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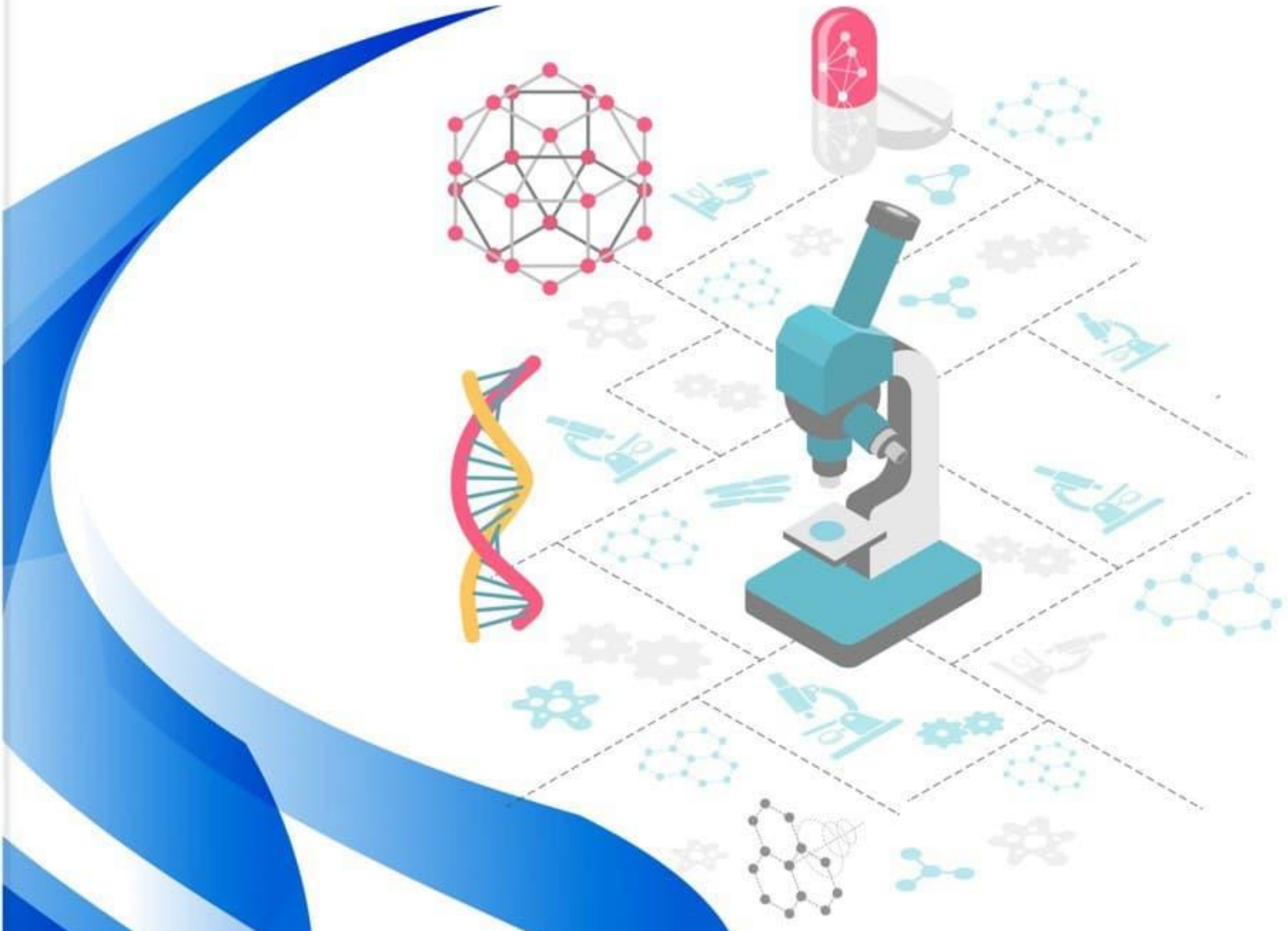

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Epidemiology and Intrafamilial Transmission of Hepatitis D: Current Trends and Challenges

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Abstract

Hepatitis D virus (HDV) remains a significant global public health concern, particularly in regions where hepatitis B virus (HBV) infection is endemic. As a defective virus that requires HBV co-infection, HDV contributes to the rapid progression of liver disease, often resulting in cirrhosis and hepatocellular carcinoma at a younger age compared to HBV monoinfection. Despite global efforts to eliminate viral hepatitis, HDV remains underdiagnosed and underreported, especially in developing countries.

