

Hepatitis D

A Review

Francesco Negro, MD; Anna S. Lok, MD

IMPORTANCE Hepatitis D virus (HDV) infection occurs in association with hepatitis B virus (HBV) infection and affects approximately 12 million to 72 million people worldwide. HDV causes more rapid progression to cirrhosis and higher rates of hepatocellular carcinoma than HBV alone or hepatitis C virus.

OBSERVATIONS HDV requires HBV to enter hepatocytes and to assemble and secrete new virions. Acute HDV-HBV coinfection is followed by clearance of both viruses in approximately 95% of people, whereas HDV superinfection in an HBV-infected person results in chronic HDV-HBV infection in more than 90% of infected patients. Chronic hepatitis D causes more rapidly progressive liver disease than HBV alone. Approximately 30% to 70% of patients with chronic hepatitis D have cirrhosis at diagnosis and more than 50% die of liver disease within 10 years of diagnosis. However, recent studies suggested that progression is variable and that more than 50% of people may have an indolent course. Only approximately 20% to 50% of people infected by hepatitis D have been diagnosed due to lack of awareness and limited access to reliable diagnostic tests for the HDV antibody and HDV RNA. The HBV vaccine prevents HDV infection by preventing HBV infection, but no vaccines are available to protect those with established HBV infection against HDV. Interferon alfa inhibits HDV replication and reduces the incidence of liver-related events such as liver decompensation, hepatocellular carcinoma, liver transplant, or mortality from 8.5% per year to 3.3% per year. Adverse effects from interferon alfa such as fatigue, depression, and bone marrow suppression are common. HBV nucleos(t)ide analogues, such as entecavir or tenofovir, are ineffective against HDV. Phase 3 randomized clinical trials of bulevirtide, which blocks entry of HDV into hepatocytes, and lonafarnib, which interferes with HDV assembly, showed that compared with placebo or observation, these therapies attained virological and biochemical response in up to 56% of patients after 96 weeks of bulevirtide monotherapy and 19% after 48 weeks of lonafarnib, ritonavir, and pegylated interferon alfa treatment.

CONCLUSIONS AND RELEVANCE HDV infection affects approximately 12 million to 72 million people worldwide and is associated with more rapid progression to cirrhosis and liver failure and higher rates of hepatocellular carcinoma than infection with HBV alone. Bulevirtide was recently approved for HDV in Europe, whereas pegylated interferon alfa is the only treatment available in most countries.

JAMA. doi:10.1001/jama.2023.23242
Published online November 9, 2023.

 [Supplemental content](#)

 [CME at \[jamacmelookup.com\]\(https://jamacmelookup.com\)](#)

Author Affiliations: Division of Gastroenterology and Hepatology, Geneva University Hospitals, Geneva, Switzerland (Negro); Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor (Lok).

Corresponding Author: Anna S. Lok, MD, Division of Gastroenterology and Hepatology, University of Michigan, 1500 E Medical Center Dr, 3912 Taubman Center, Box 5362, Ann Arbor, MI 48109 (aslok@med.umich.edu).

Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

Hepatitis D is caused by hepatitis D virus (HDV), a small RNA virus that depends on the hepatitis B virus (HBV) for entry into hepatocytes and for assembly and secretion of newly formed virions. Therefore, HDV only infects people who are also infected by HBV. HDV affects approximately 12 million to 72 million persons worldwide.¹⁻³ HDV infection may occur as an acute coinfection with HBV when both viruses are acquired together or as a superinfection when HDV infects a person who has chronic HBV infection.⁴ Acute HDV-HBV coinfection is followed by clearance of both viruses in approximately 95% of patients, whereas more than 90% of HDV superinfection result in chronic HDV-HBV infection. Compared with chronic hepatitis B alone, chronic hepatitis D is

associated with faster progression to cirrhosis and a higher incidence of liver-related mortality once cirrhosis has established.^{1,5}

HDV infection is transmitted through parenteral exposure such as injection drug use, percutaneous exposure such as needlestick injuries, or sexual exposure.⁶⁻⁸ The HBV vaccine prevents both HBV and HDV infection, but there is no vaccine to prevent HDV infection in persons already infected with HBV. Currently, there are no approved therapies for hepatitis D. Interferon alfa and its long-acting formulation, pegylated interferon alfa, inhibit HDV replication, decrease liver inflammation and fibrosis, and improve survival; however, these effects are durable in only approximately 30% of treated patients.⁹

Box. Frequently Asked Questions

Which Patients Should Be Tested for Hepatitis D?

Only people with hepatitis B and are positive for HB surface antigen (HBsAg), should be tested for hepatitis D. Hepatitis D testing should be performed in all persons who have tested positive for HBsAg, particularly those with unexplained hepatitis flares, active hepatitis, or rapid progression to cirrhosis despite low HBV-DNA levels. Hepatitis D should also be tested in people living in or emigrated from countries where hepatitis D is common and in those with increased risk of exposure (eg, injection drug users, men who have sex with men, household members of HDV-infected persons).

How Is Hepatitis D Diagnosed?

Hepatitis D is diagnosed by blood test. Presence of hepatitis D virus antibody (anti-HDV) indicates ongoing or past infection while presence of hepatitis D virus RNA indicates ongoing infection.

How Can Hepatitis D Be Prevented?

Prevention of hepatitis B through HBV vaccination is the most effective way to prevent hepatitis D. People with hepatitis D should practice standard precautions such as avoiding sharing razors and toothbrushes within the household. Sexual contacts and household members of people with hepatitis D should be screened for hepatitis B and receive HBV vaccination if they are susceptible.

This review summarizes current evidence regarding diagnosis and treatment of HDV (Box).

Methods

A PubMed search was conducted for articles published in English between January 1, 2013, and May 31, 2023, using the terms *hepatitis D*, *hepatitis delta*, and *hepatitis D virus*. References of retrieved publications were reviewed for relevant articles. Of 1812 identified articles, 386 including meta-analyses, randomized clinical trials, prospective cohort studies, and other large observational studies were reviewed. Higher-quality studies of the articles that had similar findings are reported herein. Data are summarized in this article.

Discussion

Virology

HDV was discovered in 1977 by Rizzetto and colleagues¹⁰ while examining human liver tissue for the hepatitis B core antigen. HDV may have a long evolutionary history because several HDV-like viruses have been identified in other animals including invertebrates such as termites, suggesting that the first HDV may have originated millions of years ago.^{11,12}

HDV is currently classified in the *Deltavirus* genus within the *Kolmioviridae* family, and 8 genotypes have been identified.¹³ Its genome is a circular single-stranded RNA of about 1700 nucleotides. It is the smallest pathogenic virus known to affect humans.¹⁴ Circulating virions contain a single molecule of the genome, complexed with the only HDV-encoded protein (hepatitis D antigen [HDAg]) and enveloped by HBV surface antigens (HBsAg; Figure 1). HDV re-

quires coinfection with HBV for assembly and secretion, and entry into hepatocytes occurs via interaction of the HBV surface protein with sodium taurocholate co-transporting polypeptide, a receptor on the hepatocyte membrane (Figure 1).⁹

HDV-RNA replication uses host RNA polymerases. HDAg (translated from HDV RNA) exists in 2 isoforms: the small HDAg, which activates replication, and the large HDAg, which inhibits replication and promotes virion packaging. The large HDAg has a C-terminal extension that contains a farnesylation signal allowing the addition of a farnesyl group to facilitate virion assembly.^{9,15}

HDV is not directly cytopathic and T-cell killing of infected hepatocytes may be the major driver of HDV-induced liver damage.⁹

Epidemiology

The most common routes of infection in low- or low-middle-income countries are exposure to contaminated needles, unsterilized equipment during medical procedures, and sharing of contaminated household articles, such as toothbrushes. Approximately 70% of new HDV transmission in developed countries is associated with injection drug use and high-risk sexual practices.^{6-8,16}

HDV infection has been reported worldwide. Prevalence of HDV infection is less than 1% among the general population in North America and Northern Europe and more than 2% in some countries in sub-Saharan Africa, Central Asia, and Eastern Europe (eFigure in the Supplement).¹⁻³ The actual prevalence of HDV infection in most countries is unknown because few population-based studies have been performed. The countries with a high prevalence of HDV include Benin, Gabon, Mauritania, Nauru, and Mongolia.¹⁻³ The prevalence of HDV among persons with HBsAg varies from less than 2% in some western countries to approximately 40% in Mongolia.¹⁻³ The prevalence of the HDV antibody (anti-HDV) among adults with HBsAg in the US has ranged from 3.4% and 6% to 43%.¹⁷⁻¹⁹ The wide range in estimates reflects uncertainty due to small studies or studies performed in selected patient populations.

