Commentary

Progress and Challenges in the Global Elimination of Viral Hepatitis D

Minghui Li[1,2,3,#]; Qi Wang[1]; Weihua Cao[1]; Yao Xie[1,2,3]

ABSTRACT

Hepatitis D virus (HDV) is a defective virus whose replication depends on hepatitis B virus (HBV) surface antigen (HBsAg). HBV/HDV coinfection represents the most severe form of viral hepatitis, substantially accelerating progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma. In response to the World Health Organization's (WHO) 2030 elimination target for viral hepatitis as a major public health threat, HDV elimination has emerged as one of the most formidable challenges, driven by its unique biological characteristics, widespread underdiagnosis, and historical absence of effective therapies. This article reviews key global advances in HDV epidemiology, screening and diagnosis, therapeutic development, and public health strategies. We provide an in-depth analysis of current barriers to elimination and offer strategic insights to guide future control efforts.

Hepatitis D virus (HDV) represents the most severe form of viral hepatitis, yet it has been consistently underdiagnosed and underprioritized in global hepatitis control efforts. Although HDV is a defective virus that requires hepatitis B virus (HBV) for replication, it accelerates disease progression far more rapidly than HBV monoinfection (*1*). The global burden of HDV is substantial. According to a comprehensive meta-analysis by Stockdale et al. (*2*), an estimated 12–72 million individuals worldwide are infected with HDV, with a pooled prevalence of 4.5% [95% confidence interval (*CI*) 3.6%, 5.7%] among hepatitis B surface antigen (HBsAg)-positive populations. High-burden regions include Central Asia (e.g., Mongolia, 27%), West Africa (e.g., Nigeria, 8%, 15%), and parts of the Middle East (e.g., Pakistan, 6%, 9%), although the true prevalence is likely underestimated due to heterogeneous diagnostic methods and incomplete surveillance coverage. As HBV antiviral therapy and hepatitis C virus (HCV) elimination programs continue to advance, HDV has emerged as one of the most formidable barriers to achieving the World Health Organization's 2030 viral hepatitis elimination targets (*3*). A comprehensive understanding of recent progress and persistent challenges is therefore critical for informing future control strategies.

RECENT ADVANCES IN HDV CONTROL

Over the past five years, global understanding of HDV epidemiology has advanced substantially. Enhanced population-based screening strategies and more sensitive diagnostic platforms have refined prevalence estimates and revealed a broader geographic distribution than previously recognized. Regional analyses demonstrate marked heterogeneity in HDV prevalence among HBsAg-positive populations (*4*), with rates ranging from 10%–15% in Central and West Africa, 5%–10% in Eastern Europe, and 3–8% in the Middle East, while most high-income settings in North America and East Asia report prevalence below 1% (*5*). Notably, targeted surveys have identified exceptionally high seroprevalence rates of 20%–40% among Indigenous communities in the Amazon Basin (*6*). These epidemiological insights have prompted an increasing number of countries to integrate routine anti-HDV screening into HBV management protocols and strengthen surveillance systems for high-risk populations.

Diagnostic and therapeutic capacities have similarly expanded. Standardized HDV RNA quantitative PCR assays, improved anti-HDV antibody testing platforms, and automated molecular diagnostic systems have enhanced case detection and enabled programmatic screening initiatives (*7*–*8*). For more than four decades, pegylated interferon-α (Peg-IFN α) remained the only available therapy for HDV, despite limited efficacy and poor tolerability (*9*). The regulatory approval of bulevirtide, an NTCP entry

inhibitor, represented a milestone as the first targeted antiviral therapy for HDV, demonstrating substantial reductions in HDV RNA levels and improvements in biochemical markers (*10*). Several complementary investigational agents — including lonafarnib (*11*), REP 2139-Mg (*12*), VIR-2218 (*13*), and the monoclonal antibody libetavimab (HH-003) (*14*) — have now advanced to mid- and late-stage clinical development (Table 1). Increasing policy attention from the WHO and international hepatology societies has further strengthened the integration of routine HDV testing into national viral hepatitis elimination programs (*3*).

KEY CHALLENGES TO HDV ELIMINATION

Gaps in HDV Diagnosis and Therapeutic Access

HDV control is hindered primarily by substantial diagnostic gaps. The vast majority of HBsAg-positive individuals worldwide have never been tested for HDV (*15*). Limited clinician awareness, restricted access to HDV RNA and antibody testing, and lack of reimbursement contribute to this diagnostic gap (*16*), leading many patients to be identified only at advanced liver disease stages.

