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# Hepatitis delta infection – Current and new treatment options

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A B S T R A C T

In humans, hepatitis D virus (HDV) infection only occurs in the presence of a concomitant hepatitis B virus (HBV) infection, and induces the most severe form of human viral hepatitis. Even though HDV is spread worldwide and is endemic in some regions, screening and treatment has been often neglected in part due to the lack of an effective therapy. Moreover, HDV prevalence rates are increasing in many countries driven by immigration from areas of high endemicity. Currently, no FDA-approved anti-HDV therapy is available, although interferon (IFN) alpha therapy has demonstrated benefit in a minority of patients. In this review, we present a current view of our understanding of the epidemiology, molecular virology and management of HDV infection. We additionally discuss new treatment approaches in development and describe the most promising results of recent and ongoing clinical trials of these new potential agents.



## Introduction

Hepatitis Delta virus (HDV) was identified in 1977 in a cohort of hepatitis B virus (HBV) patients presenting with severe hepatitis. Liver biopsies from these patients revealed a novel immunostaining pattern [1]. This apparent new antigenic moiety was termed δ antigen and was present in liver cell nuclei from chronic HBV patients. Although at first considered a new antigenic moiety of HBV, it was quickly recognized as a separate antigen that was associated with HBsAg [1]. Further characterization identified the δ antigen as an antigen of an infectious agent distinct from HBV that was associated with a low molecular weight RNA genome [2]. HDV infection was found to always occurs in the presence of an accompanying HBV infection—either as a de novo co-infection of an HBV naïve patient, or as a superinfection of a patient already chronically infected with HBV – a fact explained by HDV's molecular virology (see below). The presence of HDV is generally associated with worse clinical outcomes compared to HBV monoinfection, both in terms of the severity of acute disease as well as accelerating the rate of development of the sequelae of chronic disease, including cirrhosis, liver failure, HCC, or death [3]. Here, we will briefly review the molecular virology, epidemiology and pathogenesis of HDV infection and will focus on current and new therapeutic approaches that are under clinical investigation.

## Molecular virology

HDV is a single-stranded (-)RNA virus with a 1.7 kb circular genome that forms a collapsed rod structure by the self-annealing of 74% of its nucleotides [4]. The viral genome codes for one protein that exists in two forms, known as small and large delta antigen (SHDAg and LHDAg), respectively. These proteins are identical except that the large delta antigen contains an extra 19 amino acids

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at its carboxyl terminus. This extension is the result of a specific RNA editing event that occurs during replication of the genome [5]. The addition of these 19 amino acids change the carboxy terminus of the protein to possess a CXXX-box motif (where C = cysteine, and X = one of the last 3 amino acids at the carboxy terminus) that renders the protein a substrate for farnesyltransferase, an enzyme that adds a farnesyl group to the cysteine of the CXXX-box [6]. This farnesylation reaction is an essential modification for virion assembly [7]. The complete HDV virus particle consists of a complex of the viral genome and both delta antigen isoforms, all encapsulated by a lipid envelope decorated with HBV surface antigens (S, M and L HBsAg) proteins, which are provided by a co-infecting HBV [8]. The HBV proteins present in the lipid envelope provide the means for HDV particle exit and entry into the cell [8]. This dependence on HBV for a source of envelope proteins provides the molecular explanation for why HDV infection is always accompanied by HBV co-infection. This supply of HBV surface antigens is the only helper function provided by HBV.

HDV genome replication proceeds entirely through RNA-dependent RNA replication. There are no DNA intermediates and there is no archiving of HDV into DNA, yet HDV does not code for its own RNA-dependent RNA-polymerase. Rather HDV depends on host cell polymerases for its replication. Interestingly, the virus appears to recruit Pol-II, a host DNA-dependent RNA polymerase to replicate its RNA genome in a RNA dependent manner [9]. It has been hypothesized that the double stranded-like structure of the HDV genomic RNA provides a template akin to double stranded DNA that enables the recruitment of Pol-II [10]. Following HDV entry and uncoating, the incoming HDV RNA genome is transferred into the nucleus. The RNA is replicated through a so-called double rolling circle mechanism by Pol-II associated with the SHDAg to generate linear multimeric copies of antigenomic RNA, which undergo cleavage by the antigenomic ribozyme to form linear monomers that are then ligated, forming closed circular antigenomes that serve as templates for production of genomic RNA in a similar mechanism [9]. As replication proceeds, an RNA editing event, mediated by ADAR1, occurs on the antigenomic RNA that modifies the amber stop codon of the reading frame encoding SHDAg. This results in translation proceeding to the next downstream stop codon, adding an extra 19 amino acids and yielding expression of the LHDAg [11]. These extra 19 amino acids dramatically change the function of the delta antigen. For example, while the SHDAg is required for HDV RNA genome replication, the LHDAg acts as a potent transdominant inhibitor of HDV replication [12]. Moreover, only the LHDAg isoform is able to mediate assembly with HBsAg envelope proteins. Thus the above RNA editing event represents an important molecular switch in the virus life cycle, serving to turn off RNA replication and turn on packaging of newly synthesized HDV genomes, virus assembly and release [13].

