Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection

AUTHORS: Francesco Negro, MD, Anna SF Lok, MD
SECTION EDITOR: Rafael Esteban, MD
DEPUTY EDITOR: Jennifer Mitty, MD, MPH

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **May 01, 2023.**

INTRODUCTION

Hepatitis D virus (HDV) infection is caused by a defective virus: the hepatitis D virus. HDV is often referred to as hepatitis delta virus or delta agent. However, the term HDV is preferred. Individuals with hepatitis D are always dually infected with HDV and hepatitis B virus (HBV). Although HDV can replicate autonomously, the simultaneous presence of HBV is required for complete virion assembly and secretion.

This topic review will provide general information concerning the virology, epidemiology, clinical features, and diagnosis of HDV infection. Issues related to treatment, prevention, and liver transplantation are discussed separately. (See "Treatment and prevention of hepatitis D virus infection" and "Liver transplantation in adults: Hepatitis D virus reinfection in liver transplant recipients".)

VIROLOGY

HDV virion — The hepatitis D virion comprises an RNA genome, a single HDV encoded antigen, and a lipoprotein envelope provided by hepatitis B virus (HBV) (figure 1).

- **HDV genome** – The HDV genome is a small RNA molecule (1676 to 1683 nucleotides in size) bearing some structural analogies with plant viroids and virusoids [1]. HDV RNA is a

single-stranded circle, with a high degree of self-complementarity and G+C content causing the circle to collapse as a rod-like structure [1]. Significant sequence heterogeneity (as high as 40 percent) exists among the different HDV isolates that have been sequenced, and a classification into eight HDV genotypes has been proposed [2].

- **Hepatitis D antigen** – The only antigen associated with HDV, the hepatitis D antigen (HDAg), is a structural component of the virion. It consists of a protein encoded by an open reading frame present on the RNA strand complementary to the RNA genome (antigenomic strand) [1]. Approximately 70 molecules of HDAg are complexed with each molecule of HDV RNA to form the viral ribonucleoprotein.

  Two forms of HDAg are co-expressed in infected individuals. Each HDAg has a different function as described below. (See 'Pathogenesis' below.)

  The two HDAg molecules differ by 19 amino acids at the C-terminus; the molecular weights are approximately 24 and 27 kilodaltons (kd). Their synthesis arises via an RNA editing process during HDV replication [3]. (See 'Pathogenesis' below.)

  - The stop codon UAG of the messenger RNA directing the synthesis of the HDAg causes the translation of HDAg to terminate, thereby giving rise to the small HDAg. During HDV RNA replication, this stop codon is deaminated on the antigenomic HDV RNA by a cellular enzyme (the adenosine deaminase acting on RNA 1, ADAR1) to UIC (in which "I" stands for inosine).

  - During the next replication cycle, the "I" on the antigenomic RNA is read as a "G," leading to the replacement of the "A" with a "C" in the genomic HDV RNA. During the transcription of the messenger RNA directing the synthesis of the HDAg, the "C" will lead to the replacement of the UAG stop codon with a UGG codon, which directs the incorporation of tryptophan into the nascent HDAg. Translation of HDAg then proceeds until a new stop codon is reached, 19 amino acids downstream, thereby giving rise to the large HDAg.

- **Lipoprotein envelope of HDV** – The lipoprotein envelope of HDV is provided by the HBV and consists of the same proteins (large, middle, and small S) that are found in the HB virion; their relative proportion depends upon the level of HBV replication [4].

HDV life cycle — Individuals with hepatitis D are always dually infected with HDV and HBV. Although HDV can replicate autonomously [1], the simultaneous presence of HBV is typically required for complete virion assembly and secretion. Due to interference mechanisms that are not well understood, HBV replication is suppressed in most HDV-infected individuals.

HDV replicates at very high levels in hepatocytes [5]. The sodium taurocholate cotransporting polypeptide (NTCP), which is the receptor for HBV, has also been identified as the receptor for HDV [6,7]. (See "Characteristics of the hepatitis B virus and pathogenesis of infection", section on 'Replication cycle'.)

The steps in the HDV replication cycle can be summarized as follows:

- Once inside the hepatocyte, HDV RNA is found within the nucleus, where it is transcribed into its complementary RNA (antigenomic HDV RNA). Two forms of antigenomic HDV RNA exist: a 0.8 kilobase (kb) RNA, which is the messenger RNA being translated into the HDAg [8], and the full-length 1.7 kb RNA, which is the template directing the transcription back into the HDV genome [1]. The host RNA polymerase II appears to be involved in the transcription of the 0.8 kb mRNA in a process that is regulated by direct binding with the HDAg itself [9,10]. In addition, the transcription of the full-length genomic and antigenomic RNAs occurs by the cellular RNA polymerase II [11].

- HDV RNA replication is **activated** by the small HDAg through direct binding of the HDAg to the HDV RNA.

- The large HDAg **suppresses** HDV replication. In addition, it directs packaging of the HD virion through an interaction between the extra 19 amino acids at the C-terminal end and the small S protein (surface antigen of the hepatitis B virus [HBsAg]) of the helper HBV [3].

- Completion of the HD virion assembly and release is dependent on the simultaneous presence of HBV which provides the envelope. Without HBV, HDV cannot be rescued and exit the cells.

There have been some case reports of HDV infection occurring in the absence of hepatitis B coinfection in patients with hepatitis C virus (HCV) infection and Sjögren's disease [12,13]. However, these findings have not been confirmed in subsequent studies [14-16]. As an example, one study of 2123 plasma samples positive for anti-HCV antibody found that 1.9 percent of samples tested positive for HDV antibody (anti-HDV) but none were HDV RNA positive, suggesting that HCV may not have a supportive role in HDV transmission [14].

However, divergent HDV-like viruses have been detected in fish, birds, amphibians, and invertebrates, without evidence of any HBV-like agent supporting infection [17]. Another study found that HDV can be transmitted and propagated in experimental infections ex vivo and in vivo by different enveloped viruses unrelated to HBV, including HCV and flaviviruses such as Dengue and West Nile virus [18].

PATHOGENESIS

The detailed mechanisms by which HDV induces liver damage are unknown. However, the pathogenesis of hepatitis D-related liver disease appears to depend on the interplay of three major factors:

- HDV-associated factors, such as genotype [19] and the expression of specific HDV antigen (HDAg) species [20]
- Host-associated factors, such as the immune response
- Helper virus-associated factors, such as the hepatitis B virus (HBV) genotype and the level of HBV replication [21]

HDV is believed to cause direct cytopathic damage during acute infection, whereas immune-mediated damage predominates during chronic infection [1].

EPIDEMIOLOGY

Data on HDV epidemiology have mostly been gathered in chronic hepatitis B virus (HBV) carriers superinfected with HDV, in whom HDV infection has progressed to chronicity. HDV antibody (anti-HDV) is present in high titers in these patients, and the prevalence of chronic HDV infection can be reliably determined.