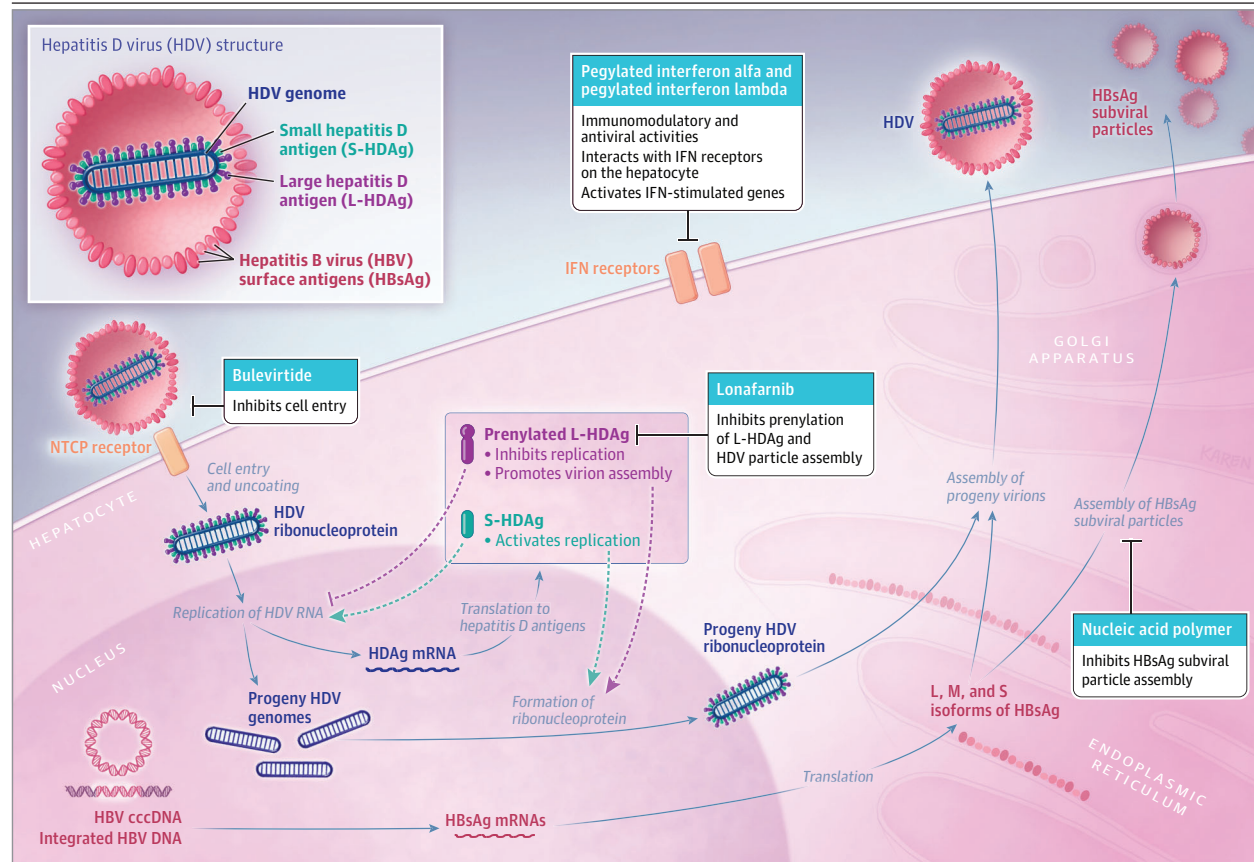
The prevalence of HDV infection is higher among patients with advanced liver disease and among those at high risk of infection such as persons who inject drugs and who are sex workers, men who have sex with men, patients undergoing hemodialysis, and who are HIV coinfecting.^{3,20} In some countries such as Italy, prevalence of HDV infection declined by more than 50% between 1987 and 2019 due to universal HBV vaccination of newborns, but this decline was offset by immigration from countries where HDV infection is prevalent.²¹

Prevention

The HBV vaccine prevents HDV infection by preventing HBV infection. Combining the HBV vaccine and hepatitis B immunoglobulin at birth prevents transmission of HBV and HDV from mothers with HDV-HBV infection to their children. The HBV vaccine is also recommended for sexual and household contacts of persons with HDV infection who are susceptible to HBV. However, no vaccine protects HBV-infected persons from HDV superinfection. Therefore, the only preventive measure for patients with chronic HBV infection is to avoid parenteral or sexual exposure to persons who are HDV-infected.

A recent study in small animals suggested that vaccination using antigens from both HBV and HDV, preS1 domain of HBsAg and large HDAg, elicited antibodies that may be protective against HDV-HBV

Figure 1. Hepatitis D Virus (HDV) Structure, Life Cycle, and Antiviral Targets



Circulating HDV virion comprises an envelope that consists of large (L), middle (M), and small (S) HBV surface antigens (HBsAg) and a ribonucleoprotein with genomic HDV RNA complexed with 2 isoforms of hepatitis D antigen (S-HDag and L-HDag).

HDV enters hepatocytes through binding to sodium taurocholate co-transporting polypeptide (NTCP). After entry, HDV ribonucleoprotein is transported into the hepatocyte nucleus where the HDV RNA is replicated using host enzymes. HDV messenger RNA (mRNA) is translated to S-HDag and L-HDag hepatitis D antigens, which bind to HDV-RNA to form a ribonucleoprotein. S-HDag activates replication, whereas L-HDag contains a farnesylation signal, inhibits replication, and promotes virion assembly.

The ribonucleoprotein is coated with HBV surface proteins and the HDV virions are secreted.

Bulevirtide is an entry inhibitor blocking interaction of HDV with its entry receptor NTCP. Lonafarnib is an inhibitor of farnesyltransferase, which is involved in the prenylation of the L-HDag, an essential step in HDV particle assembly. Pegylated interferon alfa and pegylated interferon lambda interact with interferon (IFN) receptors on the hepatocyte. Both activate IFN-stimulated genes and have antiviral and immunomodulatory activities. Nucleic acid polymer blocks assembly and secretion of HBsAg subviral particles, leading to decrease in circulating HBsAg levels, which may in turn inhibit HDV replication through restoration of host immune control.

coinfection and HDV superinfection in HBV-infected mice.²² This discovery may facilitate HDV vaccine development for use in humans.

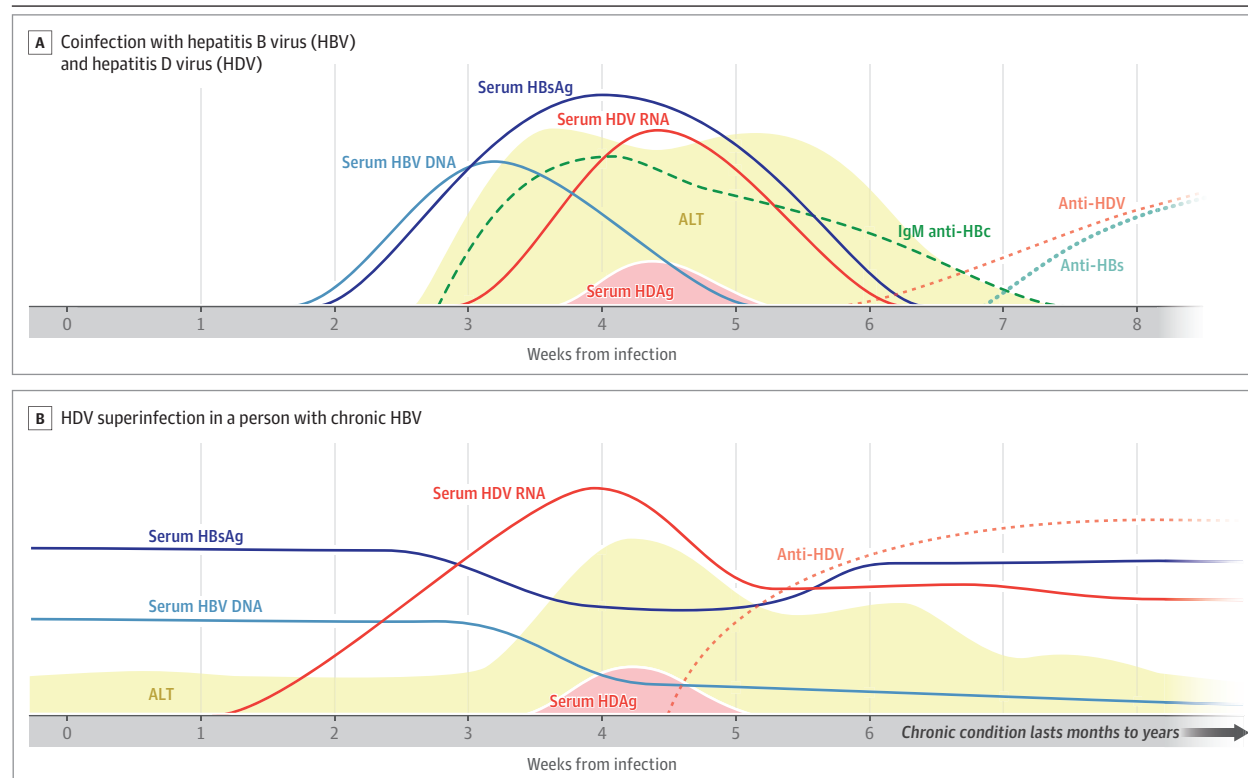
Manifestations and Outcomes of HDV Infection

