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# Hepatitis D and E Viruses Cause Liver Damage: Management and Prevention are the Best Policies of Elimination These

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**Abstract**

Viral hepatitis is a term that refers to inflammation of the liver due to a viral infection. The hepatitis D virus (HDV) is a blood-borne pathogen and only occurs as either a co-infection with hepatitis B virus (HBV) or as a super-infection of persons with chronic HBV. The hepatitis E virus (HEV) is a virus that can infect both animals and humans. The HDV infection may be severe in children. On the other hand, HEV infection may be severe in pregnant women. Common symptoms of both infections are nausea and vomiting, fever, abdominal pain, fatigue, malaise, and jaundice. Both infections can cause acute for short-term infection or become a long-term chronic infection that may cause liver failure, chronic hepatitis, and liver cirrhosis. There is no vaccine of both viruses, and treatments are supportive. The pegylated interferon alpha (Peg-IFNα) is the available therapy to treat both infections associated with significant side-effects. An attempt is taken here to discuss the management and prevention strategies of both infections.

**Keywords:** HDV, HEV, acute and chronic hepatitis, liver cirrhosis

## 1. Introduction

Hepatitis D virus (HDV) is a dependent virus that depends on hepatitis B virus (HBV) to survive, transmission, replication, and synthesize genomes in human body (Muhammad et al., 2021). Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis globally that is responsible for the major liver infection and may develop in people who have a suppressed immune system (Pilot et al., 1987). The HDV is the most aggressive form that can transform the disease rapidly to cirrhosis, hepatocellular carcinoma (HCC), and ultimately to death (Gow & Mutimer, 2001). Infection with the HEV may be related to acute illness, chronic hepatitis, liver cirrhosis, and liver failure. Liver transplantation is the only option for patients due to HDV and HEV infections when the therapies and medications do not response (Guerra et al., 2017).

The HDV is discovered in 1977 by Italian virologist Mario Rizzetto and then he thought it to be an unrecognized new HBV antigen and is characterized it as the hepatitis delta virus (Rizzetto et al., 1977). The HEV was discovered in 1983 by Russian virologist Mikhail Surenovich Balayan investigating an outbreak of unexplained hepatitis using immunoelectron microscopy among Soviet soldiers serving in Afghanistan. In 1989, the viral genome was successfully sequenced and this pathogen was formally designated as HEV (Izopet et al., 2014). Most prevalence regions of HDV are the Mediterranean, Middle East, Pakistan, Central and Northern Asia, Japan, Taiwan, Greenland, East Africa, the Amazon Basin, and certain areas of the pacific (Niro et al., 2012). The prevalence of HEV is the highest in East and South Asia. Also Bangladesh, India, China, Middle-East, Mediterranean region, Ethiopia, Mexico, South America, and Kenya carry the highest burdens of HEV infection (Zeng et al., 2021).

Incubation period of HDV is 2-8 weeks, and that of HEV is 2-9 weeks. Hepatitis E is water-borne disease that

spreads by the HEV contamination with the fecal material ingestion, and mortality is high in pregnancy (Polley et al., 2022). Hepatitis D is a neglected disease and primarily affects developing countries. The HDV mainly spreads among persons through the contact with blood or body fluids (parenterally) (horizontal transmission), such as saliva, blood, semen, vaginal secretions; sex with an infected partner (Liaw et al., 1990). The global burden of HDV is estimated to be 62-72 million, affecting nearly 1% of the general population (Chen et al., 2019). At present about 74 million of HBV surface antigen (HBsAg) positive patients worldwide are also co-infected with HDV (Chen et al., 2021). Every year there are an estimated 20 million HEV infections globally with 3.3 million symptomatic cases, 3,000 stillbirths, and 44,000-70,000 HEV-related deaths per year (WHO, 2020).

## 2. Literature Review

The literature review section is an introductory region of research, which shows the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). It helps the novice researchers to understand the subject, and it serves as an indicator of the subject that has been carried out before (Creswell, 2007). Amanda Cheung and Paul Kwo have shown that HDV is more likely to cause chronic infection in the setting of HDV superinfection in hepatitis B surface antigen positive individuals and HEV cause of chronic infection in immuno-compromised individuals and is more common in genotypes 3 and 4, with sporadic cases occurring worldwide (Cheung & Kwo, 2020). Haradhan Kumar Mohajan has studied diagnosis and management of the HDV and HEV infections in some details (Mohajan, 2024i, j).