However, the incidence of acute hepatitis D may be underestimated [22]. Although the commercial availability of assays for the detection of anti-HDV has improved our understanding of the epidemiology of HDV infection, these assays have limitations. As an example, in acute hepatitis D, anti-HDV appears very late and may be missed if repeated testing is not performed. This is especially true in immunocompromised individuals (eg, patients with human immunodeficiency virus [HIV]) in whom a strong antibody response to HDV may be delayed or absent. Furthermore, after resolution of acute hepatitis D, anti-HDV may disappear with time. Thus, in some patients, recognition of past HDV infection may be impossible. More detailed discussion of diagnostic testing is presented below. (See 'Diagnosis of HDV infection' below.)

Prevalence of disease — The prevalence of HDV in patients with chronic HBV infection varies across studies. These variations are likely due to several factors, including lack of high-quality data because of under-testing of HDV in persons with chronic HBV infection, the variable accuracy of HDV screening tests, and the lack of population-based studies (much of the

available data focuses on patients who are at high risk for HDV infection or who have more advanced liver disease).

- **Prevalence worldwide** – Historical data suggest that approximately 15 to 20 million of the 257 million HBV carriers worldwide may be infected with HDV [23,24]. Data from meta-analyses and systematic reviews on the global burden of chronic HDV infection vary widely, with an estimated number of persons infected ranging from 12 million to 72 million [25-27]. The 2017 World Health Organization (WHO) Global Hepatitis Report estimated that 5 percent of individuals with HBV infection are coinfected with HDV (ie, approximately 15 million individuals infected with HDV worldwide) [28]. In another report, the HDV prevalence was estimated at 25.8 and 19.8 percent in HBV patients with cirrhosis or hepatocellular carcinoma, respectively [26].

- **Prevalence in the United States** – In the United States, the prevalence of HDV infection also varies and reports range from 6 to 42 percent of persons with chronic HBV [29-31].

  In one study of hepatitis B surface antigen (HBsAg)-positive adults in the 2011 to 2016 National Health and Nutrition Examination Survey (NHANES) 42 percent were anti-HDV positive (33 percent among United States born and 46 percent among foreign born) [29]. However, this nationwide prevalence estimate was extrapolated from a total of 113 HBsAg-positive persons who may not be representative of the general population, and there were concerns about false positive results with the assay that was used. By contrast, a different report found that only 6 percent of persons with chronic HBV infection screened for anti-HDV in one United States hospital tested positive between 2016 to 2021 [30]. One report estimated that 14 percent of foreign-born Americans with chronic HBV had HDV infection using 2019 US census bureau data and data on HDV prevalence from the countries these persons emigrated from (although data were missing or inadequate in many countries) [31].

In some countries, such as Italy, improvements in socioeconomic conditions, increased awareness of how infectious diseases are transmitted, and aggressive vaccination campaigns against HBV led to a dramatic decrease in the incidence of HBV infection and the spread of HDV infection among young adults through 1999 [32]. However, this decline appears to have stopped, and some recrudescence of HDV prevalence has been reported in both the Mediterranean area [33] and in Central Europe [34]. Immigration from endemic countries has been suggested to be the cause for this trend [35,36], but is not the only reason: injection drug use, sexual practices, and body modification procedures may also be involved. (See 'Risk factors for disease' below.)

Risk factors for disease — HDV is predominantly confined to groups with known risk factors for HDV (persons who inject drugs, individuals who have received multiple transfusions in the past, men who have sex with men who engage in unsafe sexual behaviors [eg, condomless sex with multiple partners], and persons who emigrated from countries with a high prevalence of HDV infection). (See 'Geographic distribution' below.)

Geographic distribution — HDV is not distributed uniformly across the globe, and the geographic distribution of HDV infection does not parallel that of HBV. As an example, there is a high prevalence in the Mediterranean Basin, Mongolia, Moldova, and some countries in Sub-Saharan Africa [27], whereas other areas, including many Asian countries, are relatively spared despite the high prevalence of HBV infection. As examples:

- **The Mediterranean Basin** – HDV infection is endemic in the Mediterranean Basin, where intrafamilial spread is thought to have been prominent in the past, but data suggest that the prevalence of HDV infection has declined. In a study from Italy, anti-HDV antibodies were detected in only 69 of 834 HBsAg-positive patients (8.3 percent) in 1997, compared with 23 and 14 percent in studies from 1987 and 1992, respectively [32]. The decrease resulted principally from a reduction in chronic HDV infection in young adults. In addition, vaccination campaigns against HBV have decreased HDV infection as well. However, more recent data suggest the prevalence appears to be increasing in immigrant populations [37,38].

- **Asia** – The prevalence of HDV infection among HBV carriers in Asia is quite variable. Although low in Japan [22], other countries, especially Mongolia and those in Central Asia, are heavily affected, and the prevalence among HBV carriers can be as high as 60 percent in some areas in Pakistan [39]. HDV infection is not infrequent in Taiwan [40], being predominantly sexually transmitted, but is rare in Hong Kong, where it is largely confined to persons who inject drugs [41]. In one report from Shanghai, that evaluated 225 serum samples from persons who were HBsAg-positive, anti-HDV was detected in 4.9 percent; however, they only tested hospitalized patients with elevated transaminase levels [42]. A more recent study of 4103 HBsAg-positive sera from China found that prevalence of anti-HDV was limited to geographic hot spots in Mongolia, Xinjiang and high-risk persons who inject drugs and was not detected in any of 2364 HBsAg-positive persons in other areas [16].

- **Western countries** – HDV infection is uncommon in Western countries and predominantly confined to high-risk groups, as described above [29]. (See 'Risk factors for disease' above.)

It should be noted that much of the data describing the epidemiology of HDV are based upon studies conducted more than 20 years ago, and updated information is not available in many countries.

CLINICAL MANIFESTATIONS

Due to its dependence upon hepatitis B virus (HBV), HDV infection always occurs in association with HBV infection. The presentation depends in part upon whether the patient has acute infection (eg, HBV/HDV coinfection or acute HDV superinfection) or chronic HDV. In patients with chronic HDV, clinical manifestations can range from the asymptomatic carrier state to acute liver failure. (See 'Virology' above and 'Pathogenesis' above.)

This section will review the clinical and laboratory findings associated with the different types of HDV infection (table 1). The approach to diagnosing HDV is discussed below. (See 'Diagnosis of HDV infection' below.)

Acute HBV/HDV coinfection — Acute HBV and acute HDV coinfection can occur in individuals susceptible to HBV infection (ie, hepatitis B surface antibody [anti-HBs]-negative). Clinically, this entity is indistinguishable from classical acute HBV infection and is usually transient and self-limited. (See "Hepatitis B virus: Overview of management", section on 'Acute infection'.)

