# A MODERN APPROACH TO THE TREATMENT OF HDV INFECTION

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**Abstract:** HDV infection frequently causes progression to cirrhosis and hepatocellular carcinoma (HCC). In summer 2020, the first potentially effective drug Bulevirtide (BLV) has been approved for the treatment of HDV by the EMA. BLV is a synthetic N-acylated pre-S1 lipopeptide that blocks the binding of HBsAg-enveloped particles to the sodium taurocholate co-transporting polypeptide (NTCP), which is the cell entry receptor for both HBV and HDV. In this review, we discuss the available data from the ongoing clinical trials and from "real world series". Clinical trials and real-world experiences demonstrated that BLV 2 mg administered for 24 or 48 weeks as monotherapy or combined with pegIFNα reduces HDV viremia and normalizes ALT levels in a large proportion of patients. The combination of BLV and pegIFNα shows a synergistic on-treatment effect compared with either one of the monotherapies.

**Keywords:** treatment hepatitis D, hepatitis B, bulevirtide, interferon-alfa

## Relevance of the topic

The hepatitis D virus (HDV; Delta virus, family: Komlioviridae [1]) depends on hepatitis B virus (HBV) envelope (HBV surface antigen, HBsAg) to form infectious HDV particles. Thirteen percent of carriers of the hepatitis B virus (HBV) are co-infected with HDV [2,3], resulting in an estimated number of >11 million HDV patients worldwide based on the reported global HBsAg prevalence of 3.9% [2]. HDV infection frequently causes progression to cirrhosis and hepatocellular carcinoma (HCC) [2]. Recent epidemiologic data from Austria suggest that more than half of HDV patients develop advanced chronic liver disease (ACLD), experience liver-related morbidity or require liver transplantation [4-5].

Despite being a "defective" virus, HDV can cause severe liver disease [6-8]. Chronic HDV infection causes more severe liver disease than chronic HBV monoinfection [9], accelerates liver fibrosis [11-13], increases the risk of hepatocellular carcinoma, and leads to earlier hepatic decompensation than in patients infected with HBV alone [10]. It our opinion that, unlike HBV and hepatitis C virus (HCV), there are very few extra hepatic manifestations that are clinically important.

Unfortunately, the clinical impact of HDV has often been overlooked. Referring to the epidemiology of HDV in the United States, the Hepatitis B Foundation has noted that "low awareness, testing, and the lack of inclusion on the notifiable diseases list contribute to the unclear picture of HDV prevalence in the U.S." [14-16] The lack of awareness of the significant burden of HDV has led to underestimation of the importance of testing for HDV among patients with HBV infection. Clinicians who

wish to test for HDV may not be aware of the appropriate testing pathway and may find it difficult to access even antibody testing much less confirmatory polymerase chain reaction (PCR) testing or be aware of sensitivity thresholds for such testing. Furthermore, clinicians may have difficulty in selecting screening and confirming tests because of their complexity and limited availability, which further leads to underdiagnosis of HDV infection. Management of HDV remains challenging because patients typically present with advanced disease, current treatment options are currently limited with low rates of efficacy and significant toxicity, and, unlike treatment for hepatitis C virus (HCV), late relapse is possible even when virologic testing is negative 24 weeks following antiviral therapy [17, 18]. Moreover, no treatment is so far specifically approved by the FDA for the treatment of HDV infection [19]. However, several promising treatments are in late stages of development. Like HBV, there is no cure for HDV. The current guidelines from national and international associations have not been updated recently to incorporate new data on the diagnosis and management of HDV. For these reasons, we, as members of the Chronic Liver Disease Foundation (CLDF), have published these new guidelines on the testing, diagnosis and management of hepatitis delta virus.

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

## Materials and methods

### PATIENT POPULATION AND STUDY DESIGN

To estimate the prevalence of HDV antibody and RNA positivity within a referred population, specimens received at the NML for HDV antibody testing from January 2019 to December 2023 were considered. Submission guidelines require specimens to be HBsAg-positive, thus all patients were tested for HBV under the care of a healthcare professional. Patient replicate requests were removed and the first occurrence of HDV antibody positivity was included to create the total study population of unique referred individuals. Antibody-positive specimens were tested for HDV RNA to estimate the prevalence of active HDV infection among the referred population and to characterise HDV genotypes.

Available retrospective data elements included age at most recent laboratory testing, sex, ethnicity, country of birth, and risk factor history. Most recent values for laboratory tests were used including liver enzymes, viral serology and HBV viral load. Non-invasive tests for fibrosis included liver stiffness measurement/transient elastography (TE, FibroScan®).

Clinical outcomes including co-morbid medical conditions and complications of liver disease were captured from physician medical record reports and based on standard diagnostic criteria. Treatment in both cohorts was defined as 'treatment at any time', including those who received multiple treatment courses or prior treatments that were since discontinued. 'High-risk activities' were defined as patients who had documented injection/intranasal drug use and/or high-risk sexual contact. Countries with ≥5% prevalence of HBV were considered endemic.

## RESULTS

REFERRAL TESTING FOR HDV SEROPOSITIVITY WAS CONDUCTED ON 120 UNIQUE PATIENTS FROM 2019 TO 2023. A TOTAL OF 338 INDIVIDUALS (4.8%, 95% CI 4.3–5.3) WERE HDV IGG SEROPOSITIVE, 67 WERE SERONEGATIVE AND 6 WERE REPEATEDLY BORDERLINE. FURTHER INVESTIGATION FOCUSED ON THE 38 SEROPOSITIVE SPECIMENS. AGE AND SEX INFORMATION WAS AVAILABLE FOR 99.7% AND 98.7% OF PATIENTS, RESPECTIVELY. THERE WAS NO DIFFERENCE BETWEEN THE MEAN AGE OR SEX DISTRIBUTION OF SEROPOSITIVE AND SERONEGATIVE INDIVIDUALS. THE MAJORITY OF REFERRED PATIENTS WERE >40 YEARS; HOWEVER, THOSE 31–40 YEARS OF AGE COMPRISED THE HIGHEST PERCENTAGE AMONG THE ENTIRE COHORT (27.3% HDV SEROPOSITIVE; 26.3% HDV SERONEGATIVE). MALES WERE MORE FREQUENTLY REPRESENTED AMONG THOSE TESTED FOR ANTI-HDV ANTIBODY (62.0%) AND THOSE SEROPOSITIVE (69.3%; P = 0.0055).

## CONCLUSIONS

Nearly 5% of the HBV referral population is HDV seropositive. HDV infection is highly associated with risk behaviours and both domestic and foreign-born patients with CHB. HDV was significantly associated with progressive liver disease highlighting the need for increased screening and surveillance of HDV.

Evidence of HDV infection was observed in approximately 5% of who were infected with HBV referred to medical specialists. HDV-positive patients were more likely to be male, born ompared to Asian, and to have reported high-risk activities such as injection or intranasal drug use or high-risk sexual contact compared with patients infected with only HBV. Patients infected with HDV were also more likely to suffer

severe liver disease, including liver cancer, compared with HBV mono-infected patients.

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