This review summarizes current knowledge on the epidemiology of hepatitis D, highlighting regional variations, risk factors, and population groups at elevated risk. Special emphasis is placed on the mechanisms and prevalence of intrafamilial transmission, an aspect that has received limited attention despite its critical role in maintaining viral circulation. Challenges in diagnosis, the lack of standardized testing, and limited antiviral treatment options are discussed. Recent advances in HDV therapeutics and prevention strategies are also explored, with a focus on public health implications.

Keywords

Hepatitis D, HDV, intrafamilial transmission, epidemiology, viral hepatitis, liver cirrhosis, HBV co-infection, public health, Uzbekistan.

Introduction

Hepatitis D virus (HDV) infection is a critical global health issue and remains a significant challenge in the prevention and management of viral hepatitis. HDV is a

defective RNA virus that relies on the presence of hepatitis B virus (HBV) for its replication and pathogenicity. Co-infection or superinfection with HDV results in a more severe clinical course compared to HBV monoinfection, often accelerating the onset of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) at a younger age (Rizzetto et al., 1977; Farci et al., 2004).

Currently, it is estimated that approximately 12 to 72 million people worldwide are living with HDV infection, though these figures vary widely due to the lack of standardized diagnostic protocols and limited screening (Stockdale et al., 2020). The global distribution of HDV is uneven, with higher prevalence reported in Central Asia, Eastern Europe, parts of Africa, and the Amazon Basin. Notably, HDV remains underdiagnosed in both developed and developing countries, partly due to the absence of routine screening among HBV-positive individuals and insufficient awareness among healthcare professionals.

In the context of family-based transmission, HDV presents unique challenges. While the parenteral route is well recognized as the primary mode of transmission, intrafamilial spread—especially among close household contacts—has also been documented. Such transmission may occur through shared personal hygiene items, minor skin lesions, or unrecognized percutaneous exposure, particularly in environments where HBV is already endemic (Yen et al., 2003; Gish et al., 2013).

This review explores the current epidemiological landscape of HDV infection, with a particular focus on intrafamilial transmission patterns, their public health implications, and the key challenges in HDV diagnosis and prevention. By identifying knowledge gaps and recent advances, this article aims to contribute to the global effort of viral hepatitis elimination.

Epidemiology of Hepatitis D

Hepatitis D virus (HDV) is a unique and highly pathogenic satellite virus that depends on hepatitis B virus (HBV) for its replication. Globally, HDV infection remains largely neglected in both research and clinical practice, despite causing the most aggressive form of viral hepatitis, with a higher risk of fulminant hepatitis, rapid progression to cirrhosis, and hepatocellular carcinoma (HCC). The global burden is estimated to range from 12 to 72 million individuals, yet accurate figures are difficult to determine due to underdiagnosis, lack of standardized surveillance, and limited access to HDV RNA testing (Stockdale et al., 2020; Chen et al., 2022).

Global Distribution and Endemic Hotspots

HDV shows remarkable geographic variability. In high-income countries, prevalence among HBsAg-positive individuals is generally low (<5%), whereas in endemic areas it can exceed 30–40%. High-prevalence areas include:

- Amazon Basin (Brazil, Colombia, Venezuela): Genotype 3 predominates, with a well-documented association with fulminant hepatitis and high mortality.

Transmission often occurs in indigenous communities through ritual scarification, shared blades, or unsterile injections.

- Sub-Saharan Africa (e.g., Nigeria, Gabon, Cameroon): Genotypes 5–8 circulate, often underrecognized. In some communities, HDV affects over 30% of HBV carriers due to horizontal transmission in childhood and lack of vaccination infrastructure.
- Middle East (Iran, Turkey, Egypt): HDV prevalence ranges from 10% to 25% among HBsAg carriers, with genotype 1 being most common. Intrafamilial and nosocomial transmission were historically widespread.
- Eastern Europe (Russia, Moldova, Romania): Prevalence among HBV-infected individuals varies from 10% to 20%. Injection drug use, incarceration, and insufficient harm-reduction services contribute significantly to transmission.
- East Asia (Japan, Taiwan, China): Genotype 2 dominates. Prevalence has declined significantly due to national HBV vaccination programs, but remains detectable in older, unvaccinated populations.
- Southern Europe (Italy, Greece, Romania): Historic endemicity persists among older adults, particularly in southern Italy and rural Balkan regions.

Central Asia: A Critical Hotspot

Among the most affected regions globally is Central Asia, where HBV remains endemic and HDV co-infection is significantly under-reported. The situation is particularly acute in Uzbekistan and Kazakhstan.