Most patients with acute HBV/HDV infection recover from both HBV and HDV infection, but acute HBV/HDV infection is associated with a higher risk of acute liver failure than acute HBV monoinfection. The rate of progression to chronic HDV infection is similar to that observed for HBV since the persistence of HDV infection is dependent upon persistence of HBV infection [43].

Acute HDV superinfection — HDV superinfection in a patient with chronic HBV may present as a severe acute hepatitis in a previously unrecognized HBV carrier or as an exacerbation of pre-existing chronic hepatitis B. Progression to chronic HDV infection occurs in almost all patients [44]; however, HBV replication is usually suppressed by HDV. Clinically, the presentation is often indistinguishable from those with acute HBV/HDV infection, but serologic testing may be able to separate the two entities (figure 2).

Chronic HDV infection — Once chronic HDV infection is established, it usually exacerbates the pre-existing liver disease due to HBV. In general, chronic HDV infection is associated with more rapid progression to cirrhosis and an increased risk of hepatocellular carcinoma [45].

- **Cirrhosis** – In patients with chronic HDV, the initial progression towards cirrhosis tends to be rapid [46,47] and is generally faster than among patients with HBV monoinfection [48].

Progression from compensated to decompensated cirrhosis is less accelerated but still more rapid than that of HBV monoinfection. This was illustrated in a report from Italy in which the estimated 5- and 10-year probability of survival (free of liver transplantation) in patients who had already developed clinically overt cirrhosis was 49 and 40 percent, respectively [48]. A more detailed discussion of the clinical manifestations of cirrhosis are presented elsewhere. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis" and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

- **Hepatocellular carcinoma** – There also appears to be an increased risk of hepatocellular carcinoma in patients with chronic HDV. In a meta-analysis that included 93 observational studies, the pooled odds ratio of hepatocellular carcinoma in persons with HBV/HDV coinfection compared to HBV monoinfection was 2.77 (95% CI 1.79-4.28) [49]. This association was seen even after adjusting for a higher prevalence of cirrhosis in those with HBV/HDV coinfection compared with HBV monoinfection; the association was particularly strong in prospective cohort studies.

However, the clinical course of chronic HDV can vary, and in some patients HDV-associated chronic liver disease may run an indolent course [49]. The clinical course is influenced by several factors, such as persistent HDV replication and HDV genotype. In a study of 299 patients with hepatitis D infection who were followed for up to 28 years, persistent HDV replication was associated with annual rates of development of cirrhosis and hepatocellular carcinoma of 4 and 2.8 percent, respectively [50]. In this study, the only predictor of liver-related mortality was persistent HDV replication. The importance of genotypes is discussed below. (See 'Importance of HDV genotypes' below.)

Importance of HDV genotypes — Studies have demonstrated that clinical outcomes may be related to the different HDV genotypes [19,51,52], which seem to cluster in distinct geographical areas. However, superinfection, or mixed infection with different genotypes, can occur, particularly in patients who are at high risk for multiple exposures. In such patients, a single genotype usually predominates, with the minor genotype representing only approximately 10 percent of the total viral population [53].

- **Genotype 1** – In the Western world, where the predominant genotype is genotype 1, the clinical presentation can vary [52]. As an example, patients with genotype 1 infection with acute hepatitis D infection have an increased risk of acute liver failure when compared with those with acute hepatitis B [54]. In addition, once chronic HDV infection is established, it usually exacerbates the preexisting liver disease due to HBV [44], and progression towards cirrhosis may be rapid [46,47]. However, HDV-associated chronic liver

disease may also run an indolent course [55], and asymptomatic HDV carriers have been found in some geographical areas [56]. (See 'Geographic distribution' above.)

Many patients who are referred for evaluation of HDV were infected years ago; in such persons, HDV-related disease rapidly progressed to cirrhosis, but then subsequent disease progression was slow. This was illustrated in a report from Italy in which the estimated 5- and 10-year probability of survival free of liver transplantation in patients who had already developed clinically overt cirrhosis was 49 and 40 percent, respectively [48]. However, patients with active HBV and HDV replication are more likely to develop liver decompensation [21].

Whether superimposed HDV infection accelerates the development of hepatocellular carcinoma in patients with hepatitis B surface antigen (HBsAg)-positive cirrhosis is controversial. However, a retrospective study involving 200 patients with compensated HBV-related cirrhosis, of whom 20 percent were HDV antibody (anti-HDV) positive, found that HDV infection increased the risk of hepatocellular carcinoma threefold and mortality twofold [57]. After adjustment for clinical and serological differences at baseline, the estimated five-year risk for developing hepatocellular carcinoma was 13, 4, and 2 percent for anti-HDV-positive/hepatitis B e antigen (HBeAg)-negative, anti-HDV-negative/HBeAg-negative, and anti-HDV-negative/HBeAg-positive patients, respectively. The corresponding figures for hepatic decompensation were 18, 8, and 14 percent, respectively. In addition, a recent meta-analysis found that patients with superimposed HDV infection had a higher risk of hepatocellular carcinoma compared to those with HBV monoinfection.

- **Genotype 2** – In the Far East, where the predominant genotype is genotype 2, the risk of acute liver failure and rapidly progressive liver disease is low compared to other HDV genotypes [51,58].

- **Genotype 3** – Severe outbreaks of acute hepatitis D with a high incidence of acute liver failure have been reported in the Yukpa Indians of Venezuela [59]; the Sierra Nevada de Santa Marta in Colombia [60]; and some remote areas of the Brazilian [61], Peruvian [19], and Amazon basin. Viral factors have been postulated to be related to the fulminant course in these outbreaks, as HDV isolates from Colombia and Peru belong to a distinct viral genotype denoted genotype 3 [19].

- **Other genotypes** – At least five additional HDV genotypes have been described [2,62]. Sequences previously assigned to genotype 2b are now classified as genotype 4, and African sequences seem to cluster into four additional genotypes, named from 5 to 8.

These new genotypes are less well characterized as to their disease features compared with genotypes 1 to 3.

DIAGNOSIS OF HDV INFECTION

Due to the dependence of HDV on hepatitis B virus (HBV), the presence of hepatitis B surface antigen (HBsAg) is necessary for the diagnosis of HDV infection. The additional presence of immunoglobulin (Ig)M antibody to hepatitis B core antigen (IgM anti-HBc) is necessary for the diagnosis of acute HBV/HDV coinfection (table 1).

Diagnostic approach — The diagnostic approach depends upon the clinical scenario.

Acute HBV and risk factors for HDV — In patients with acute HBV infection, testing for HDV coinfection should be performed in those who present with unusually severe or protracted hepatitis and those who have risk factors for HDV. (See 'Risk factors for disease' above.)

Patients being evaluated for acute HBV/HDV coinfection should be tested for HBsAg, IgM anti-HBc, serum HDV RNA, and HDV antibody (anti-HDV).