Haris Muhammad and his coauthors have discussed the epidemiology, pathogenesis, clinical presentation, treatment options, and ultimately liver transplantation of HDV patients (Muhammad et al., 2021). Christopher Dietz-Fricke and his coworker have confirmed on the safety and efficacy of bulevirtide monotherapy in a large real-world cohort of patients with hepatitis D treated in Germany. More studies are needed to explore the long-term benefits and optimal duration of bulevirtide treatment (Dietz-Fricke, 2023).

Silvia E. Tritz and her coauthors have investigated zoonotic transmission of HEV in rural settings of Lao People's Democratic Republic where humans are in close contacts with ruminants and where pigs are rare. They have highlighted on the need to raise the awareness of the rural population about water- and food- borne pathogens, and about the role of cattle as a possible source of infection (Tritz et al., 2018). Chunchen Wu and her coworkers have shown that the HEV causes self-limiting viral hepatitis, and among pregnant women the infection can be severe that has been associated with up to 30% mortality in the third trimester. They have also indicated that in pregnancy HEV is also associated with high rates of preterm labor and vertical transmission. They have summarized the current knowledge about HEV infection during pregnancy that focuses on the epidemiology, clinical manifestations, and mechanisms underlying severe liver injury; and also management and prevention of HEV infection during pregnancy (Wu et al., 2020).

## 3. Research Methodology of the Study

Research is a logical and systematic search for new useful information on a specific topic, which investigates to find solutions of scientific and social problems through systematic analysis (Rajasekar et. al., 2013). Methodology is the systematic and theoretical analysis of the methods is applied to a field of study. Therefore, research methodology is the science of studying how research is done scientifically (Patel & Patel, 2019). I have used both published and unpublished secondary data sources of HDV and HEV infections to prepare the research paper (Mohajan, 2017, 2018, 2020). I have also taken help from the journal articles, conference papers, published books and handbooks, internet, websites, etc. (Mohajan, 2024a-f).

## 4. Objective of the Study

Main objective of this article is to discuss the aspects of HDV and HEV (Mohajan, 2024m, n). At present there are about 74 million patients worldwide infected with HDV and about 20 million people globally infected with HEV (WHO, 2020). Other minor objectives of the study are as follows:

- to focus on HDV and HEV infections,
- to highlight on virology and transmission of HDV and HEV, and
- to demonstrate the treatment of HDV and HEV.

## 5. Hepatitis D Virus (HDV)

The HDV causes infection only in human that can be an acute, short-term infection or become a long-term, chronic infection. The HDV affects about 72 million people worldwide that is the severe form of viral hepatitis, leading to accelerated liver disease progression, cirrhosis and its complications, such as end-stage-liver disease and hepatocellular carcinoma (Lampertico et al., 2023).

### *5.1 Virology of HDV*

The HDV genome is an unusual, 1,700 nucleotides defective, single-stranded circular minus RNA virus that requires the presence of HBV in order to replicate. The HDV infection develops only in patients who are positive for the hepatitis B surface antigen (HBsAg). Infection may be acquired along with HBV (co-infection) or after HBV infection (superinfection) (Miao et al., 2020). The hepatitis D virion consists of the hepatitis D RNA genome, hepatitis D antigen (HDAg), and a lipoprotein envelope containing HBV surface antigen (HBsAg) proteins. Thus, HDV requires HBV in addition to cellular RNA polymerases for replication and cannot infect individuals without the presence of HBsAg, which is required for cell entry, virion assembly and export (Rizzetto & Verme, 1985). HDV co-infection with HBV may be associated with increased risk of severe clinical hepatitis, fulminant hepatic failure, chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (Ni et al., 2014).

