acceptable but are research tools at this time, and the choice of screening test can be based on local availability.

Patients who test positive for anti-HDV antibodies should be tested for HDV RNA using a quantitative (not qualitative) test to simplify linkage to care. Quantitative HDV RNA testing should follow World Health Organization standards. Analogous to a now standard practice in HCV testing, we recommend the availability of reflexive testing by laboratories for HDV RNA in patients who test positive for HDV antibody.

Unless contraindicated, all patients who have detectable HDV RNA should be considered for treatment with PEG-IFN-α for at least 12 months or referred to a clinical trial. Quantitative HDV RNA testing should be performed at 24 weeks, at the end of treatment, and at intervals after treatment completion. While eradicating both HBV and HDV infection is the optimal goal of treatment, this outcome is not attained in most patients [6, 91]. A decrease in HDV RNA of at least 2 log predicts clinical benefit (e.g., decreased liver necroinflammation). Indeed, a decrease in HDV RNA of at least 2 log at week 24 of treatment identifies patients who will test negative for HDV RNA 24 weeks after the end of 48 weeks treatment with a negative predictive value of 95% [92]. Some patients may require treatment PEG-IFN-α beyond 12 months, and late relapse may occur in more than 50% of patients after initial treatment completion [58]. Liver transplantation should be offered to all patients who meet United Network for Organ Sharing criteria and local protocols, Current standards and precautions should be taken to prevent HBV infection of the new graft.

Conclusion and Future Directions

The prevalence and severity of chronic HDV infection are underappreciated, which is leading to substantial underdiagnosis and, along with inadequate therapy, progression of liver disease in many patients to cirrhosis, and hepatocellular carcinoma. There is an urgent need to improve awareness of HDV infection among healthcare professionals. Improving detection rates involves reflexively screening patients with HBV for total anti-HDV and, in turn, reflexively performing quantitative HDV RNA testing in all patients who screen positive. To further improve detection, we eagerly await the development and widespread use of rapid anti-HDV testing at the point-of-care for patients who are HBsAg-positive.

Immunization against HBV remains the best preventative strategy for HDV infection. The ideal goal of treatment is to eradicate HBV, which would be expected to terminate the HDV life cycle and eliminate HDV as well.

A practical and clinically useful treatment goal is to reduce HDV RNA by at least 2 log below baseline. At these levels of HDV replication, disease activity "resets" and clinical outcomes improve. Patients who achieve > 2 log reduction in HDV RNA at the end of treatment are likely to maintain persistent HDV replication suppression at 24 weeks after treatment [92]. Future work should examine the role of other predictors of response to hepatitis D treatments such as treatment-sensitive/-resistant genotypes or early response biomarkers.

A greater understanding of the life cycle of HDV has provided numerous promising therapeutic targets and potential treatments. While PEG-IFNα remains the first line treatment for chronic HDV, other agents are likely to soon supplement or, in the case of PEG-IFN-λ, replace PEG-IFNα as initial treatment. Experience from Phase 2 clinical trials suggests that a combination of treatments is likely needed to achieve profound HDV replication suppression in the greatest number of patients. We believe that that therapy with bulevirtide, if approved in the US, in combination PEG-IFN in patients who are deemed to be capable of tolerating interferon side effects, is a reasonable first choice. If a patient is unlikely to tolerate interferon side effects, bulevirtide monotherapy should be used.

A Phase 3 study of lonafarnib plus ritonavir (NCT05229991) is currently recruiting that could also be practice-changing. Phase Two trials with NAPs, particularly REP 2139, have provided sound justification for Phase 3 pivotal trials.

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; CLDF, Chronic Liver Disease Foundation; EASL, European Association for the Study of the Liver; HBsAg. Hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis c virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NIH, National Institute of Health.

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