- Those with acute HBV are positive for HBsAg and have high titers of IgM anti-HBc. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Acute hepatitis'.)
- For those with HDV coinfection, serum HDV RNA is usually detectable at presentation; by contrast, anti-HDV is often negative at presentation. If HDV RNA testing is not available, repeated testing for anti-HDV (total or IgM) should be performed to document anti-HDV seroconversion.

Markers of HBV replication may precede or follow those of HDV. In addition, occasional patients have already seroconverted to hepatitis B surface antibody (anti-HBs) if they present during the second phase of biphasic hepatitis. These patients should still be positive for high-titer IgM anti-HBc (table 1).

Persons with chronic HBV and hepatitis flare — HDV superinfection should be evaluated in patients with chronic HBV who have acute hepatitis of unclear etiology. Patients should be tested for serum HDV RNA and anti-HDV.

In persons with previously unrecognized chronic HBV, it can be difficult to determine if the person has HDV superinfection versus HDV coinfection; however, it is important to make this distinction because of the differences in prognosis (table 1). When evaluating the patient, clinicians should be aware that:

- HBsAg is present in both situations, but IgM anti-HBc should be negative in acute HDV superinfection (figure 3).

- HDV superinfection may cause transient suppression of HBV replication, resulting in very low and, rarely, undetectable levels of HBsAg.

- As in patients with acute HBV/HDV coinfection, patients with acute HDV superinfection usually have detectable HDV RNA in serum at the time of presentation. However, in contrast to acute coinfection, acute HDV superinfection is characterized by persistent detection of HDV RNA in serum and rapidly increasing titers of anti-HDV (total and IgM).

Persons with chronic HBV without hepatitis flare — We test all patient with chronic HBV for HDV. Screening is particularly important for persons with risk factors for HDV. In a study from Spain, routine testing for anti-HDV in HBsAg-positive persons increased the number of anti-HDV-positive persons who were identified by a factor of five [63]. Risk factors for HDV are described above. (See 'Risk factors for disease' above.)

- Initial testing should be performed by testing for total anti-HDV antibody. (See 'Detection of anti-HDV antibody' below.)

- The presence of HDV infection should be confirmed by testing for serum HDV RNA. (See 'Serum HDV RNA' below.)

Patients with chronic HDV/HBV may also have certain characteristic findings on HBV testing. As an example, serum HBV DNA is usually present at low levels but may be undetectable. In addition, patients are often hepatitis B e antigen (HbeAg) negative and hepatitis B e antibody (anti-Hbe) positive. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Phases of chronic HBV infection'.)

Identifying persons with chronic HDV/HBV is important since patients with coinfection may have more severe liver disease, and the presence of HDV can impact treatment decisions. In addition, the information can be used for counseling purposes so patients without HDV infection can reduce behaviors that might put them at risk for HDV superinfection. (See 'Risk factors for disease' above and "Treatment and prevention of hepatitis D virus infection".)

Our approach to screening is consistent with European and Asian-Pacific guidelines, which recommend that persons with chronic HBV be evaluated for other causes of chronic liver disease, including HDV [64,65]. However, other guidelines differ. As an example, United States guidelines recommend testing only for HbsAg-positive persons at high risk of HDV infection since there are no US Food and Drug Administration (FDA) approved HDV diagnostic tests, the

reliability of tests in reference laboratories is variable, and the estimated prevalence of HDV infection ranges from very low to modest [66].

Diagnostic tests

Serum HDV RNA — HDV RNA can be detected in serum by reverse transcriptase-polymerase chain reaction (RT-PCR)-based assays (table 1).

RT-PCR assays are very sensitive and may detect viral loads as low as 10 genomes per mL [58,67-70]. However, the extensive sequence heterogeneity of different HDV isolates makes it difficult to choose suitable primers for the amplification of HDV RNA since only a few conserved regions exist in the HDV genome. In addition, the secondary and tertiary structure of the HDV RNA may hamper efficient amplification, even of highly conserved regions [70]. The best efficiency is obtained by amplifying the C-terminal half of the HDV antigen (HDAg)-encoding region [70]. Although automated assays are commercially available to allow quantification of HDV RNA in the serum of patients with HDV infection before and during treatment [71,72], none of them have been approved for clinical use by the FDA, and performance of these assays is variable. Furthermore, it appears that differences in sample extracting and processing procedures may also influence accuracy of HDV RNA testing.

HDV genotyping can be performed by direct sequencing [19,51,52,73], but this test is not routinely recommended since the clinical relevance of HDV genotyping is uncertain. Furthermore, the phylogenetic classification of the various HDV genotypes is in debate [2]. (See 'Clinical manifestations' above.)

Sequence analysis of HDV RNA can also be used to detect common sources of infection, such as after intrafamilial or perinatal transmission [74,75]. However, it is unclear if HDV RNA levels in the blood can be used as a prognostic factor to determine disease progression [36].

Detection of anti-HDV antibody — Total (IgM and IgG) anti-HDV antibodies can be detected by enzyme immunoassays (EIAs) or radioimmunoassays (RIAs) (table 1).

- Total anti-HDV antibody usually appears after four weeks of acute infection in acute hepatitis D (figure 2). As a result, its clinical value is limited unless repeated testing is performed [76,77]. A well-documented anti-HDV seroconversion may be the only way to diagnose acute HDV infection in the absence of other markers of HDV infection. However, limited data suggest anti-HDV is short-lived in patients who do not develop chronic HBV.

- High-titer anti-HDV of the IgG class is present in chronic HDV infection. It correlates well with ongoing HDV replication and may help in differentiating current from past HDV

infection [78].

- Anti-HDV of the IgM class can be detected by EIAs or RIAs, but these assays are not available for clinical use in the United States [79]. IgM anti-HDV is transient and delayed if the course of acute hepatitis D is self-limited, but it may be the only serum marker of acute HDV infection [76]. In patients who progress to chronic HDV infection, which is usually the case in those with HDV superinfection, IgM anti-HDV is brisk and long-lasting. It should be remembered, however, that differentiating between HBV/HDV coinfection and HDV superinfection in an HBV carrier relies mainly on the detection of high-titer IgM anti-HBc in patients with coinfection.

- IgM anti-HDV is present in high titers during chronic HDV infection, and the titers correlate with the level of HDV replication and severity of liver disease [79], although HDV replication is best assessed by quantifying HDV RNA in serum. IgM anti-HDV gradually disappears from serum in patients who have persistent remission after interferon therapy and following liver transplantation [80].

Detection of serum HDAg — Serum HDV antigen (HDAg) can be detected by EIA or RIA. However, these assays are rarely used and are not approved for clinical diagnosis in the United States.

- In acute HDV infection, serum HDAg appears early, but its detection by EIA is short-lived and may require repeated testing (figure 2) [76,77,81,82], except in immunocompromised individuals [83].

- In chronic HDV infection, anti-HDV is present in high titers, but HDAg cannot be detected by EIA since it is complexed with anti-HDV. In this setting, serum HDAg is best detected by immunoblot assay [4], which is more sensitive [84]; however, this assay is technically difficult and time- and labor-consuming.