Acute HDV-HBV coinfection may manifest as acute hepatitis, typically followed by clearance of both viruses, although the risk of acute liver failure is higher in patients with acute HDV-HBV coinfection than in patients with acute HBV mono-infection.^{4,23}

HDV superinfection may manifest as acute hepatitis in a person with previously undiagnosed chronic HBV infection or as an exacerbation of chronic liver disease in a person with known chronic hepatitis B. HDV superinfection typically results in chronic HDV-HBV infection, defined as HDV viremia lasting more than 6 months; however, spontaneous resolution of chronic HDV infection with intermittent or persistently undetectable HDV RNA was reported in approximately 20% to 30% of patients, generally after many years of infection.⁴ HBsAg loss has rarely been reported.²⁴

HDV interferes with HBV replication.²⁵ Therefore, most patients with chronic hepatitis D have low serum HBV-DNA levels.²⁶ Nevertheless, chronic hepatitis D has an accelerated course with more rapid progression to cirrhosis, and a higher incidence of liver-related mortality and hepatocellular carcinoma than chronic hepatitis B infection alone. Approximately 30% to 70% of patients with chronic hepatitis D had cirrhosis at diagnosis and 15% to 50% of people with chronic hepatitis D who did not have cirrhosis at presentation developed cirrhosis within 5 years of diagnosis. More than 50% of people with chronic hepatitis D had liver-related mortality within 10 years.^{5,27-29} People with chronic hepatitis D have variable rates of disease progression.³⁰⁻³² This heterogeneity is related in part to selection bias, in which patients with advanced liver disease are selectively included in studies. Heterogeneity in outcomes is also related to inclusion of patients based on positive results for anti-HDV but not HDV RNA in some studies, and geographic region, which may reflect differences in HDV genotype, host, and environmental factors.

Figure 2. Profile of Acute HDV-HBV Coinfection and Superinfection in Persons Testing Positive for Hepatitis B Surface Antigens



A, Coinfection of HDV and HBV usually manifests as an acute hepatitis. Diagnosis is made by detection of HBsAg, HBV DNA, and IgM anti-HBc, followed by detection of HDV RNA and anti-HDV. Serum HDAG may appear early, but it is short-lived and difficult to detect. Anti-HDV appears late. If assays for HDV RNA are not available, anti-HDV may be the only marker of recent HDV infection, so follow-up testing may be needed to document seroconversion. Coinfection is usually followed by recovery, with undetectable HBsAg, HBV DNA, and HDV RNA in serum; development of anti-HBs; and persistent detection of anti-HDV.

B, HDV superinfection may manifest as an acute hepatitis or an exacerbation of

chronic hepatitis B. Diagnosis is made by the detection of HDV RNA and anti-HDV in a person who is positive for HBsAg but is negative for IgM anti-HBc. HDV superinfection is often accompanied by a decrease in HBsAg levels and HBV DNA levels but both HBV and HDV infection persist, and the person remains positive for HBsAg, HBV DNA, anti-HDV, and HDV RNA.

ALT indicates alanine aminotransferase; IgM anti-HBc, IgM antibody to HB core antigen; anti-HBs, HB surface antibodies; anti-HDV, antibody to HDV, HBsAg, HB surface antigen; and HDAG, HD antigen.

In a study of 1576 patients with chronic hepatitis D from 15 countries, 7.5% to 30.4% of patients developed hepatic decompensation or hepatocellular carcinoma or required a liver transplant. Variability in outcomes was associated with the geographic region in which the patients resided.³⁰

Persistent HDV RNA has been consistently shown to be the most important factor associated with progression to cirrhosis and with mortality.³²⁻³⁵ Other factors associated with increased risk of liver disease progression include HDV genotype (eg, genotype 1 is associated with poorer outcomes than other genotypes),³⁵ high serum HBV-DNA levels, alcohol use (>2 drinks/d for men and >1 drink/d for women), obesity, and diabetes.

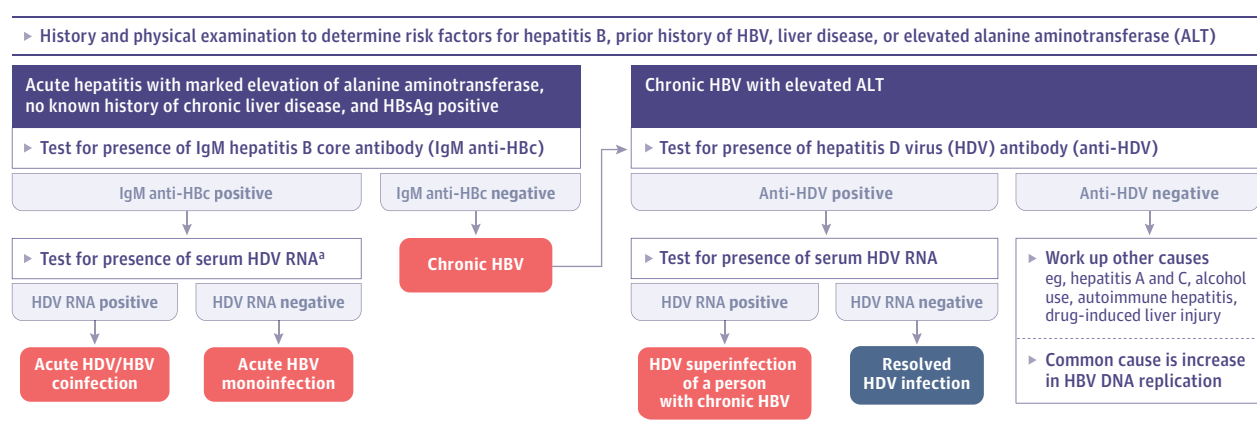
A retrospective cohort study showed that the adjusted 5-year risk of hepatocellular carcinoma was 13% in patients with cirrhosis due to HDV-HBV infection vs 2% to 4% in those with HBV infection only.⁵ Three systematic reviews and meta-analyses showed that chronic hepatitis D was associated with a 1.3- to 2.8-fold increased risk of hepatocellular carcinoma compared with HBV monoinfection.³⁶⁻³⁸

Diagnosis

Acute HDV-HBV coinfection is diagnosed by the simultaneous presence of HBsAg and IgM hepatitis B core antibody (IgM anti-HBc), and HDV RNA (Figure 2A and Figure 3). Serum HDAG may be present for only a few days. Therefore, if HDV-RNA assays are not available, anti-HDV (total, IgG and IgM) may be the only marker of acute HDV-HBV coinfection even though its appearance may be delayed for several months. The diagnosis of HDV infection is confirmed by detection of HDV RNA in serum. The diagnostic workup should include evaluation of other causes of acute hepatitis such as hepatitis A and C, and drug-induced liver injury. Resolution of HBV infection is indicated by disappearance of HBsAg and appearance of the hepatitis B surface antibody and by resolution of HDV infection by disappearance of HDV RNA. HDV testing should be performed in patients with acute hepatitis B particularly those with acute liver failure or risk factors for HDV infection.

HDV superinfection is characterized by the presence of HBsAg but not IgM anti-HBc, and detection of anti-HDV and HDV RNA (Figure 2B and Figure 3). The detection of HBsAg in a patient with

Figure 3. Diagnostic Algorithm of Hepatitis D Infection



All persons who test positive for hepatitis B surface antigen (HBsAg), including those with normal ALT levels, should have a 1-time screening for HDV by testing for anti-HDV. If patients test positive for anti-HDV, they should undergo further testing for HDV RNA to confirm ongoing infection. The 1-time HDV screening is particularly important for those with risk factors for HDV infection or rapidly

progressive liver disease. People with ongoing risk of exposure to HDV should be rescreened annually.