## Epidemiology

It is estimated that HDV's worldwide prevalence is 15–20 million people, with an overall average of ~5% of the HBV population harboring HDV, but the percentage of HBV patients co-infected with HDV is variable in different geographic regions [14]. Some areas have been identified as endemic for HDV infection, including regions in Africa, South America, Turkey, Southern Italy and countries from the former Soviet Union [14]. In the United States and Northern Europe HDV prevalence has settled at around 8% in HBsAg positive patients with higher prevalence in populations of intravenous drug users (IVDU) and hemophiliacs [15]. This represents a balance between declines from the originally reported prevalences when HDV was first discovered, and the influx of immigrants into western European countries from areas of high endemicity, such as Turkey, Eastern Europe and Africa [14–18]. Higher prevalence of HDV infection is observed in the eastern Mediterranean basin, Middle East, central and northern Asia and central western Africa [14]. For example, in Brazil, while the prevalence in the general population is around 8%, the prevalence in the Amazonian Basin is 65% in HBsAg positive outpatients, with similar observations in other South American countries [19]. In Africa, HDV affects mostly Western and Central Africa with prevalence ranging from 33% in Mauritania [20] to up to 66% in Gabon [21,22]. In Asia, a mixed picture emerges with some areas demonstrating low HDV prevalence such as Malaysia, Thailand, Philippines and Japan, while a higher prevalence is observed in India and Pakistan [23]. In Taiwan while prevalence in the general population is around 6%, in IVDU patients, the prevalence has been reported to be 67% [24]. In Mongolia, some studies have reported populations with extremely high rates of HDV co-infection (>88%). A recent large nationwide survey using validated assays documented ~60% HDV co-infection among HBsAg subjects—an extraordinarily high prevalence that may help explain the world's highest rate of hepatocellular carcinoma being observed in that country [25,26]. It is noteworthy that diagnostics for anti-HDV infection are not standardized, and although there is an international standard for HDV RNA detection to enable conversion to International Units (IU), commercial pangenotypic assays for HDV RNA are not readily available in many countries. In addition, many HBsAg-positive patients are simply not screened for HDV. Together these factors combine to potentially underestimate HDV prevalence in many countries.

## Pathogenesis

From its discovery, it was noted that HDV infection worsens the liver disease of HBV infected patients when compared to individuals with HBV infection alone [1], however clinically there is no difference between HBV and HDV induced hepatitis [27]. Indeed, HDV induces the worst form of hepatitis in humans and is associated with higher risk of liver decompensation and death compared to HBV infection alone [3].

HDV infection can occur in one of two ways: coinfection, by which HBV and HDV infection happens simultaneously, or superinfection, where HDV infects an individual already chronically infected with HBV [28]. As for acute HBV infection, coinfection in adults is less likely to induce chronic hepatitis (>5%) [29], however development of severe acute hepatitis with a potential to result in acute liver failure (2–20%) is the major risk [27]. Superinfection on the other hand, results in 70–90% of infected individuals developing chronic hepatitis [30]. Chronically infected HDV patients are at high risk of developing cirrhosis [31], with an estimated 80% of infected individuals developing cirrhosis within 30 years after infection [30]. Additionally, 10–15% of chronically infected patients may develop cirrhosis within two years of infection [30]. These observations on the pathogenesis of HDV-infected patients clearly demonstrate the high health burden of this infection and the need for the development of better diagnostic tools as well as more effective antivirals.

HDV infection is associated with HCC, although the precise risk estimate is somewhat controversial. In one study, Fattovich et al. [31] reported a 3-fold increased risk of developing HCC with a 2-fold increased risk for death. A similar result was obtained in a US study conducted among veteran patients demonstrating that HDV was an independent predictor with 3-fold increased risk for HCC development [32]. In a Swedish study, the Standard Incidence Ratio (SIR) to develop HCC in chronic HDV patients was higher compared to HBV infection alone [33]. In contrast, Romeo et al. [34] showed that 15% of