Tissue markers of HDV infection — Both HDAg and HDV RNA can be detected in liver tissues routinely processed for histopathologic evaluation.

- HDAg can be detected by direct immunofluorescence or immunohistochemistry. Although initially proposed as the "gold" standard for diagnosis of current HDV infection [85], as many as 50 percent of liver biopsy specimens from patients who have been infected for 10 or more years may be negative for HDAg, suggesting that the levels of HDV replication may decrease with time [58,86].

In patients who are negative for HDAg, the diagnosis of current HDV infection has to rely on the detection of HDV RNA or high-titer anti-HDV antibodies in the serum. (See 'Serum HDV RNA' above and 'Detection of anti-HDV antibody' above.)

- HDV RNA can be detected by in-situ hybridization. However, the techniques involved are time-consuming and tedious; they are not recommended for clinical use [87].

SUMMARY AND RECOMMENDATIONS

- **Virology** – Individuals with hepatitis D are always dually infected with hepatitis D virus (HDV) and hepatitis B virus (HBV). Although HDV can replicate autonomously, the simultaneous presence of HBV is required for complete virion assembly and secretion. Due to mechanisms that are not well understood, HBV replication is suppressed in most HDV-infected individuals.

- **Epidemiology**

  - **Prevalence** – The prevalence of HDV in patients with chronic HBV infection varies across studies. Historical data suggest that approximately 15 to 20 million of the 257 million HBV carriers worldwide may be infected with HDV. In more recent studies, the prevalence has varied ranging from 12 to 60 million infections globally. In the United States, the prevalence of HDV infection has ranged from 6 to 42 percent of persons with chronic HBV. (See 'Prevalence of disease' above.)

  - **Risk factors for HDV** – HDV is predominantly confined to groups with known risk factors for HDV (persons who inject drugs, individuals who have received multiple transfusions in the past, men who have sex with men who engage in unsafe sexual behaviors [eg, condomless sex with multiple partners], and persons who emigrated from countries with a high prevalence of HDV infection). (See 'Risk factors for disease' above.)

  - **Geographic distribution** – HDV is not distributed uniformly across the globe, and the geographic distribution of HDV infection does not parallel that of HBV. As an example, there is a high prevalence in the Mediterranean Basin, Mongolia, Moldova, and some countries in Western and Middle Africa, whereas other areas, including many Asian countries, are relatively spared despite the high prevalence of HBV infection. (See 'Geographic distribution' above.)

- **Clinical manifestations** – Patients with acute HDV may present with acute HBV/HDV coinfection or, in persons with pre-existing chronic HBV, acute HDV superinfection. Clinically, the presentation is often indistinguishable, but serologic testing may be able to separate the two entities (table 1). (See 'Acute HBV/HDV coinfection' above and 'Acute HDV superinfection' above.)

  In patients with chronic HDV, infection ranges from the asymptomatic carrier state to acute liver failure. The clinical course is influenced by several factors, such as persistent HDV replication and HDV genotype. (See 'Chronic HDV infection' above and 'Importance of HDV genotypes' above.)

- **Diagnostic approach** – The diagnostic approach depends upon the clinical scenario. Diagnostic tests for HDV typically include HDV antibody (anti-HDV) antibody and HDV RNA. (See 'Diagnostic approach' above and 'Diagnostic tests' above.)

  - **Persons with acute HBV infection and risk factors for HDV** – In patients with acute HBV infection, testing for HDV coinfection should be performed in those who have risk factors for HDV or those who present with unusually severe or protracted hepatitis. Patients being evaluated for acute HBV/HDV coinfection should be tested for hepatitis B surface antigen (HbsAg), (hepatitis B core antigen) anti-HBc total and anti-HBc IgM, hepatitis B surface antibody (anti-HBs), serum HDV RNA, and HDV antibody (anti-HDV). (See 'Acute HBV and risk factors for HDV' above and "Hepatitis B virus: Screening and diagnosis in adults".)

  - **Persons with chronic HBV and hepatitis flare** – HDV superinfection should be evaluated in patients with chronic HBV who have acute hepatitis of unclear etiology. Patients should be tested for serum HDV RNA and anti-HDV. In persons with previously unrecognized chronic HBV, it can be difficult to determine if the person has HDV superinfection versus HDV coinfection (table 1); however, it is important to make this distinction because of the differences in prognosis. (See 'Persons with chronic HBV and hepatitis flare' above.)

  - **Persons with chronic HBV without hepatitis flare** – We perform routine screening for HDV in all patients with chronic HBV. Initial testing should assess for total anti-HDV antibody; if positive, HDV infection should be confirmed by testing for serum HDV RNA. Identifying persons with chronic HDV/HBV is important since patients with coinfection may have more severe liver disease, and the presence of HDV coinfection can impact treatment decisions. This information can also be used for counseling purposes so

patients without HDV infection can reduce behaviors that might put them at risk for HDV superinfection. (See 'Persons with chronic HBV without hepatitis flare' above.)

REFERENCES

1. Bichko V, Netter HJ, Wu TT, Taylor J. Pathogenesis associated with replication of hepatitis delta virus. Infect Agents Dis 1994; 3:94.
2. Dény P. Hepatitis delta virus genetic variability: from genotypes I, II, III to eight major clades? Curr Top Microbiol Immunol 2006; 307:151.
3. Polson AG, Bass BL, Casey JL. RNA editing of hepatitis delta virus antigenome by dsRNA-adenosine deaminase. Nature 1996; 380:454.
4. Bonino F, Heermann KH, Rizzetto M, Gerlich WH. Hepatitis delta virus: protein composition of delta antigen and its hepatitis B virus-derived envelope. J Virol 1986; 58:945.
5. Negro F, Korba BE, Forzani B, et al. Hepatitis delta virus (HDV) and woodchuck hepatitis virus (WHV) nucleic acids in tissues of HDV-infected chronic WHV carrier woodchucks. J Virol 1989; 63:1612.
6. Ni Y, Lempp FA, Mehrle S, et al. Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. Gastroenterology 2014; 146:1070.
7. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012; 3.
8. Lo K, Hwang SB, Duncan R, et al. Characterization of mRNA for hepatitis delta antigen: exclusion of the full-length antigenomic RNA as an mRNA. Virology 1998; 250:94.
9. Yamaguchi Y, Filipovska J, Yano K, et al. Stimulation of RNA polymerase II elongation by hepatitis delta antigen. Science 2001; 293:124.
10. Modahl LE, Macnaughton TB, Zhu N, et al. RNA-Dependent replication and transcription of hepatitis delta virus RNA involve distinct cellular RNA polymerases. Mol Cell Biol 2000; 20:6030.
11. Chang J, Nie X, Chang HE, et al. Transcription of hepatitis delta virus RNA by RNA polymerase II. J Virol 2008; 82:1118.
12. Weller ML, Gardener MR, Bogus ZC, et al. Hepatitis Delta Virus Detected in Salivary Glands of Sjögren's Syndrome Patients and Recapitulates a Sjögren's Syndrome-Like Phenotype in Vivo. Pathog Immun 2016; 1:12.