^a If there is no access to HDV RNA assays, test for the presence of anti-HDV in convalescent phase.

previously undiagnosed chronic HBV infection presenting with symptoms of acute hepatitis may lead to an erroneous diagnosis of acute hepatitis B if HDV testing is not performed. Patients with chronic HBV infection may experience hepatitis flares due to changes in the balance between HBV replication and host immune control, increased alcohol use, hepatitis A and C, or drug-induced liver injury. Those experiencing an unexplained hepatitis flare or unexplained rapid progression to cirrhosis should be tested for HDV superinfection. Patients with chronic HDV infection should be tested for hepatitis C and HIV infection, hepatitis A immunity, and HBV replication (hepatitis B e antigen and HBV DNA) and assessed for liver disease activity and fibrosis stage (Figure 3). Serum marker panels (such as the aspartate aminotransferase to platelet ratio index and fibrosis 4 markers [FIB-4]; age, aspartate aminotransferase, alanine aminotransferase, and platelets) and elastography are widely used in assessing fibrosis in liver diseases; however, threshold values for advanced fibrosis or cirrhosis have not been validated for hepatitis D and liver biopsy remains the most reliable method for fibrosis staging.³⁹ All patients with chronic hepatitis D should be monitored every 6 to 12 months with tests for blood cell counts, liver panel, HDV RNA and HBV DNA, and assessment of fibrosis stage with noninvasive tests every 2 to 3 years. Identifying patients with advanced fibrosis or cirrhosis is important because these patients require close monitoring and screening for hepatocellular carcinoma and esophageal varices.⁴⁰

The performance of diagnostic tests for HDV is highly variable. Because of the high-sequence heterogeneity of the HDV genome, some HDV-RNA assays may yield false-negative results in up to 5% of samples⁴¹ or underestimate viral load with certain genotypes, and up to a 2-log₁₀ (100-fold) difference in quantitative results have been reported when the same sample was tested in different laboratories.^{42,43}

Screening

International guidelines for HDV screening vary from testing all persons who have tested positive for HBsAg³⁹ to only those at

high-risk of HDV infection or those with active liver disease despite low or undetectable HBV-DNA levels.^{44,45} The American Association for the Study of Liver Diseases HBV Guidelines⁴⁴ recommend testing of persons who tested positive for HBsAg and who are at high risk of HDV, including those with HIV infection, persons who inject drugs, men who have sex with men, and immigrants from areas of high HDV endemicity. HDV screening rates among persons who tested positive for HBsAg are low both in the US (9%-13%), where risk-based screening is recommended,⁴⁴ and in Europe (8%-35%), where universal screening is recommended.³⁹ This is likely due to low awareness of hepatitis D, a perception that HDV infection is rare, or the belief that the patient is at low risk of HDV infection. Low rates of screening may also be due to lack of approved therapies, and limited access to reliable and/or affordable HDV tests. With increased recognition that HDV infection is underdiagnosed, despite causing more severe liver disease than HBV mono-infection, and with new treatment options likely to be approved soon, many experts have recommended universal screening of persons who tested positive for HBsAg with reflex anti-HDV testing, which if positive, is followed by HDV-RNA testing. One study from Spain showed that implementation of reflex testing for anti-HDV in patients with HBsAg increased screening rates from 7.6% to 93%. Although the rate of anti-HDV positivity remained stable, the reflex testing led to an increase in number of patients diagnosed with HDV infection.⁴⁶ Notably, 60% of those who tested positive had no known risk factors for HDV infection. If universal testing is adopted, yearly retesting is recommended for persons with HBsAg at increased risk of HDV infection.³⁹ A modeling study suggested that universal screening is cost-effective for countries with low prevalence of HBV or high prevalence of HDV but not for countries where HBV prevalence is high and HDV prevalence is low.⁴⁷ An alternative approach is targeted screening as recommended by the American Association for the Study of Liver Diseases.⁴⁴ Other considerations that may influence the adoption of universal screening include the availability of reliable and affordable tests, as well as effective, safe, and affordable treatment.

Table 1. Overview of Hepatitis D Treatment

Definitions of HDV treatment response			
Virological response	HDV RNA undetectable or decrease by $\geq 2 \log_{10}$ from baseline		
Biochemical response	Normal alanine aminotransferase levels		
Combined response	Virological + biochemical response, HDV RNA undetectable or decrease by $\geq 2 \log_{10}$ from baseline, and normal alanine aminotransferase levels		
HDV treatment indication			
Chronic hepatitis D (positive for HBsAg, anti-HDV, and HDV RNA) with elevated alanine aminotransferase levels or evidence of fibrosis or cirrhosis on liver biopsy or noninvasive tests			
Currently available treatment			
Name of drug	Dose regimen	Mechanism of action	Adverse effects
Peginterferon alfa-2a	180 $\mu\text{g/wk}$ subcutaneously $\times$ 48 wk, provided there are no contraindications to interferon (such as decompensated liver disease) Without HBV nucleos(t)ide analogues, used off-label, available in most countries	Inhibits HDV-RNA replication via enhancement of immune response and/or direct antiviral effects	Fatigue, influenza-like symptoms, decrease in white blood cell and platelet counts, unmask or exacerbate autoimmune illnesses, depression Can cause hepatitis flares and serious infections in patients with decompensated liver disease
Bulevirtide	2 mg/d subcutaneously as long as there is benefit, with or without HBV nucleos(t)ide analogues; not to be used in decompensated liver disease Approved by European Medicine Agency, availability and accessibility varies among European countries	Block interaction of HBV surface proteins on HDV viral particles with sodium taurocholate co-transporting polypeptide receptor for HDV entry into hepatocytes	Increase in bile acid levels but rarely associated with symptoms
Liver transplant	Peginterferon alfa and bulevirtide should not be used in decompensated liver disease Patients with decompensated liver disease should be referred for liver transplant evaluation	Removes infected and damaged liver and replaces it with a healthy uninfected liver	Death and complications associated with major surgery Risks associated with long-term use of antirejection medications including infections, kidney injury, hypertension, and diabetes Potential for acute and chronic rejection Potential for HBV and HDV reinfection if not adherent to prophylactic regimens to prevent reinfection

Abbreviations: anti-HDV, antibody to hepatitis D antigen; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus.

Treatment

The primary goal of HDV treatment is to improve clinical outcomes by preventing cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality through inhibition of HDV replication and decreasing hepatic inflammation and fibrosis. Ideally, the end point of HDV treatment is HBsAg seroclearance because this has been associated with improved clinical outcomes and HBsAg is necessary to complete the HDV life cycle.⁴⁸ Suppression of HDV replication with undetectable HDV RNA 24 weeks after cessation of treatment with pegylated interferon alfa was associated with improved event-free survival even in patients with occasional virological relapses during long-term follow-up.^{48,49} However, these end points were achieved in only approximately 30% of patients who received pegylated interferon alfa treatment.⁵⁰ Based on data from a small interferon alfa study,⁵¹ *virological response* defined as an HDV-RNA decrease by $2 \log_{10}$ or more (≥ 100 -fold) or undetectable HDV RNA, together with *biochemical response* (normal alanine aminotransferase) is considered a *combined response*. These definitions of end points have been adopted by regulatory agencies to evaluate new therapies.⁵²

Currently, no treatments for hepatitis D are approved by the US Food and Drug Administration. Interferon alfa and pegylated interferon alfa have shown some efficacy in clinical trials. They were approved for hepatitis B and hepatitis C but not for hepatitis D. HBV nucleos(t)ide analogues inhibit HBV replication by inhibit-

ing HBV polymerase, but they do not inhibit HDV RNA replication, which uses host enzymes.⁵³⁻⁵⁶ However, HBV nucleos(t)ide analogues should be used in patients with chronic hepatitis D who have indications for HBV treatment, ie, patients with cirrhosis and those with high levels of HBV DNA (>2000 IU/mL) and elevated alanine aminotransferase levels or liver fibrosis, unless the patient is receiving pegylated interferon alfa, which can inhibit both HBV and HDV replication.^{39,44,45}

Thus, therapies for hepatitis D are directed to deprive the virus of functions necessary to complete its life cycle that are provided by HBV or by the host.

Indications for HDV Treatment

All patients with chronic hepatitis D (HDV-RNA positive with elevated alanine aminotransferase levels or evidence of hepatic fibrosis) should be considered for antiviral treatment when safe and efficacious treatments are available (Table 1).³⁹ Currently, pegylated interferon alfa is the only HDV treatment that can be used off-label in most countries. Patients with HDV viremia and evidence of liver fibrosis with no decompensation and no contraindications should be treated with pegylated interferon alfa-2a. In some European countries, bulevirtide is available, but access and insurance coverage vary, and optimal dose and duration remain unclear. Results of phase 3 randomized clinical trials of bulevirtide and Isonafarnib may lead to expansion of treatment options for chronic

hepatitis D. Neither pegylated interferon alfa nor bulevirtide is recommended for patients with decompensated cirrhosis, and these patients should be referred for liver transplant evaluation.