*5.2 Symptoms and Transmission of HDV*

The symptoms of HDV infection are fever, fatigue, loss of appetite, malaise, nausea and vomiting, joint pain, abdominal pain, dark urine, and jaundice (Kamal et al., 2020). The HDV is transmitted through the infected blood, serous body fluids, and plasma derivatives, such as anti-hemophilic factor, contaminated needles, drugs, and also sexual transmission may possible (Mohajan, 2024l, m). The perinatal transmission is rare. It only occurs primarily in drug addicts and persons with hemophilia (Urban et al., 2021). The HDV needs hepadnavirus to function and for its propagation in hepatocytes, and is therefore acquired as a co-infection with HBV, or as a super-infection in those with existing chronic HBV infection. It can be transmitted percutaneously and sexually (Stockdale et al., 2020).

*5.3 Diagnosis and Treatment of HDV*

HDV is diagnosed for confirmation through HBsAg or IgM anti-HBc positive and positive research laboratory result for HDV RNA or detection of antibody to HDV (Wranke et al., 2014). It is also diagnosed by high levels of anti-HDV immunoglobulin G (IgG) and immunoglobulin M (IgM), and confirmed by detection of HDV RNA in serum. The HBV deoxyribonucleic acid (DNA) and HDV RNA tests are helpful in understanding how active hepatitis B and hepatitis D are in the body (Le Gal, 2017).

There are no vaccines and no known treatments for acute HDV (Urban et al., 2021). The HDV may be self-limiting or progress to chronic infection. The pegylated interferon alpha (Peg-IFNα) is the generally recommended treatment to suppress the HDV for some patients. Evidence shows that bulevirtide is effective in adults compared with standard care but there are some uncertainties on how long it works (De Ledinghen et al., 2021).

**6. Hepatitis E Virus (HEV)**

The HEV infection can cause acute liver failure, chronic hepatitis, and liver cirrhosis that remain a clinical challenge and still account for high mortality. It is water-borne disease that spreads by the HEV contamination with the fecal material ingestion. It may prove to be dangerous in pregnant women, especially during the third trimester; older people; and people who have existing chronic liver disease (Polley et al., 2022).

*6.1 Virology of HEV*

The HEV is a small, icosahedral, non-enveloped, single-stranded, positive-sense RNA virus with genome of 7.2 kb and 27-34nm in diameter that is highly unstable due to the lack of a lipid membrane (Mayr et al., 2018). At present HEV can be clustered genetically into 8 genotypes (GTs); HEV 1-8 that recognize with distinct differences in geographic distribution. HEV GTs 3 and 4 can cause liver disease in humans (Sridhar et al., 2017).

*6.2 Symptoms and Transmission of HEV*

Consistent symptoms of HEV are fever, headache, anorexia, nausea, vomiting, diarrhea, abdominal pain, and jaundice. Incubation period of HEV is 2-9 weeks. The HEV is usually a self-limiting illness. There are no reports of chronic infection with HEV. Fulminant disease occurs in about 10% of cases. In pregnancy, the mortality rate may be as high as 15-20% (Heymann, 2015).

The HEV is transmitted through the person to person fecal-oral spread. Contaminated drinking water is the most common source of infection. Maternal-neonatal transmission may occur. Zoonotic spread may occur through the cows, pigs, sheep, goats, and rodents (Wu et al., 2020). Higher rates of HEV seroprevalence are detected in slaughterhouse workers and vets. It is evaluated that one third of the worldwide population has been in contact with the virus (Patra et al., 2007).

*6.3 Diagnosis and Treatment of HEV*

Diagnosis can be made indirectly by detecting antibodies against HEV in the serum, or directly by detecting the genome of the virus in blood or other body fluids. Diagnosis of hepatitis E depends on clinical and epidemiologic features to detect IgM and IgG anti-HEV in serum (Kamar et al., 2014). No vaccine is currently

available to prevent HEV. The treatment of HEV is supportive. Good hygiene and sanitation are the best practice to prevent the virus. Current therapeutics are used to treat HEV infection are the nucleoside analog ribavirin and pegylated interferon-α (PEG IFN-α) (Wu et al., 2020).

**7. Conclusions**

From this study, I have observed that the HDV and HEV infections are significant causes of acute and chronic viral hepatitis worldwide. To reduce the transmission of HDV, all people infected with HBV must be screened for HDV. The HEV is potentially preventable by simple improving hygiene and sanitary measures, and clean and healthy food intake. Both of the infections are increasing global morbidity and mortality due to millions of chronically infected people.

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