13. Chemin I, Pujol FH, Scholtès C, et al. Preliminary Evidence for Hepatitis Delta Virus Exposure in Patients Who Are Apparently Not Infected With Hepatitis B Virus. Hepatology 2021; 73:861.
14. Cappy P, Lucas Q, Kankarafou N, et al. No Evidence of Hepatitis C Virus (HCV)-Assisted Hepatitis D Virus Propagation in a Large Cohort of HCV-Positive Blood Donors. J Infect Dis 2021; 223:1376.
15. Pflüger LS, Schulze Zur Wiesch J, Polywka S, Lütgehetmann M. Hepatitis delta virus propagation enabled by hepatitis C virus-Scientifically intriguing, but is it relevant to clinical practice? J Viral Hepat 2021; 28:213.
16. Roggenbach I, Chi X, Lempp FA, et al. HDV Seroprevalence in HBsAg-Positive Patients in China Occurs in Hotspots and Is Not Associated with HCV Mono-Infection. Viruses 2021; 13.
17. Pérez-Vargas J, Pereira de Oliveira R, Jacquet S, et al. HDV-Like Viruses. Viruses 2021; 13.
18. Perez-Vargas J, Amirache F, Boson B, et al. Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo. Nat Commun 2019; 10:2098.
19. Casey JL, Brown TL, Colan EJ, et al. A genotype of hepatitis D virus that occurs in northern South America. Proc Natl Acad Sci U S A 1993; 90:9016.
20. Tang JR, Hantz O, Vitvitski L, et al. Discovery of a novel point mutation changing the HDAg expression of a hepatitis delta virus isolate from Central African Republic. J Gen Virol 1993; 74 (Pt 9):1827.
21. Smedile A, Rosina F, Saracco G, et al. Hepatitis B virus replication modulates pathogenesis of hepatitis D virus in chronic hepatitis D. Hepatology 1991; 13:413.
22. Rizzetto M, Ponzetto A, Forzani I. Epidemiology of hepatitis delta virus: overview. Prog Clin Biol Res 1991; 364:1.
23. Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat Rev Gastroenterol Hepatol 2010; 7:31.
24. World Health Organization. Global Hepatitis Report, 2017. http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf;jsessionid=21B5AA5BEFA9E117AF03AAEAB7EECAD1?sequence=1 (Accessed on July 09, 2018).
25. 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; 68:512.
26. 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; 221:1677.
27. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol 2020; 73:523.

28. Global hepatitis report, 2017. World Health Organization. Available at: https://www.who.int/publications/i/item/9789241565455. (Accessed on December 12, 2022).

29. Patel EU, Thio CL, Boon D, et al. Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011-2016. Clin Infect Dis 2019; 69:709.

30. Time for universal screening for hepatitis D - A study describing screening patterns, characteristics, and outcomes of hepatitis D virus infection. National AIDS Treatment Advocacy Project. Available at: https://www.natap.org/2022/HDV/110322_01.htm. (Accessed on January 02, 2023).

31. Estimating the Prevalence of Hepatitis Delta Infection among Foreign-Born Adults with Chronic Hepatitis B in the United States. National AIDS Treatment Advocacy Project. Available at: https://www.natap.org/2022/HDV/070122_03.htm. (Accessed on January 02, 2023).

32. Gaeta GB, Stroffolini T, Chiaramonte M, et al. Chronic hepatitis D: a vanishing Disease? An Italian multicenter study. Hepatology 2000; 32:824.

33. Gaeta GB, Stroffolini T, Smedile A, et al. Hepatitis delta in Europe: vanishing or refreshing? Hepatology 2007; 46:1312.

34. Wedemeyer H, Heidrich B, Manns MP. Hepatitis D virus infection--not a vanishing disease in Europe! Hepatology 2007; 45:1331.

35. Coppola N, Alessio L, Onorato L, et al. HDV infection in immigrant populations. J Med Virol 2019; 91:2049.

36. Kamal H, Aleman S, D-SOLVE Consortium. Natural history of untreated HDV patients: Always a progressive disease? Liver Int 2023; 43 Suppl 1:5.

37. Pisaturo M, Alessio L, Di Fraia A, et al. Hepatitis D virus infection in a large cohort of immigrants in southern Italy: a multicenter, prospective study. Infection 2022; 50:1565.

38. 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; 27:941.

39. Abbas Z, Jafri W, Raza S. Hepatitis D: Scenario in the Asia-Pacific region. World J Gastroenterol 2010; 16:554.

40. Liaw YF, Chiu KW, Chu CM, et al. Heterosexual transmission of hepatitis delta virus in the general population of an area endemic for hepatitis B virus infection: a prospective study. J Infect Dis 1990; 162:1170.

41. Lok AS, Wong A, Sporton S, et al. Hepatitis D virus superinfection remains a rare occurrence in non-drug abusers in Hong Kong. J Hepatol 1992; 14:332.

42. Wu S, Zhang Y, Tang Y, et al. Molecular epidemiology and clinical characteristics of hepatitis delta virus (HDV) infected patients with elevated transaminases in Shanghai, China. BMC

Infect Dis 2020; 20:565.

43. Caredda F, d'Arminio Monforte A, Rossi E, et al. Prospective study of epidemic delta infection in drug addicts. Prog Clin Biol Res 1983; 143:245.
44. Smedile A, Dentico P, Zanetti A, et al. Infection with the delta agent in chronic HBsAg carriers. Gastroenterology 1981; 81:992.
45. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. J Hepatol 2021; 74:1200.
46. 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; 98:437.
47. Govindarajan S, De Cock KM, Redeker AG. Natural course of delta superinfection in chronic hepatitis B virus-infected patients: histopathologic study with multiple liver biopsies. Hepatology 1986; 6:640.
48. Rosina F, Conoscitore P, Cuppone R, et al. Changing pattern of chronic hepatitis D in Southern Europe. Gastroenterology 1999; 117:161.
49. Alfaiate D, Clément S, Gomes D, et al. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. J Hepatol 2020; 73:533.
50. Romeo R, Del Ninno E, Rumi M, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology 2009; 136:1629.
51. Wu JC, Choo KB, Chen CM, et al. Genotyping of hepatitis D virus by restriction-fragment length polymorphism and relation to outcome of hepatitis D. Lancet 1995; 346:939.
52. Niro GA, Smedile A, Andriulli A, et al. The predominance of hepatitis delta virus genotype I among chronically infected Italian patients. Hepatology 1997; 25:728.
53. Wu JC, Huang IA, Huang YH, et al. Mixed genotypes infection with hepatitis D virus. J Med Virol 1999; 57:64.
54. Smedile A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. Lancet 1982; 2:945.
55. Bonino F, Negro F, Baldi M, et al. The natural history of chronic delta hepatitis. Prog Clin Biol Res 1987; 234:145.
56. Hadziyannis SJ, Papaioannou C, Alexopoulou A. The role of the hepatitis delta virus in acute hepatitis and in chronic liver disease in Greece. Prog Clin Biol Res 1991; 364:51.
57. 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; 46:420.