Although bulevirtide represents a therapeutic milestone, its high cost and restrictive reimbursement policies limit availability to only a few countries. Other emerging agents are also expected to be expensive, leaving patients in low- and middle-income regions with few effective treatment options (*17*). Peg-IFN α further adds limitations due to modest efficacy and poor suitability for decompensated cirrhosis.

Critical Barriers to Effective HDV Control

Effective HDV control is fundamentally linked to HBV prevention strategies. Given that HDV transmission requires concurrent HBV infection, robust HBV immunization programs represent a cornerstone of HDV prevention. However, substantial gaps persist: adult vaccination coverage remains below 20%–30% in many regions (*18*), and prevention of mother-to-child transmission fails in 5%–10% of births in some low- and middle-income countries (*19*). With nearly 300 million individuals living with chronic HBV infection globally, sustained immunoprevention and comprehensive long-term management are critical to reducing HDV incidence. Figure 1 illustrates the substantial gap between HBV-infected populations and HDV patients who ultimately access effective treatment.

Disease heterogeneity further complicates the evaluation of HDV treatment efficacy. While HBsAg clearance represents the ideal therapeutic endpoint, it remains difficult to achieve in clinical practice. Consequently, most trials rely on surrogate markers such as HDV RNA reduction and ALT normalization. However, these markers lack full validation, introducing uncertainty when assessing long-term clinical benefit (*20*).

HDV in Vulnerable Populations

HDV disproportionately affects several high-risk groups, particularly people who inject drugs (PWID) and migrants from high-endemic regions. Among PWID, HDV seroprevalence can reach 10%–30%, substantially exceeding rates observed in the general HBsAg-positive population. Similarly, migrants from high-burden areas demonstrate elevated anti-HDV

TABLE 1. Investigational agents for HDV.

Drug	Mechanism of action	Development stage	Representative company	Key features/challenges
Bulevirtide (BLV)	NTCP receptor antagonist (viral entry inhibitor)	Conditional approval (European Union, 2020)	Gilead Sciences	First HDV-specific antiviral therapy; subcutaneous administration; high cost limits accessibility
Lonafarnib	Farnesyltransferase inhibitor (prenylation inhibitor)	Phase III clinical trials	Eiger BioPharmaceuticals	Oral administration; requires ritonavir boosting; gastrointestinal adverse effects
VIR-2218	HBV/HDV siRNA	Phase II	Vir Biotechnology	Subcutaneous administration; demonstrates potential for sustained HDV RNA suppression
REP 2139-Mg	Nucleic acid polymer (inhibits HBsAg release)	Phase II	Replicor	Requires combination therapy with Peg-IFNα; administered intravenously
Interferon-λ	Immunomodulatory agent	Phase II	Eiger BioPharmaceuticals	Improved tolerability compared with IFN-α