Interferon Alfa

Interferon inhibits HDV replication and activates immune responses to HDV (Figure 1). A randomized clinical trial in which 41 patients with chronic hepatitis D were randomized to 3 times weekly subcutaneous injections of interferon alfa 9 mega units (MU) or 3 MU or no treatment for 48 weeks showed that the higher dose of interferon alfa increased the proportion of patients with undetectable HDV RNA (71% vs 36% vs 0%) at the end of treatment⁵⁷ (Table 2).^{54,55,57-63} At 12 years of follow-up, liver-related death or liver transplants occurred in 2 of 14 patients treated with 9 MU doses compared with 7 of 14 treated with 3-MU doses of interferon alfa and 7 of 13 untreated controls.⁵¹ Histological decrease in hepatic inflammation and fibrosis and clinical improvement were observed in the 9-MU dose group despite persistent detection of HDV RNA concentration in participant's serum, although HDV-RNA levels were on average at least 2 log₁₀ lower than baseline.⁵¹

Efficacy of interferon alfa as well as pegylated interferon alfa have been demonstrated in other randomized clinical trials (Table 2).⁵⁰ The Hep-Net-International Delta Hepatitis Intervention Trial I (HIDIT-I) trial⁵⁴ randomized 61 patients to pegylated interferon alfa with adefovir or adefovir alone for 48 weeks. At the end of treatment, 23% vs 0% patients who received combination therapy vs adefovir had undetectable HDV RNA. The HIDIT-II trial randomized 120 patients to pegylated interferon alfa-2a with or without tenofovir for 96 weeks.⁵⁵ Undetectable or a 2-log₁₀ or more HDV-RNA decrease was achieved in 48% of patients receiving both drugs and 33% of patients receiving only pegylated interferon alfa-2a at the end of treatment, and in 31% and 23%, respectively, at 24 weeks after treatment. These trials showed that adding an HBV nucleotide or extending treatment from 48 to 96 weeks did not increase HDV-RNA response or prevent posttreatment relapse. In the HIDIT-II trial, most patients with liver biopsies at week 96 had stable or improved liver histology. Overall, randomized clinical trials and case series have shown that interferon alfa and pegylated interferon alfa can inhibit HDV replication with approximately 30% of patients achieving undetectable HDV RNA 24 weeks after treatment,⁵⁰ although relapses can occur in up to 50% of patients after 10 years.^{49,64} Some case series found that repeated courses of interferon alfa or extending treatment beyond 2 years might increase the rate of attaining undetectable HBsAg, but this has not been demonstrated in randomized clinical trials.^{65,66}

Pegylated interferon alfa-2a is administered as weekly subcutaneous injections in doses of 180 µg for 48 weeks. It is associated with adverse effects including fatigue, flu-like symptoms, depression, neutropenia, and thrombocytopenia and risk of inducing severe hepatitis flare and exacerbation of underlying autoimmune illnesses; it is contraindicated in decompensated liver disease because of the risk of worsening liver failure due to hepatitis flares and serious infections.

Pegylated Interferon Lambda

Interferon lambda can induce antiviral activity similar to interferon alfa (Figure 1), but unlike interferon alfa receptors, which are expressed on most cell types, interferon lambda receptors are largely

restricted to cells of epithelial origin.⁶⁷ Pegylated interferon lambda was better tolerated than pegylated interferon alfa in patients with hepatitis B and hepatitis C, although it has not been approved for either condition.^{68,69} The open label, phase 2 LIMT-1⁵⁸ clinical trial evaluated pegylated interferon lambda for 48 weeks in 33 patients. At the 24-week follow-up, 36% and 16% of patients who received 180 µg vs 120 µg weekly doses, respectively, had undetectable HDV RNA (Table 2). There were no significant changes in blood cell counts and only 1 patient had mild depression, but 8 patients (24%) discontinued treatment due to hyperbilirubinemia, which resolved during follow-up.

Bulevirtide

Bulevirtide is a lipopeptide corresponding to 47 amino acids of the pre-S1 domain of HBsAg. It blocks the interaction between HDV (and HBV) virions and their hepatocyte receptor sodium taurocholate co-transporting polypeptide (Figure 1). Bulevirtide is administered as daily subcutaneous injections and is well tolerated, although it is associated with small increases in bile acid levels. Phase 2 clinical trials showed that up to 77% of patients achieved a 2-log₁₀ or more decline in or undetectable HDV-RNA levels after 24 weeks of 2-, 5-, or 10-mg daily doses of bulevirtide monotherapy, and higher rates of virological response were observed when bulevirtide was combined with pegylated interferon alfa (Table 2).^{59,70,71}

The phase 3 MYR301 trial⁶⁰ randomized 150 patients to either bulevirtide monotherapy 2 mg daily for 144 weeks, bulevirtide monotherapy 10 mg daily for 144 weeks, or a comparator group that was not treated during the first 48 weeks followed by treatment with bulevirtide 10 mg daily for 96 weeks. At 48 weeks, a virological response occurred in 71%, 76%, and 4%, biochemical response in 51%, 56%, and 12%, and combined response in 45%, 48%, and 2%, in the groups receiving 2 mg or 10 mg of bulevirtide or no treatment, respectively (Table 2). At 96 weeks, virological response (≥ 2 -log₁₀ decrease in HDV RNA) occurred in 76% and 82%, undetectable HDV RNA in 20% and 36%, biochemical response in 63% and 64%, and combined response in 55% and 56% of patients in the 2 groups treated with 2 mg and 10 mg of bulevirtide, respectively, at the start of the trial.⁶¹ Serious adverse events occurred in 4% and 8%, respectively. Serious adverse events included COVID-19, asthenia, cholelithiasis, foot fracture, and pneumonia, none of which was related to study treatment. There was minimal change in HBsAg level.

In 2020, the European Medicines Agency provided conditional approval of 2 mg of bulevirtide daily and standard approval in July 2023, for maintenance therapy for patients with chronic hepatitis D and compensated liver disease benefitting from the drug, alone or in combination with an HBV nucleos(t)ide analogue.⁷²

The antiviral effect of 2-mg doses of bulevirtide monotherapy has been confirmed in several observational studies in Europe, which showed that more than 50% achieved a 2-log or more decrease in HDV-RNA levels after 24 weeks of treatment, with some patients achieving undetectable HDV RNA during extended treatment.⁷³⁻⁷⁵ The 2-mg doses of bulevirtide appeared safe in patients with compensated cirrhosis and clinically significant portal hypertension.⁷⁶ However, there remain many unanswered questions regarding bulevirtide's exact mode of action, optimal dose, long-term safety, and role of HBV nucleos(t)ide analogue therapy. Adding pegylated interferon alfa consistently increased HDV virological response rates, with approximately 5% of patients clearing HBsAg.^{70,71} These

Table 2. Summary of Effects of Hepatitis D Virus Treatment in Selected Randomized Clinical Trials

Source	Treatment schedule	No. of patients	End of treatment response, No. (%) ^a			End of follow-up response, No. (%) ^b				
			Virological ^c	Biochemical ^d	Combined ^e	HBSAg ^f	Virological ^c	Biochemical ^d	Combined ^e	HBSAg ^f
Interferon alfa										
Farci et al., ⁵⁷ 1994	Interferon alfa 9 MU 3 × /wk × 48 wk	14	10 (71) ^g	10 (71)	7 (50)	0 ⁱ	6 (43) ^g	7 (50)	3 (21)	0 ⁱ
	Interferon alfa 3 MU 3 × /wk × 48 wk	14	5 (36) ^g	4 (29)	3 (21)	0 ⁱ	2 (14) ^g	1 (7)	0	0 ⁱ
	No treatment	13	0 ^g	1 (8)	0	0 ⁱ	0	1 (8)	0	0 ⁱ
Pegylated interferon alfa										
Wedemeyer, et al., ⁵⁴ 2011 (HIDIT-1)	Pegylated interferon alfa-2a 180 µg weekly + adefovir 10 mg daily × 48 wk	31	8 (26) ^h 7 (23) ^g	10 (32)		10 (32) ^j 0 ⁱ	10 (32) ^g	11 (35)		2 (6) ⁱ
	Adefovir 10 mg daily × 48 wk	30	0 ^h	2 (7)		0 ⁱ 0 ⁱ	2 (7) ^g	3 (10)		0 ⁱ 0 ⁱ
Wedemeyer et al., ⁵⁵ 2019 (HIDIT-2)	Pegylated interferon alfa-2a 180 µg weekly + tenofovir disoproxil fumarate 300 mg daily× 96 wk	59	28 (48) ^g	26 (44)		2 (3) ⁱ	18 (31) ^g	27 (46)		3 (5) ⁱ
	Pegylated interferon alfa-2a 180 µg weekly × 96 wk	61	20 (33) ^g	23 (38)		5 (8) ⁱ	14 (23) ^g	16 (26)		3 (5) ⁱ
Pegylated interferon lambda										
Etzion et al., ⁵⁸ 2023 (LIMT)	Pegylated interferon lambda 180 µg weekly × 48 wk	14	7 (50) ^h 5 (36) ^g	2 (14)	2 (14)	0 ⁱ	5 (36) ^h 5 (36) ^g	5 (36)	4 (29)	0 ⁱ
	Pegylated interferon lambda 120 µg weekly × 48 wk	19	4 (21) ^h 3 (16) ^g	2 (11)	1 (5)	0 ⁱ	3 (16) ^h 2 (10) ^g	5 (26)	2 (11)	0 ⁱ
Bulevirtide										
Results after 24 weeks of treatment										
Asselah et al., ⁵⁹ 2021 (MYR204)	Peginterferon alfa 180 µg weekly × 48 wk	25	10 (38) ^h 3 (13) ^g	3 (13)	3 (13)					
	Bulevirtide 2 mg/d + pegylated interferon alfa × 48 wk, then bulevirtide 2 mg/d × 48 wk	50	44 (88) ^h 12 (24) ^g	15 (30)	15 (30)					
	Bulevirtide 10 mg/d + pegylated interferon alfa × 48 wk, then bulevirtide 10 mg/d × 48 wk	50	46 (92) ^h 17 (34) ^g	12 (24)	12 (24)					
	Bulevirtide 10 mg/d × 96 wk	50	36 (72) ^h 8 (4) ^g	32 (64)	25 (50)					
Results after 48 weeks of treatment										
Wedemeyer et al., ^{60,61} 2023 (MYR301)	No medication × 48 wk, then bulevirtide 10 mg/d × 96 wk	51	2 (4) ^h 0 ^g	6 (12)	1 (2)	0 ⁱ				
	Bulevirtide 2 mg/d × 144 wk	49	35 (71) ^h 6 (12) ^g	25 (51)	22 (45)	0 ⁱ				
	Bulevirtide 10 mg/d × 144 wk	50	38 (76) ^h 10 (20) ^g	28 (56)	24 (48)	0 ⁱ				