58. Wu JC, Chen TZ, Huang YS, et al. Natural history of hepatitis D viral superinfection: significance of viremia detected by polymerase chain reaction. Gastroenterology 1995; 108:796.

59. Hadler SC, Alcala de Monzon M, Rivero D, et al. Epidemiology and long-term consequences of hepatitis delta virus infection in the Yucpa Indians of Venezuela. Am J Epidemiol 1992; 136:1507.

60. Popper H, Thung SN, Gerber MA, et al. Histologic studies of severe delta agent infection in Venezuelan Indians. Hepatology 1983; 3:906.

61. Bensabath G, Hadler SC, Soares MC, et al. Hepatitis delta virus infection and Labrea hepatitis. Prevalence and role in fulminant hepatitis in the Amazon Basin. JAMA 1987; 258:479.

62. Le Gal F, Gault E, Ripault MP, et al. Eighth major clade for hepatitis delta virus. Emerg Infect Dis 2006; 12:1447.

63. 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; 4:100547.

64. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370.

65. 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.

66. 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; 67:1560.

67. Zignego AL, Deny P, Feray C, et al. Amplification of hepatitis delta virus RNA sequences by polymerase chain reaction: a tool for viral detection and cloning. Mol Cell Probes 1990; 4:43.

68. Madejón A, Castillo I, Bartolomé J, et al. Detection of HDV-RNA by PCR in serum of patients with chronic HDV infection. J Hepatol 1990; 11:381.

69. Cariani E, Ravaggi A, Puoti M, et al. Evaluation of hepatitis delta virus RNA levels during interferon therapy by analysis of polymerase chain reaction products with a nonradioisotopic hybridization assay. Hepatology 1992; 15:685.

70. Dinolfo L, Abate ML, Bertolo P, et al. Detection of hepatitis D virus RNA in serum by a reverse transcription, polymerase chain reaction-based assay. Int J Clin Lab Res 1995; 25:35.

71. Mederacke I, Bremer B, Heidrich B, et al. Establishment of a novel quantitative hepatitis D virus (HDV) RNA assay using the Cobas TaqMan platform to study HDV RNA kinetics. J Clin Microbiol 2010; 48:2022.
72. Schaper M, Rodriguez-Frias F, Jardi R, et al. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. J Hepatol 2010; 52:658.
73. Casey JL, Niro GA, Engle RE, et al. Hepatitis B virus (HBV)/hepatitis D virus (HDV) coinfection in outbreaks of acute hepatitis in the Peruvian Amazon basin: the roles of HDV genotype III and HBV genotype F. J Infect Dis 1996; 174:920.
74. Niro GA, Casey JL, Gravinese E, et al. Intrafamilial transmission of hepatitis delta virus: molecular evidence. J Hepatol 1999; 30:564.
75. Huang YH, Wu JC, Lu SN, et al. Phylogenetic analysis to document a common source of hepatitis D virus infection in a mother and her child. Zhonghua Yi Xue Za Zhi (Taipei) 1999; 62:28.
76. Aragona M, Macagno S, Caredda F, et al. Serological response to the hepatitis delta virus in hepatitis D. Lancet 1987; 1:478.
77. Buti M, Esteban R, Jardí R, et al. Serological diagnosis of acute delta hepatitis. J Med Virol 1986; 18:81.
78. Negro F, Bergmann KF, Baroudy BM, et al. Chronic hepatitis D virus (HDV) infection in hepatitis B virus carrier chimpanzees experimentally superinfected with HDV. J Infect Dis 1988; 158:151.
79. Smedile A, Lavarini C, Crivelli O, et al. Radioimmunoassay detection of IgM antibodies to the HBV-associated delta (delta) antigen:" clinical significance in delta infection. J Med Virol 1982; 9:131.
80. Borghesio E, Rosina F, Smedile A, et al. Serum immunoglobulin M antibody to hepatitis D as a surrogate marker of hepatitis D in interferon-treated patients and in patients who underwent liver transplantation. Hepatology 1998; 27:873.
81. Govindarajan S, Valinluck B, Peters L. Relapse of acute B viral hepatitis--role of delta agent. Gut 1986; 27:19.
82. Shattock AG, Morgan BM. Sensitive enzyme immunoassay for the detection of delta antigen and anti-delta, using serum as the delta antigen source. J Med Virol 1984; 13:73.
83. Grippon P, Ribiere O, Cadranel JF, et al. Long-term delta antigenaemia without appearance of delta antibody in two immunodeficient patients. Lancet 1987; 1:1031.

84. Buti M, Esteban R, Jardi R, et al. Chronic delta hepatitis: detection of hepatitis delta virus antigen in serum by immunoblot and correlation with other markers of delta viral replication. Hepatology 1989; 10:907.

85. Di Bisceglie AM, Negro F. Diagnosis of hepatitis delta virus infection. Hepatology 1989; 10:1014.

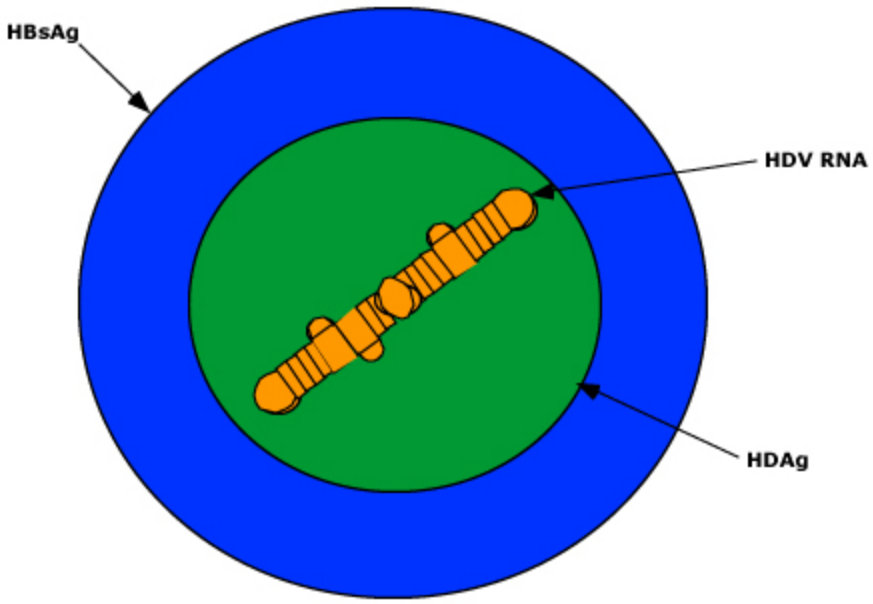
86. Bonino F, Negro F, Baldi M, et al. The natural history of chronic delta hepatitis. In: The hepat itis delta virus and its infection, Rizzetto M, Gerin JL, Purcell RH (Eds), Alan R Liss, New York 1987. p.145.