Abbreviation: HDV=Hepatitis D virus

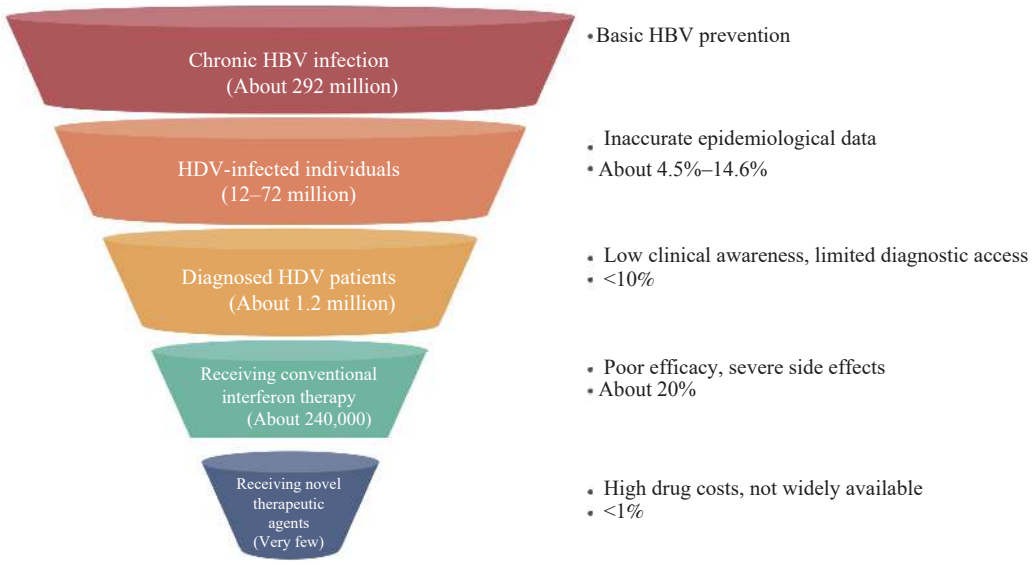

FIGURE 1. Global estimated prevalence of HDV infection and the diagnostic and therapeutic gaps.
Note: This figure depicts the cascade from HBV infection to HDV diagnosis and treatment, highlighting critical gaps at each stage. Data sources include WHO Global Hepatitis Reports (2022–2024), multi-country HDV screening surveys, and regional epidemiological analyses. Estimated proportions represent: 1) the global HBsAg-positive population; 2) the proportion screened for anti-HDV antibodies; 3) the proportion diagnosed with HDV RNA viremia; and 4) the proportion receiving HDV-targeted therapy. Values illustrate the substantial magnitude of missed diagnoses and limited treatment access rather than country-specific estimates.
Abbreviation: HBV=hepatitis B virus; HDV=hepatitis D virus; WHO=World Health Organization; HBsAg=hepatitis B surface antigen.

positivity compared with local residents. Despite this heightened risk, screening coverage in these populations frequently remains below 20%. Tailored, community-engaged approaches will be essential to strengthen prevention, expand testing, and improve linkage-to-care.

PUBLIC HEALTH IMPLICATIONS

Achieving HDV elimination requires coordinated efforts to address critical gaps in prevention, diagnosis, and treatment access.

Global Priority Actions

Expand universal screening by implementing one-time anti-HDV testing for all HBsAg-positive individuals and improving access to affordable diagnostics. Improve access to emerging therapies by establishing pricing mechanisms and targeted access programs in high-burden settings. Strengthen HBV prevention by maintaining high infant immunization coverage and expanding adult catch-up vaccination programs. Enhance linkage-to-care by increasing provider awareness and integrating HDV services into existing HBV management programs.

Priority Actions for China

Integrate anti-HDV testing into national HBV screening programs, with particular emphasis on newly diagnosed HBsAg-positive individuals. Strengthen laboratory and surveillance capacity through expanded HDV RNA testing and incorporation of HDV indicators into national reporting systems. Improve management of high-burden and mobile populations through targeted outreach programs and standardized referral pathways.

Conflict of interest: No conflicts of interest.

Funding: Supported by the Beijing Municipal Health Commission High-Level Public Health Technical Personnel Construction Project (Discipline Leader-03-26) and the Beijing Hospitals Authority "Peak" Talent Training Program (DFL20241803).

doi: 10.46234/ccdcw2025.263

[#] Corresponding author: Minghui Li, liminghui0809@ccmu.edu.cn.

[1] Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing, China; [2] HBV Infection, Clinical Cure and Immunology Joint Laboratory for Clinical Medicine, Capital Medical University, Beijing, China; [3] Department of Hepatology Division 2, Peking University Ditan Teaching Hospital, Beijing, China.

Submitted: October 10, 2025
Accepted: December 08, 2025
Issued: December 12, 2025