(continued)

Table 2. Summary of Effects of Hepatitis D Virus Treatment in Selected Randomized Clinical Trials (continued)

Source	Treatment schedule	No. of patients	End of treatment response, No. (%) ^a			End of follow-up response, No. (%) ^b				
			Virological ^c	Biochemical ^d	Combined ^e	HBsAg ^f	Virological ^c	Biochemical ^d	Combined ^e	HBsAg ^f
			Results after 96 weeks of treatment							
Lonafarnib	No medication × 48 wk, then bulevirtide 10 mg/d × 96 wk	51	NA	22 (43)	20 (39)	1 (2) ^j 0 ⁱ				
	Bulevirtide 2 mg/d × 144 wk	49	37 (76) ^h 10 (20) ^g	31 (63)	27 (55)	0 ⁱ 0 ⁱ				
	Bulevirtide 10 mg/d × 144 wk	50	41 (82) ^h 18 (36) ^g	32 (64)	28 (56)	1 (2) ^j				
Etzion et al, ⁶² 2023 (D-LIVR)	Lonafarnib 50 mg 2 × /d + ritonavir 100 mg 2 × /d + pegylated interferon alfa 180 µg weekly × 48 wk	125	40 (32) ^h 26 (21) ^g	43 (34)	24 (19)		38 (35) ^h	42 (38)	29 (26)	
	Lonafarnib 50 mg 2 × /d + ritonavir 100 mg 2 × /d × 48 wk	178	26 (15) ^h 15 (8) ^g	44 (25)	18 (10)		32 (22) ^h	42 (28)	21 (16)	
	Pegylated interferon alfa 180 µg weekly × 48 wk	52	19 (37) ^h 14 (27) ^g	6 (12)	5 (10)		15 (37) ^h	9 (22)	6 (15)	
	Placebo × 48 wk	52	2 (4) ^h 2 (4) ^g	4 (8)	1 (2)		1 (3) ^h	2 (5)	0	
Nucleic acid polymer REP 2139										
Bazinet et al, ⁶³ 2021			Results for 11 patients			One-year posttreatment				
	REP 2139 500 mg IV weekly × 15 wk, then REP 2139 250 mg IV + pegylated interferon alfa 180 µg subcutaneously weekly × 15 wk, then pegylated interferon alfa 180 µg subcutaneously weekly × 33 wk	12	9 (82) ^g	1 (9)	1 (9)	5 (45) ⁱ	9 (82) ^h 7 (64) ^g	8 (73)	6 (55)	5 (45) ^j

Abbreviations: ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; IV, intravenous; MU, mega units; NA, not applicable.

^a For ongoing trials, on-treatment response at specified time points are presented in lieu of end of treatment response.

^b End of follow-up response indicates responses assessed 24 weeks after stopping treatment except for REP 2139 where responses 1 year after stopping treatment were reported.

^c Virological responses are defined as HDV-RNA undetectable or below limit of quantification or a 2 log₁₀ or more decline from pretreatment (assays with different limits of detection/quantification used in different studies).

^d Biochemical response is defined as normal ALT levels (different cutoffs used to define normal ALT in different studies).

^e Combined response is defined as a combination of virological and biochemical responses.

^f HBsAg responses are categorized as a more than 1-log₁₀ decline from pretreatment and undetectable or below limit of quantification.

^g Virological response defined as undetectable HDV-RNA levels or below the limit of quantification.

^h Virological responses defined as an HDV-RNA decline of a 2-log₁₀ or more from pretreatment.

ⁱ Response defined as undetectable HBsAg levels or below the limit of quantification.

^j Response defined as HBsAg as more than a 1-log₁₀ decline from pretreatment.

potential benefits need to be balanced against the adverse effects of pegylated interferon alfa. Data from observational studies from Europe suggest that bulevirtide may improve clinical outcomes in patients with cirrhosis,^{74,76} but these data require confirmation. There is a theoretical concern that hepatitis flares may occur after bulevirtide is discontinued, but only one case has been reported despite return of HDV viremia.

Lonafarnib

Lonafarnib is an oral drug that inhibits host farnesyltransferase (Figure 1). Farnesyltransferase is involved in the prenylation of the large HDAg, an essential step of HDV particle assembly.¹⁵ Lonafarnib is approved in the US and the European Union for progeria. Lonafarnib monotherapy has a dose-dependent antiviral effect, but high doses were associated with severe gastrointestinal adverse effects (nausea, diarrhea, weight loss). This led to the combination of a lower dose of lonafarnib with ritonavir, a cytochrome P450-3A4 inhibitor. This combination is intended to reduce adverse effects associated with lonafarnib while still attaining sufficiently high postabsorption levels of lonafarnib for efficacy against HDV. In a phase 2 clinical trial⁷⁷ of 55 participants, 50 mg of lonafarnib plus 100 mg of ritonavir twice daily provided the highest rate of virological response. The phase 3 Delta Liver Improvement and Virologic Response (D-LIVR) trial⁶² randomized 407 participants to 4 groups: lonafarnib plus ritonavir with or without pegylated interferon alfa, pegylated interferon alfa monotherapy, and placebo for 48 weeks. Preliminary results showed a combined response of 19%, 10%, 10%, and 2% at the end of treatment and 26%, 16%, 15%, and 0%, respectively, in the 4 treatment groups 24 weeks after treatment (Table 2).

Nucleic Acid Polymer

REP-2139, nucleic acid polymer, is a methylated derivative of a phosphorothioate oligodeoxyribonucleotide that blocks release of HBsAg particles from the liver into the bloodstream.⁷⁸ In a phase 2 clinical trial,⁶³ 12 patients received REP-2139 monotherapy followed by therapy with REP-2139 combined with pegylated interferon alfa, fol-

lowed by pegylated interferon alfa monotherapy for a total of 63 weeks. At the end of treatment, 9 patients had undetectable HDV RNA, and 1 had a combined response. One year after completing therapy, 7 patients continued with undetectable HDV RNA and 6 had a combined response. Marked alanine aminotransferase elevation (>300 U/L) occurred in 4 patients (33%) during treatment.

Other Drugs in Development

Given that HDV is dependent on HBV, specifically the surface proteins, and that both bulevirtide and lonafarnib have minimal effects on HBsAg levels, other drugs in clinical development such as short-interfering RNA to block HBsAg production or antibodies and other molecules to block binding of HBsAg to sodium taurocholate co-transporting polypeptide are being evaluated as single therapies and as part of combination therapies to increase rates of attaining sustained responses.

Limitations

This review has several limitations. First, some relevant articles may have been missed. Second, a systematic review to formally evaluate literature quality was not performed. Third, many studies on the natural history of hepatitis D included small numbers of patients with different inclusion criteria and variable follow-up duration. Results may not be widely generalizable. Fourth, the sensitivity and specificity of HDV-RNA assays have improved over time, which affects interpretation of data on HDV infection prevalence and the role of HDV viremia on clinical outcomes.

Conclusions

HDV infection affects approximately 12 million to 72 million people worldwide and is associated with more rapid progression to cirrhosis and liver failure and higher risk of hepatocellular carcinoma than infection with HBV alone. Bulevirtide was recently approved in Europe, whereas pegylated interferon alfa is the only treatment available in most countries.

ARTICLE INFORMATION

Accepted for Publication: October 23, 2023.