Uzbekistan

In Uzbekistan, HDV is now recognized as the leading cause of HBV-related cirrhosis and liver failure. According to the landmark study published in *Liver International* (2019), which analyzed 6,589 patients with viral liver cirrhosis across three years (2016–2018), the seroprevalence of anti-HDV among HBsAg-positive cirrhotics increased dramatically:

- 76.5% in 2016
- 80.5% in 2017
- 84.0% in 2018

By 2018, HDV accounted for nearly half (49.1%) of all viral cirrhosis cases, whereas HBV monoinfection contributed only 9.3% and HCV approximately 41.5%. Moreover, the median age of HDV-cirrhosis patients was only 39 years, significantly younger than that of patients with HBV (46 years) or HCV (55 years), indicating aggressive disease progression (Khodjaeva et al., 2019).

Subsequent studies (Karabaeva et al., 2020) confirm these findings, with particularly high rates in rural and under-immunized populations. The intrafamilial clustering of HDV, shared hygiene tools, and lack of HBV birth-dose administration contribute to persistent transmission. Despite the inclusion of HBV vaccination in Uzbekistan's national immunization program since 2002, coverage gaps persist, especially in rural maternity care.

Kazakhstan

In Kazakhstan, clinical and molecular studies have also documented high rates of HDV co-infection among HBsAg-positive individuals. In some regions, especially in the south (e.g., Shymkent, Turkestan) and west (e.g., Aktobe, Atyrau), anti-HDV prevalence ranges from 15% to 25%. Studies by Shakhanova et al. (2018) highlight that co-infected patients experience more severe fibrosis and earlier HCC onset than HBV monoinfected individuals.

Healthcare infrastructure for HDV screening and treatment remains underdeveloped, and most testing is limited to referral hepatology centers in major cities. As a result, many patients are diagnosed late, after cirrhosis has already developed.

HDV Genotypes and Clinical Implications

HDV is classified into eight genotypes (HDV-1 to HDV-8), each with distinct geographic patterns and clinical manifestations:

- Genotype 1: The most widespread, found in Central Asia, Europe, and the Middle East. It is associated with variable disease severity and poor interferon response.
- Genotype 2: Predominates in East Asia (Japan, Taiwan). Linked to milder disease.
- Genotype 3: Found in the Amazon Basin. Known for rapid progression and fulminant hepatitis.
- Genotypes 4–8: Found mainly in Africa and some parts of Asia, with limited clinical data available.

In Uzbekistan and Kazakhstan, HDV genotype 1 is dominant. Molecular studies have confirmed its circulation in Tashkent and Almaty, correlating with the aggressive clinical presentations observed in regional liver centers.

Challenges and Future Directions

Despite the heavy disease burden, HDV remains neglected in national health policies across Central Asia. Major challenges include:

- Lack of routine HDV testing among HBsAg-positive patients
- Absence of HDV RNA confirmatory assays in most provincial laboratories
- No access to novel antivirals such as bulevirtide
- Weak public awareness and physician education about HDV

To achieve WHO’s goal of viral hepatitis elimination by 2030, national strategies must prioritize HDV screening in HBV-positive populations, ensure full HBV vaccination (especially birth dose), and invest in diagnostic and treatment infrastructure. Robust epidemiological surveillance is critical to inform and monitor progress.

Intrafamilial Transmission of Hepatitis D

The intrafamilial transmission of hepatitis D virus (HDV) remains a significant yet often underrecognized route of infection, particularly in regions with a high prevalence of hepatitis B virus (HBV). Since HDV requires HBV co-infection for replication, household settings where chronic HBV carriers reside present a conducive environment for HDV spread. Although the dominant route of HDV transmission is parenteral, a growing body of evidence supports the potential for horizontal transmission within families, independent of injection drug use or transfusions.

Epidemiological investigations have identified a higher seroprevalence of HDV among household contacts of HDV-infected individuals. A study by Sagnelli et al. (2000) in southern Italy revealed that HDV infection was significantly more common among first-degree relatives, especially spouses, suggesting that prolonged exposure to infected bodily fluids contributes to transmission. Similarly, studies conducted in Turkey and Iran have reported HDV clustering within families, particularly among siblings and children born before the widespread implementation of HBV vaccination programs (Mumtaz et al., 2005; Alavian et al., 2008).

Mechanisms of intrafamilial transmission likely involve shared use of personal hygiene items (e.g., razors, toothbrushes), minor unrecognized skin breaches, and cultural practices such as tattooing or ear piercing performed in unsanitary conditions. Additionally, children living in households with HDV-positive parents may be at risk through close contact in early childhood, a period marked by high rates of exposure to bodily fluids.

