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Hepatitis D Co-Infection in HBV Patients: Challenges in Diagnosis and Treatment

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Introduction

Hepatitis D Virus (HDV) co-infection in individuals with chronic Hepatitis B Virus (HBV) infection presents a significant clinical and public health challenge. HDV is a defective RNA virus that relies on the presence of HBV Surface Antigen (HBsAg) to replicate and propagate. It is considered the most severe form of viral hepatitis due to its association with accelerated progression to cirrhosis, hepatic decompensation and Hepatocellular Carcinoma (HCC). Globally, an estimated 12–20 million people are co-infected with HBV and HDV, though the true burden may be higher due to underdiagnosis and limited surveillance. Despite advances in HBV management, HDV remains a neglected infection with limited therapeutic options and insufficient awareness among clinicians. The challenges in diagnosing and treating HDV co-infection are rooted in diagnostic limitations, the aggressive natural history of the disease and a historical lack of effective antiviral agents. This article explores the clinical and epidemiological implications of HDV co-infection in HBV patients, emphasizing the diagnostic obstacles, treatment challenges and recent therapeutic advancements [1].

Description

HDV infection occurs in two main forms: co-infection and superinfection. Co-infection refers to simultaneous acquisition of HBV and HDV, often resulting in an acute, self-limiting hepatitis but with a risk of fulminant liver failure. In contrast, superinfection HDV infection in a patient already chronically infected with HBV typically leads to persistent HDV replication, rapid progression to fibrosis and worse clinical outcomes. The pathogenesis of HDV-induced liver damage is thought to be largely immune-mediated and viral load does not always correlate with disease severity. However, persistent HDV RNA in serum is associated with progressive liver injury and a higher risk of complications compared to HBV mono-infection. Despite the significant impact of HDV on liver-related morbidity and mortality, it remains underdiagnosed. This is due in part to the lack of routine HDV screening in HBV patients, particularly in non-endemic regions. HDV prevalence varies geographically, with high rates observed in parts of Eastern Europe, Central Asia, the Middle East and sub-Saharan Africa. Migrant populations from endemic areas may carry the infection undetected, emphasizing the need for global awareness and universal screening policies among HBsAg-positive individuals. The diagnostic work-up begins with anti-HDV Antibody Testing (IgG and IgM), followed by confirmatory testing for HDV RNA by Polymerase Chain Reaction (PCR) to assess active replication. However, HDV RNA assays are not universally available and lack standardization, posing a major barrier to accurate diagnosis. Additionally, there are no widely accepted thresholds for HDV RNA levels to guide treatment initiation or monitoring, unlike the clearly established benchmarks for HBV DNA or HCV RNA in their respective infections [2]. Treatment options for HDV have historically been limited. For many years, the only available therapy was pegylated interferon-alpha (PEG-IFNα), which shows modest efficacy, with sustained virological response rates ranging between 20% and 30%. PEG-IFNα is associated with significant side effects, including flu-like symptoms, cytopenias and neuropsychiatric complications, limiting its use in many patients.

It is also contraindicated in individuals with decompensated cirrhosis, autoimmune disease, or certain psychiatric disorders. Moreover, there are no effective oral antivirals for HDV, as nucleos(t)ide analogs used to suppress HBV replication do not impact HDV directly due to its distinct replication mechanism. As such, patients with HBV/HDV co-infection have been left with few effective treatment options. Recent developments in HDV therapy have provided some hope. BuLeVirtide (BLV), a first-in-class entry inhibitor, has emerged as a promising treatment. Approved by the European Medicines Agency (EMA) under conditional marketing authorization in 2020, bulevirtide blocks the sodium taurocholate co-transporting polypeptide (NTCP), a receptor critical for HBV and HDV entry into hepatocytes. Clinical trials have shown that bulevirtide can lead to significant reductions in HDV RNA and normalization of liver enzymes, either as monotherapy or in combination with PEG-IFNα. Importantly, bulevirtide has been well tolerated with a favorable safety profile. However, long-term data on sustained virological response, relapse rates and clinical outcomes such as fibrosis regression or prevention of liver-related events are still being gathered. In addition, access to bulevirtide remains limited in many parts of the world, particularly in low-resource settings.

Conclusion

Hepatitis D co-infection in HBV patients represents a severe and often under-recognized clinical entity associated with rapid disease progression and poor outcomes. Diagnosis remains challenging due to limited awareness, inconsistent screening practices and restricted access to HDV RNA testing. The historical reliance on interferon-based therapy, with its limited efficacy and poor tolerability, has underscored the urgent need for new treatment options. Recent advances such as bulevirtide and emerging therapeutics offer a new frontier in HDV management, but widespread implementation will require expanded access, clinical training and integration into treatment guidelines. Moving forward, global strategies should prioritize universal HDV screening in HBsAg-positive individuals, improve diagnostic infrastructure and ensure equitable availability of novel therapies. With concerted efforts across research, public health and clinical practice, meaningful progress in managing HBV/HDV co-infection and reducing its global burden is increasingly within reach.

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Conflict of Interest

None.

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