Published Online: November 9, 2023.
doi:10.1001/jama.2023.23242

Conflict of Interest Disclosures: Dr Negro reported receiving speaker or consulting fees from Gilead Sciences, Roche Diagnostics, and AbbVie outside the submitted work. Dr Lok reported receiving consulting fees from Abbott, Arbutus, Chroma, Clear B, Enanta, Enochian, GNI, GlaxoSmithKline, Grifol, Janssen, Novo Nordisk, Pfizer, Roche, and Virion; and grants from the TARGET HBV study outside the submitted work.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

- Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. *J Infect Dis*. 2020;221(10):1677-1687. doi:10.1093/infdis/jiz633
- Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*. 2019;68(3):512-521. doi:10.1136/gutjnl-2018-316601
- Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020;73(3):523-532. doi:10.1016/j.jhep.2020.04.008
- Caviglia GP, Ciancio A, Rizzetto M. A review of HDV infection. *Viruses*. 2022;14(8):1749. doi:10.3390/v14081749
- Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B: the European Concerted Action on Viral Hepatitis (Eurohep). *Gut*. 2000;46(3):420-426. doi:10.1136/gut.46.3.420
- Niro GA, Casey JL, Gravinese E, et al. Intrafamilial transmission of hepatitis delta virus: molecular evidence. *J Hepatol*. 1999;30(4):564-569. doi:10.1016/S0168-8278(99)80185-8
- Davaalkham D, Ojima T, Uehara R, et al. Hepatitis delta virus infection in Mongolia: analyses of geographic distribution, risk factors, and disease severity. *Am J Trop Med Hyg*. 2006;75(2):365-369. doi:10.4269/ajtmh.2006.75.365
- Stroffolini T, Ferrigno L, Cialdea L, et al; SEIEVA Collaborating Group. Incidence and risk factors of acute delta hepatitis in Italy: results from a national surveillance system. *J Hepatol*. 1994;21(6):1123-1126. doi:10.1016/S0168-8278(05)80629-4
- Urban S, Neumann-Haefelin C, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. *Gut*. 2021;70(9):1782-1794. doi:10.1136/gutjnl-2020-323888
- Rizzetto M, Canese MG, Aricò S, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut*. 1977;18(12):997-1003. doi:10.1136/gut.18.12.997
- Netter HJ, Barrios MH, Littlejohn M, Yuen LKW. Hepatitis delta virus (HDV) and delta-like agents:

- insights into their origin. *Front Microbiol.* 2021;12:652962. doi:10.3389/fmicb.2021.652962
12. Pérez-Vargas J, Pereira de Oliveira R, Jacquet S, Pontier D, Cosset FL, Freitas N. HDV-like viruses. *Viruses.* 2021;13(7):1207. doi:10.3390/v13071207
 13. Current ICTV taxonomy release: taxonomy browser. International Committee on Taxonomy. Accessed May 18, 2023. <https://ictv.global/taxonomy>
 14. Sureau C, Negro F. The hepatitis delta virus: replication and pathogenesis. *J Hepatol.* 2016;64(1)(suppl):S102-S116. doi:10.1016/j.jhep.2016.02.013
 15. Glenn JS, Watson JA, Havel CM, White JM. Identification of a prenylation site in delta virus large antigen. *Science.* 1992;256(5061):1331-1333. doi:10.1126/science.1598578
 16. Besombes C, Njoum R, Paireau J, et al. The epidemiology of hepatitis delta virus infection in Cameroon. *Gut.* 2020;69(7):1294-1300. doi:10.1136/gutjnl-2019-320027
 17. Kushner T, Serper M, Kaplan DE. Delta hepatitis within the Veterans Affairs medical system in the United States: prevalence, risk factors, and outcomes. *J Hepatol.* 2015;63(3):586-592. doi:10.1016/j.jhep.2015.04.025
 18. Patel EU, Thio CL, Boon D, Thomas DL, Tobian AAR. Prevalence of hepatitis B and hepatitis D virus infections in the United States, 2011-2016. *Clin Infect Dis.* 2019;69(4):709-712. doi:10.1093/cid/ciz001
 19. Nathani R, Leibowitz R, Giri D, et al. The delta delta: gaps in screening and patient assessment for hepatitis D virus infection. *J Viral Hepat.* 2023;30(3):195-200. doi:10.1111/jvh.13779
 20. Béguin C, Atkinson A, Boyd A, et al; for EuroSIDA and SHCS. Hepatitis delta infection among persons living with HIV in Europe. *Liver Int.* 2023;43(4):819-828. doi:10.1111/liv.15519
 21. Stroffolini T, Ciancio A, Furlan C, et al. Migratory flow and hepatitis delta infection in Italy: a new challenge at the beginning of the third millennium. *J Viral Hepat.* 2020;27(9):941-947. doi:10.1111/jvh.13310
 22. Burm R, Maravelia P, Ahlen G, et al. Novel prime-boost immune-based therapy inhibiting both hepatitis B and D virus infections. *Gut.* 2023;72(6):1186-1195. doi:10.1136/gutjnl-2022-327216
 23. Smedile A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. *Lancet.* 1982;2(8305):945-947. doi:10.1016/S0140-6736(82)90156-8
 24. Chin KP, Govindarajan S, Redeker AG. Permanent HBsAg clearance in chronic hepatitis B viral infection following acute delta superinfection. *Dig Dis Sci.* 1988;33(7):851-856. doi:10.1007/BF01550975
 25. Lucifora J, Alfaiate D, Pons C, et al. Hepatitis D virus interferes with hepatitis B virus RNA production via interferon-dependent and -independent mechanisms. *J Hepatol.* 2023;78(5):958-970. doi:10.1016/j.jhep.2023.01.005
 26. Sagnelli E, Felaco FM, Rapicetta M, et al. Interaction between HDV and HBV infection in HBsAg-chronic carriers. *Infection.* 1991;19(3):155-158. doi:10.1007/BF01643238
 27. Rizzetto M, Verme G, Recchia S, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen: an active and progressive disease unresponsive to immunosuppressive treatment. *Ann Intern Med.* 1983;98(4):437-441. doi:10.7326/0003-4819-98-4-437
 28. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. *J Viral Hepat.* 2010;17(11):749-756. doi:10.1111/j.1365-2893.2010.01353.x
 29. Niro GA, Smedile A, Ippolito AM, et al. Outcome of chronic delta hepatitis in Italy: a long-term cohort study. *J Hepatol.* 2010;53(5):834-840. doi:10.1016/j.jhep.2010.06.008
 30. Wranke A, Pinheiro Borzacov LM, Parana R, et al; Hepatitis Delta International Network. Clinical and virological heterogeneity of hepatitis delta in different regions world-wide: the Hepatitis Delta International Network (HDIN). *Liver Int.* 2018;38(5):842-850. doi:10.1111/liv.13604
 31. Kamal H, Aleman S; D-SOLVE Consortium. Natural history of untreated HDV patients: always a progressive disease? *Liver Int.* 2023;43(suppl 1):5-21. doi:10.1111/liv.15467
 32. Palom A, Rodríguez-Tajes S, Navascués CA, et al. Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia. *Aliment Pharmacol Ther.* 2020;51(1):158-166. doi:10.1111/apt.15521
 33. Romeo R, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. *PLoS One.* 2014;9(3):e92062. doi:10.1371/journal.pone.0092062
 34. Kamal H, Westman G, Falconer K, et al. Long-term study of hepatitis delta virus infection at secondary care centers: the impact of viremia on liver-related outcomes. *Hepatology.* 2020;72(4):1177-1190. doi:10.1002/hep.31214
 35. Roulot D, Brichler S, Layese R, et al; Deltavir study group. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. *J Hepatol.* 2020;73(5):1046-1062. doi:10.1016/j.jhep.2020.06.038
 36. Alfaiate D, Clément S, Gomes D, Goossens N, Negro F. Chronic hepatitis D and hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. *J Hepatol.* 2020;73(3):533-539. doi:10.1016/j.jhep.2020.02.030
 37. Kamal H, Fornes R, Simin J, et al. Risk of hepatocellular carcinoma in hepatitis B and D virus co-infected patients: a systematic review and meta-analysis of longitudinal studies. *J Viral Hepat.* 2021;28(10):1431-1442. doi:10.1111/jvh.13577
 38. Chang TE, Su CW, Huang YS, Huang YH, Hou MC, Wu JC. Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono infection: a meta-analysis. *J Chin Med Assoc.* 2022;85(1):30-41. doi:10.1097/JCMA.0000000000000606
 39. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis delta virus. *J Hepatol.* 2023;79(2):433-460. doi:10.1016/j.jhep.2023.05.001
 40. Tapper EB, Parikh ND. Diagnosis and management of cirrhosis and its complications: a review. *JAMA.* 2023;329(18):1589-1602. doi:10.1001/jama.2023.5997
 41. Wedemeyer H, Leus M, Battersby TR, et al; HDV RNA Assays Writing Group at the HBV Forum. HDV RNA assays: performance characteristics, clinical utility and challenges. *Hepatology.* Published online August 28, 2023. doi:10.1097/HEP.0000000000000584
 42. Le Gal F, Brichler S, Sahli R, Chevrete S, Gordien E. First international external quality assessment for hepatitis delta virus RNA quantification in plasma. *Hepatology.* 2016;64(5):1483-1494. doi:10.1002/hep.28772
 43. Stelzl E, Ciesek S, Cornberg M, et al. Reliable quantification of plasma HDV RNA is of paramount importance for treatment monitoring: a European multicenter study. *J Clin Virol.* 2021;142:104932. doi:10.1016/j.jcv.2021.104932
 44. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560-1599. doi:10.1002/hep.29800
 45. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int.* 2016;10(1):1-98. doi:10.1007/s12072-015-9675-4
 46. Palom A, Rando-Segura A, Vico J, et al. Implementation of anti-HDV reflex testing among HBsAg-positive individuals increases testing for hepatitis D. *JHEP Rep.* 2022;4(10):100547. doi:10.1016/j.jhepr.2022.100547
 47. Razavi HA, Buti M, Terrault NA, et al; Polaris Observatory. Hepatitis D double reflex testing of all hepatitis B carriers in low-HBV- and high-HBV/HDV-prevalence countries. *J Hepatol.* 2023;79(2):576-580. doi:10.1016/j.jhep.2023.02.041
 48. Wranke A, Serrano BC, Heidrich B, et al. Antiviral treatment and liver-related complications in hepatitis delta. *Hepatology.* 2017;65(2):414-425. doi:10.1002/hep.28876
 49. Heidrich B, Yurdaydin C, Kabaçam G, et al; HDIT-1 Study Group. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. *Hepatology.* 2014;60(1):87-97. doi:10.1002/hep.27102
 50. Abdrakhman A, Ashimkhanova A, Almawi WY. Effectiveness of pegylated interferon monotherapy in the treatment of chronic hepatitis D virus infection: a meta-analysis. *Antiviral Res.* 2021;185:104995. doi:10.1016/j.antiviral.2020.104995
 51. Farci P, Roskams T, Chessa L, et al. Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology.* 2004;126(7):1740-1749. doi:10.1053/j.gastro.2004.03.017
 52. Chronic hepatitis D virus infection: developing drugs for treatment guidance for industry. US Food and Drug Administration. November 2019. Accessed July 2, 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chronic-hepatitis-d-virus-infection-developing-drugs-treatment-guidance-industry>
 53. Niro GA, Ciancio A, Tillman HL, et al. Lamivudine therapy in chronic delta hepatitis: a multicentre randomized-controlled pilot study. *Aliment Pharmacol Ther.* 2005;22(3):227-232. doi:10.1111/j.1365-2036.2005.02542.x