REFERENCES

1. Asselah T, Rizzetto M. Hepatitis D virus infection. N Engl J Med 2023;389(1):58 – 70. https://doi.org/10.1056/NEJMra2212151.
2. Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. J Hepatol 2020;73(3):523 – 32. https://doi.org/10.1016/j.jhep.2020.04.008.
3. Njuguna HN, Hiebert L, Harris A, Morgan RL, Gupta N, Ward JW. An assessment of national strategic action plans for viral hepatitis elimination, 2016-2021. J Infect Dis 2023;228(Suppl 3):S148 – 53. https://doi.org/10.1093/infdis/jiad346.
4. Blaney H, Khalid M, Heller T, Koh C. Epidemiology, presentation, and therapeutic approaches for hepatitis D infections. Expert Rev Anti Infect Ther 2023;21(2):127 – 42. https://doi.org/10.1080/14787210.2023.2159379.
5. Miao Z, Zhang S, Ou X, Li S, Ma Z, Wang W, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. J Infect Dis. 2020;221(10):1677 – 1687 https://doi.org/10.1093/infdis/jiz633.
6. Hayashi T, Takeshita Y, Hutin YJF, Harmanci H, Easterbrook P, Hess S, et al. The global hepatitis delta virus (HDV) epidemic: what gaps to address in order to mount a public health response? Arch Public Health 2021;79(1):180. http://dx.doi.org/10.1186/s13690-021-00693-2.
7. Illescas-López M, Chaves-Blanco L, de Salazar A, Hernández-Febles M, Carracedo R, Lagarejos E, et al. Assessment of performance and comparison of three commercial HDV RNA detection assays: implications for diagnosis and treatment monitoring. Front Cell Infect Microbiol 2024;14:1422299. https://doi.org/10.3389/fcimb.2024.1422299.
8. Akuffo GA, Ouoba S, Ko K, Chhoung C, Phyo Z, Mirzaev UK, et al. Assessing the diagnostic accuracy of serological tests for hepatitis delta virus diagnosis: a systematic review and meta-analysis. Sci Rep 2024;14(1):18475. https://doi.org/10.1038/s41598-024-69304-8.
9. Negro F, Lok AS. Hepatitis D: a review. JAMA 2023;330(24):2376 – 87. https://doi.org/10.1001/jama.2023.23242.
10. Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, et al. A phase 3, randomized trial of bulevirtide in chronic hepatitis D. N Engl J Med 2023;389(1):22 – 32. https://doi.org/10.1056/NEJMoa2213429.
11. Yang Q, Xue B, Liu FJ, Lu YZ, Tang JL, Yan MR, et al. Farnesyltransferase inhibitor lonafarnib suppresses respiratory syncytial virus infection by blocking conformational change of fusion glycoprotein. Signal Transduct Target Ther 2024;9(1):144. https://doi.org/10.1038/s41392-024-01858-5.
12. Buti M, Gonzalez A, Riveiro-Barciela M, Bourliere M. Management of chronic HBV-HDV patients chronic HBV-HDV infection: a review on new management options. United Eur Gastroenterol J 2024;12(2):210 – 8. https://doi.org/10.1002/ueg2.12494.
13. Zhou JY, Kaiser H, Rocha E, Terrell AN, Corti D, Purcell LA, et al. Therapy with murinized tobevibart and elebsiran is efficacious in a liver-chimeric mouse model of HDV infection. JHEP Reports 2025;7(6):101400. https://doi.org/10.1016/j.jhepr.2025.101400.
14. Wang XR, Chi XM, Zhang YY, Gu YM, Xiao L, Qi YH, et al. Safety and efficacy of anti-pre-S1 domain monoclonal antibody (HH-003) treatment in patients with co-infection of chronic hepatitis B virus (HBV) and hepatitis D virus (HDV): a single center, open-label, phase 2 trial. J Hepatol 2023;78(Suppl S1):S117. https://doi.org/10.1016/S0168-8278(23)00606-2.
15. Buti M, Spearman CW, Siebelt K, El-Sayed M. Hepatitis D epidemiology and access to diagnostic testing among healthcare providers in Africa: a multi-country survey. JHEP Rep 2025;7(9):101495. https://doi.org/10.1016/j.jhepr.2025.101495.
16. World Health Organization. Global Health Sector Strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. Geneva: WHO; 2022. https://www.who.int/publications/i/item/9789240053779.
17. Cooke GS, Flower B, Cunningham E, Marshall AD, Lazarus JV, Palayew A, et al. Progress towards elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission update. Lancet Gastroenterol Hepatol 2024;9(4):346 – 65. https://doi.org/10.1016/s2468-1253(23)00321-7.
18. Bai XX, Chen L, Liu XY, Tong YJ, Wang L, Zhou MR, et al. Adult hepatitis B virus vaccination coverage in China from 2011 to 2021: a systematic review. Vaccines 2022;10(6):900. https://doi.org/10.3390/vaccines10060900.
19. Matthews PC, Ocama P, Wang S, El-Sayed M, Turkova A, Ford D, et al. Enhancing interventions for prevention of mother-to-child-transmission of hepatitis B virus. JHEP Rep 2023;5(8):100777. https://doi.org/10.1016/j.jhepr.2023.100777.
20. Ghany MG, Buti M, Lampertico P, Lee HM, 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference Faculty. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. Hepatology 2023;78(5):1654 – 73. https://doi.org/10.1097/hep.0000000000000431.