Vertical transmission of HDV from mother to child has been rarely documented and is believed to be inefficient. This is primarily due to the typically transient and low viremia levels of HDV in mothers, along with the requirement of simultaneous HBV replication. Nevertheless, when maternal HBV and HDV viral loads are both high, and especially in the absence of neonatal HBV prophylaxis, the risk of co-transmission may increase (Gish et al., 2013; Rizzetto, 2012).

Preventive strategies against intrafamilial HDV transmission should prioritize the identification and monitoring of HBV/HDV co-infected individuals. All household contacts of HDV-positive patients should be screened for HBV and HDV markers, followed by immunization of susceptible individuals against HBV. Additionally, health education campaigns emphasizing safe personal hygiene practices and awareness of non-parenteral transmission routes are vital. In low-resource settings, integrating HDV screening into existing HBV programs could significantly enhance early detection and containment of household spread.

Despite these insights, data on intrafamilial transmission remain limited due to the absence of systematic contact-tracing studies and the restricted availability of HDV RNA testing in many endemic regions. Further longitudinal and case–control studies are necessary to better quantify the risk and clarify the exact modes of non-parenteral HDV transmission within families.

Diagnosis and Therapeutic Challenges in Hepatitis D

The diagnosis of hepatitis D virus (HDV) infection remains a major global health challenge due to the lack of standardized testing algorithms, limited access to HDV-specific diagnostics, and insufficient awareness among clinicians. HDV should be suspected in all individuals who test positive for hepatitis B surface antigen (HBsAg), particularly in those with elevated alanine aminotransferase (ALT) levels or rapidly progressive liver disease despite low or undetectable HBV DNA levels (Rizzetto et al., 1980; Wedemeyer et al., 2020).

The initial diagnostic step involves serological detection of anti-HDV antibodies (IgG and IgM). However, the presence of anti-HDV IgG indicates exposure rather than active infection, and thus should be followed by confirmatory testing for HDV RNA using nucleic acid amplification techniques (NAATs) to identify ongoing viral replication. Unfortunately, HDV RNA testing is unavailable in many low- and middle-income countries, and variability in assay sensitivity and standardization further complicates diagnosis (Farci & Niro, 2012).

Another diagnostic challenge is the dynamic interaction between HBV and HDV. Since HDV suppresses HBV replication, many coinfected patients may present with low or undetectable HBV DNA, leading to a misdiagnosis of inactive HBV carrier state. Consequently, clinicians must remain vigilant and assess liver function and fibrosis severity using non-invasive tools such as transient elastography (FibroScan) or liver biopsy, when necessary (Chen et al., 2022).

Therapeutic options for HDV remain limited. The only approved treatment for chronic HDV infection until recently has been pegylated interferon-alpha (PEG-IFN-α), which yields sustained virological response rates of only 25–30% and is associated with considerable side effects (Rizzetto et al., 2009). Moreover, relapse after treatment cessation is common, and PEG-IFN is contraindicated in patients with decompensated cirrhosis or significant psychiatric comorbidities.

In recent years, several novel therapeutic agents have entered clinical development. Bulevirtide (formerly Myrcludex B), a first-in-class entry inhibitor targeting the sodium taurocholate co-transporting polypeptide (NTCP) receptor, has demonstrated efficacy in phase II and III clinical trials. It was conditionally approved by the European Medicines Agency (EMA) in 2020 for the treatment of adults with chronic HDV and compensated liver disease (Wedemeyer et al., 2020; Bogomolov et al., 2016).

Other promising compounds include lonafarnib (a prenylation inhibitor), and pegylated interferon lambda, both of which are undergoing further evaluation. Combination therapies targeting multiple stages of the HDV life cycle may represent the future of HDV management.

Despite these advances, treatment access remains inequitable across regions. Most HDV-endemic countries, including those in Central Asia and sub-Saharan

Africa, lack regulatory approval, financial resources, and infrastructure to implement advanced therapeutic strategies. Global efforts must focus on expanding access to affordable diagnostics, enhancing provider education, and advocating for inclusion of HDV drugs into national formularies and viral hepatitis elimination programs.

Preventive Strategies and Public Health Implications

Effective prevention of hepatitis D virus (HDV) infection fundamentally depends on the control and elimination of hepatitis B virus (HBV), given HDV's reliance on HBV for replication. Therefore, universal HBV vaccination remains the most critical and cost-effective strategy for preventing new HDV infections. Countries that have successfully implemented nationwide HBV immunization programs, particularly those including the timely birth dose, have observed a marked decline in HBV—and consequently HDV—incidence (WHO, 2017; Schweitzer et al., 2015).