87. Negro F, Rizzetto M. Diagnosis of hepatitis delta virus infection. J Hepatol 1995; 22:136.

Topic 3666 Version 21.0

GRAPHICS

HDV virion



Schematic representation of the hepatitis D virus virion. The HD virion comprises an RNA genome, a single HDV encoded antigen, and a lipoprotein envelope provided by HBV.

Graphic 63575 Version 1.0

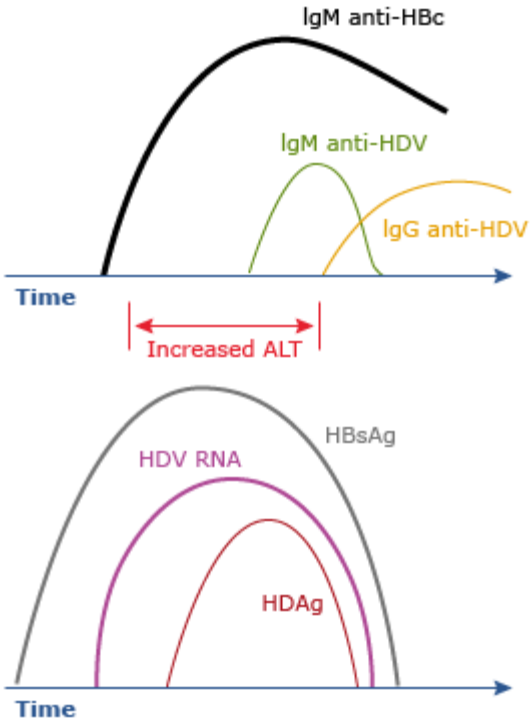
Diagnosis of hepatitis D virus infection in different clinical settings

Diagnostic markers	Acute HBV/HDV coinfection	Acute HDV superinfection	Chronic HDV infection
HBsAg	Positive	Positive	Positive
Anti-HBc, IgM	Positive	Negative	Negative
Serum HDAg (by EIA/RIA)	Early and short-lived, frequently missed	Early and transient, and frequently missed	Not detectable
Serum HDV RNA (by RT-PCR)	Early, transient but last longer than HDAg	Early and persistent	Positive
Anti-HDV, total	Late, low titer	Rapidly increasing titers	High titers
Anti-HDV, IgM	Transient, may be the only marker	Rapidly increasing and persistent titers	Variable titers, usually high
Liver HDAg	Not indicated	Positive	Usually positive, may be negative in late stages

HBV: hepatitis B virus; HDV: hepatitis D virus; HBsAg: surface antigen of the hepatitis B virus; Anti-HBc: hepatitis B core antigen; IgM: immunoglobulin M; HDAg: hepatitis D virus antigen; EIA: enzyme immunoassay; RIA: radioimmunoassay; RT-PCR: reverse transcription polymerase chain reaction; Anti-HDV: antibody to hepatitis D virus.

Graphic 52583 Version 3.0

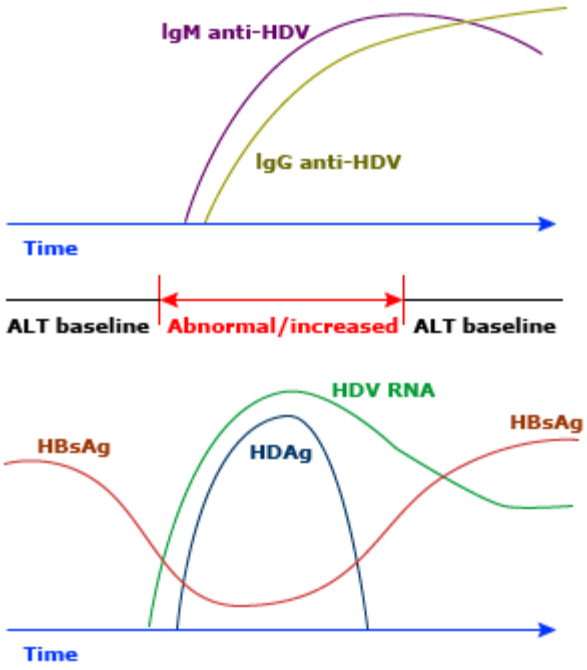
Serum markers of acute, self-limiting HBV/HDV coinfection



Schematic representation of the typical serologic response to acute HBV/HDV infection. Patients should be positive for HBsAg and have high titer IgM anti-HBc; serum HDAg and/or HDV RNA are usually positive at presentation.

Graphic 60216 Version 3.0

Serum markers of an HDV superinfection of a chronic HBV carrier



The serologic response to acute HDV superinfection in a chronic HBV carrier must be distinguished from acute HBV/HDV coinfection. HBsAg is present in both situations, but IgM anti-HBc should be negative in acute HDV superinfection. The diagnosis is made more difficult since HDV superinfection may cause transient suppression of HBV replication, transiently resulting in very low and rarely undetectable levels of HBsAg. As in patients with acute HBV/HDV coinfection, patients with acute HDV superinfection are usually positive for HDAg and/or HDV RNA in serum at the time of presentation. However, in contrast to acute coinfection, acute HDV superinfection is characterized by persistent detection of HDV RNA in serum and rapidly increasing titers of anti-HDV (total and IgM).

Graphic 54793 Version 2.0

Contributor Disclosures

Francesco Negro, MD Consultant/Advisory Boards: Gilead [Hepatitis C, hepatitis D]. Speaker's Bureau: Roche Diagnostics [Hepatitis B]. All of the relevant financial relationships listed have been mitigated. **Anna SF Lok, MD** Grant/Research/Clinical Trial Support: Target Pharma [NAFL, hepatitis B virus, PBC]. Consultant/Advisory Boards: Arbutus [Hepatitis B virus]; Chroma [Hepatitis B virus]; CLEAR-B [Hepatitis B virus]; GlaxoSmithKline [Hepatitis B virus]; Novo Nordisk [NAFLD]; Target [Hepatitis B virus, PBC, and NAFLD treatment]; Virion [Hepatitis B virus]. All of the relevant financial relationships listed have been mitigated. **Rafael Esteban, MD** Grant/Research/Clinical Trial Support: Gilead [Hepatitis B]. Consultant/Advisory Boards: Abbvie [Hepatitis C]; Gilead [Hepatitis C]. Speaker's Bureau: Gilead [Hepatitis C]. All of the relevant financial relationships listed have been mitigated. **Jennifer Mitty, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→