54. Wedemeyer H, Yurdaydin C, Dalekos GN, et al; HIDIT Study Group. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *N Engl J Med*. 2011;364(4):322-331. doi:10.1056/NEJMoa0912696
55. Wedemeyer H, Yurdaydin C, Hardtke S, et al; HIDIT-II study team. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial. *Lancet Infect Dis*. 2019;19(3):275-286. doi:10.1016/S1473-3099(18)30663-7
56. Wedemeyer H, Schöneweis K, Bogomolov P, et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infect Dis*. 2023;23(1):117-129. doi:10.1016/S1473-3099(22)00318-8
57. Farci P, Mandas A, Coiana A, et al. Treatment of chronic hepatitis D with interferon alfa-2a. *N Engl J Med*. 1994;330(2):88-94. doi:10.1056/NEJM199401133300202
58. Etzion O, Hamid SS, Lurie Y, et al. Treatment of chronic hepatitis D with peginterferon lambda-the phase 2 LINT-1 clinical trial. *Hepatology*. 2023;77(6):2093-2103. doi:10.1097/HEP.0000000000000309
59. Asselah T, Arama SS, Bogomolov P, et al. Safety and efficacy of bulevirtide monotherapy and in combination with peginterferon alfa-2a in patients with chronic hepatitis delta: 24 weeks interim data of MYR204 phase 2b study. *J Hepatol*. 2021;75(suppl 2):S291. July 2, 2021. Accessed October 17, 2023. https://easl.eu/wp-content/uploads/2021/06/EASL_2021_Version-3-new.pdf
60. Wedemeyer H, Aleman S, Brunetto MR, et al; MYR 301 Study Group. A phase 3, randomized trial of bulevirtide in chronic hepatitis D. *N Engl J Med*. 2023;389(1):22-32. doi:10.1056/NEJMoa2213429
61. Wedemeyer H, Aleman S, Brunetto M, et al. Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D: results from an interim analysis of a phase 3 randomized study. *J Hepatol*. 2023;78(suppl 1):S57. doi:10.1016/S0168-8278(23)00522-6
62. Etzion O, Hamid SS, Asselah T, et al. Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of lonafarnib-boosted with ritonavir with or without peginterferon alfa in patients with chronic hepatitis delta. *J Hepatol*. 2023;78(suppl 1):S10. doi:10.1016/S0168-8278(23)00451-8
63. Bazinet M, Pântea V, Cebotarescu V, et al. Persistent control of hepatitis B virus and hepatitis delta virus infection following REP 2139-Ca and pegylated interferon therapy in chronic hepatitis B virus/hepatitis delta virus coinfection. *Hepatology Commun*. 2020;5(2):189-202. doi:10.1002/hep4.1633
64. Wranke A, Hardtke S, Heidrich B, et al. Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta. *J Viral Hepat*. 2020;27(12):1359-1368. doi:10.1111/jvh.13366
65. Lau DT, Kleiner DE, Park Y, Di Bisceglie AM, Hoofnagle JH. Resolution of chronic delta hepatitis after 12 years of interferon alfa therapy. *Gastroenterology*. 1999;117(5):1229-1233. doi:10.1016/S0016-5085(99)70409-9
66. Yurdaydin C, Keskin O, Kalkan Ç, et al. Interferon treatment duration in patients with chronic delta hepatitis and its effect on the natural course of the disease. *J Infect Dis*. 2018;217(8):1184-1192. doi:10.1093/infdis/jix656
67. Sommereyns C, Paul S, Staeheli P, Michiels T. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. *PLoS Pathog*. 2008;4(3):e1000017. doi:10.1371/journal.ppat.1000017
68. Muir AJ, Arora S, Everson G, et al; EMERGE study group. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J Hepatol*. 2014;61(6):1238-1246. doi:10.1016/j.jhep.2014.07.022
69. Chan HLY, Ahn SH, Chang TT, et al; LIRA-B Study Team. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: a randomized phase 2b study (LIRA-B). *J Hepatol*. 2016;64(5):1011-1019. doi:10.1016/j.jhep.2015.12.018
70. Wedemeyer H, Schöneweis K, Bogomolov P, et al. 48 weeks of high dose (10 Mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection. *J Hepatol*. 2020;73(suppl 1):S52-S53. doi:10.1016/S0168-8278(20)30651-6
71. Lampertico P, Roulot D, Wedemeyer H. Bulevirtide with or without pegIFNα for patients with compensated chronic hepatitis delta: from clinical trials to real-world studies. *J Hepatol*. 2022;77(5):1422-1430. doi:10.1016/j.jhep.2022.06.010
72. Hepcludex. European Medicines Agency. Accessed October 6, 2023. <https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex>
73. Loglio A, Ferenci P, Uceda Renteria SC, et al. Safety and effectiveness of up to 3 years' bulevirtide monotherapy in patients with HDV-related cirrhosis. *J Hepatol*. 2022;76(2):464-469. doi:10.1016/j.jhep.2021.10.012
74. Jachs M, Schwarz C, Panzer M, et al. Response-guided long-term treatment of chronic hepatitis D patients with bulevirtide—results of a "real world" study. *Aliment Pharmacol Ther*. 2022;56(1):144-154. doi:10.1111/apt.16945
75. Dietz-Fricke C, Tacke F, Zöllner C, et al. Treating hepatitis D with bulevirtide—real-world experience from 114 patients. *JHEP Rep*. 2023;5(4):100686. doi:10.1016/j.jhepr.2023.100686
76. Degasperis E, Anolli MP, Uceda Renteria SC, et al. Bulevirtide monotherapy for 48 weeks in patients with HDV-related compensated cirrhosis and clinically significant portal hypertension. *J Hepatol*. 2022;77(6):1525-1531. doi:10.1016/j.jhep.2022.07.016
77. Yurdaydin C, Keskin O, Yurdcu E, et al. A phase 2 dose-finding study of lonafarnib and ritonavir with or without interferon alpha for chronic delta hepatitis. *Hepatology*. 2022;75(6):1551-1565. doi:10.1002/hep.32259
78. Boulon R, Blanchet M, Lemasson M, Vaillant A, Labonté P. Characterization of the antiviral effects of REP 2139 on the HBV lifecycle in vitro. *Antiviral Res*. 2020;183:104853. doi:10.1016/j.antiviral.2020.104853