In endemic areas, however, the absence of comprehensive vaccination coverage, inconsistent vaccine delivery, and insufficient awareness among vulnerable populations continue to hinder progress. Strengthening national immunization infrastructure, particularly in low-resource settings, is essential. This includes ensuring cold-chain logistics, increasing vaccine uptake in rural regions, and integrating HBV/HDV education into maternal and child health services.

Secondary prevention efforts focus on reducing transmission risks in HBV-infected individuals. All HBsAg-positive patients should undergo HDV screening, especially those with risk factors such as injection drug use, multiple sexual partners, or a family history of liver disease. Contact tracing and targeted immunization of household members and close contacts remain critical tools in controlling intrafamilial transmission chains (El-Shabrawi & Kamal, 2011).

Public health systems must also address the current diagnostic and therapeutic gaps. Incorporating HDV RNA testing into existing hepatitis programs can facilitate earlier detection and linkage to care. Additionally, training healthcare providers to recognize HDV risk factors and interpret serological profiles correctly is key to closing the diagnostic gap.

On a broader scale, integrating HDV into global and regional viral hepatitis elimination strategies, as outlined in the WHO Global Health Sector Strategy (GHSS), is essential. Surveillance systems should be strengthened to track HDV epidemiology, treatment outcomes, and programmatic impact. Equitable access to new HDV therapies, particularly in middle- and low-income countries, should be prioritized through partnerships with pharmaceutical companies, international health organizations, and government bodies.

Ultimately, eliminating HDV will require a coordinated, multi-sectoral approach that combines vaccination, education, screening, early diagnosis, and access to emerging antiviral therapies. Investing in HDV prevention is not only critical for

affected individuals but also represents a significant step forward in achieving the broader goals of hepatitis elimination and global health equity.

Discussion

Hepatitis D virus (HDV) infection presents a persistent and largely underappreciated threat to global liver health, particularly in regions where hepatitis B virus (HBV) remains endemic. As demonstrated in recent epidemiological studies, including data from Uzbekistan and Kazakhstan, HDV is responsible for a disproportionately high share of HBV-related liver cirrhosis and hepatocellular carcinoma, often affecting patients at a younger age and with a more aggressive clinical course.

The dramatic rise in HDV prevalence in Uzbekistan—from 76.5% to 84% among HBsAg-positive cirrhotic patients between 2016 and 2018—underscores the urgent need for targeted public health interventions. This trend reflects a combination of factors: persistent gaps in HBV vaccination coverage (particularly the timely birth dose), limited HDV diagnostic capacity outside major cities, and ongoing intrafamilial and nosocomial transmission. Similar patterns have been observed in southern and western Kazakhstan, where HDV prevalence among HBsAg-positive patients ranges from 15% to 25%.

Despite global advances in hepatitis B prevention through vaccination, the integration of HDV screening into national hepatitis control strategies remains inadequate. Most HBsAg-positive patients are not routinely tested for HDV, resulting in underdiagnosis and delayed treatment initiation. This diagnostic gap is exacerbated by the limited availability of HDV RNA testing in low- and middle-income countries.

The recent approval of HDV-specific antivirals, such as bulevirtide, has opened new possibilities for effective treatment. However, access remains geographically and economically limited, and interferon-based regimens continue to be the only available option in much of Central Asia. Furthermore, the natural history of HDV varies by genotype, and in regions where genotype 1 predominates (such as Central Asia), outcomes tend to be more severe and less responsive to therapy.

Addressing these challenges will require multisectoral strategies that include expanded vaccination, decentralized diagnostic infrastructure, physician education, and international collaboration to ensure equitable access to novel therapies.

Conclusion

Hepatitis D remains a neglected but devastating component of the global viral hepatitis epidemic, particularly in Central Asia. In countries such as Uzbekistan and Kazakhstan, HDV has become a leading cause of advanced liver disease among HBV carriers, with a high burden of premature cirrhosis and hepatocellular carcinoma.

To confront this threat effectively, national and regional health authorities must integrate HDV screening into routine care for all HBsAg-positive individuals, expand

the availability of confirmatory HDV RNA testing, and close immunization gaps through strengthened perinatal HBV vaccination programs. Public health education on HDV transmission and intrafamilial spread must also be prioritized.

Most critically, governments and global health partners must work to ensure that emerging HDV treatments are accessible to populations in low-resource settings. Without urgent and coordinated action, HDV will continue to undermine progress toward hepatitis elimination goals and impose a growing burden on healthcare systems across endemic regions.

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