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EDITORIAL

OPEN

A call to reclassify the delta hepatitis virus as an orphan disease

Chronic infection with HDV is considered the most aggressive and severe form of viral hepatitis,[1] associated with an increased risk of cirrhosis and liver cancer.[2] Due to high morbidity and mortality, there is a clear need for additional therapies for this disease. The Food and Drug Administration (FDA)'s Office of Orphan Products Development should continue to recognize chronic HDV as an orphan disease for current and future medication treatment applications.[3] It is important to note that lonafarnib and myrcludex have previously received FDA orphan status designation. The Orphan Drug Act defines a rare disease or condition as one that affects $<200{,}000$ people in the United States.[4] As outlined in this article, the great majority of the current and historical data support an orphan designation.

Despite causing severe liver disease, HDV remains largely neglected in research, testing, epidemiology, and public health policy settings. Because the Orphan Drug Act provides incentives to drug companies to research, develop, and distribute therapeutics for people with rare diseases, the designation of HDV as orphan status will open up the development of therapies for this virus and improve outcomes for patients with HDV.

PREVALENCE OF HDV

Because HDV is a replication-defective RNA virus requiring HBV surface proteins as its envelope proteins, the prevalence and geographic distribution of HDV may closely correlate with HBV in some regions.[5] Traditionally, regions with low HBV prevalence, such as Northern Europe and North America, were deemed low-endemic (prevalence) areas for HDV.[6] Because of the low estimated prevalence in the United States, it does not receive the same priority for research, testing, epidemiology, and public health policies as other diseases thought to be more prevalent.

Our ability to establish the true prevalence of the HDV is limited by the availability of testing. There is neither an FDA-cleared or FDA-approved test nor a standardized diagnostic molecular testing method available for HDV antibody or HDV-RNA.[7,8] Testing is conducted using laboratory-developed tests, which are limited in availability and lack standard screening criteria for HDV. This lack of standardized testing limits epidemiological studies on the virus and introduces some bias into the studies conducted, including a focus on populations and regions at high risk in many studies and possibly using tests with low specificity.

Recognizing these limitations, reported HDV prevalence data range from 0.02% to 42% among patients who are HBV-positive.[5] The assays used in these studies, which measured HDV antibody positivity (anti-HDV seroprevalence), were not standardized and were also characterized by a potentially high rate of false positives.[9,10] Furthermore, anti-HDV seroprevalence is a poor indicator of active HDV infection compared with HDV-RNA detection by PCR[9,10]; clinical experience from experts suggests that at most two-thirds of patients who are anti-HDV-positive in the United States are HDV-RNA-positive.[11–13] These studies indicate that HDV-RNA prevalence among patients who are HBV-positive in the United States is far less than 10% (well below the 200,000 threshold for Orphan Drug Designation).

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

The highest HDV seroprevalence rate in the United States, reported by Patel et al in 2019,[14] was 42% among adults infected with hepatitis B (adults who were

Abbreviations: CDA, Center for Disease Analysis; CDC, Centers for Disease Control and Prevention; CROI, Conference on Retroviruses and Opportunistic Infections; FDA, Food and Drug Administration; NHANES, National Health and Nutrition Examination Survey; NIH, National Institutes of Health; PCR, polymerase chain reaction.

HBsAg-positive), based on data from the 2011–2016 National Health and Nutrition Examination Survey (NHANES)—an unusually high figure potentially due to lack of reliability of the assay used.[9] Of 16,143 individuals tested for HDV, 113 adults were positive for HBsAg. Given that HDV can only occur in the setting of HBV infection, calculations of HDV prevalence should only be based on individuals with HBV. In this cohort of 113 individuals with HBV who were additionally tested for anti-HDV, 43 (42%) were positive.

However, this should be interpreted with caution in light of the following limitations.

- The accuracy of the anti-HDV diagnostic assay used in this study is in doubt. A study in Mongolia noted a 21% false-positive rate for the anti-HDV antibody assay used in this study.[9]
- The cohort of 113 patients is small when considering that multiple US-based studies have since been published with much larger and potentially more generalizable cohorts.
- As noted by the authors, the data evaluated by Patel et al encompassed a study period from 2011 to 2016; several US-based and cohort-based studies with more recent data and larger sample sizes have been published since then (see below).
- These positive samples are undergoing review by NHANES in collaboration with the Centers for Disease Control and Prevention (CDC) for possible retesting.

Both the authors of the study by Patel et al and external researchers[15] have pointed out that the potentially high false-positive rate of the assay used may have led to overestimations. In addition, the sample size of the HBV-infected population in the Patel study was relatively small (113 patients), compared with other studies.[16–21] Hence, we believe that this study significantly overestimates the true prevalence of HDV in the United States.

RECENT EVIDENCE

Since the publication of the aforementioned paper by Patel et al,[14] there have been several US cohort-based studies with larger sample sizes and data from more recent time periods that may more accurately reflect recent HDV infection trends (Table 1).

Data published since the original publication consistently dispute the high prevalence numbers in the study by Patel et al. A recent meta-analysis found that the pooled HDV seroprevalence among persons with chronic HBV infection in the United States was below 5%, with only 75,005 persons estimated to have HDV antibodies in the United States.[22] Emerging data from Quest Diagnostics using remnant samples that were presented at the 2024 Conference on Retroviruses and Opportunistic Infections (CROI) found that HDV seroprevalence using antibody tests for HDV, among persons with HBsAg in the United States was 1.6%.[12] Even in selected and high-risk US populations, such as

TABLE 1 Studies on the prevalence of HDV in the United States, including generalizability of results and limitations

Literature	Prevalence estimate	Population	Generalizability of results/limitations of study
Patel et al[14] Chen et al[9]	42%	HBsAg-positive adults	Assays were not standardized and were characterized by a high rate of false positives Small sample size
Fong et al[25]	41.2%	HBV-infected people	High-risk population of Mongolian-Americans in Southern California
Da et al[24]	Anti-HDV, 19.2% Viremic HDV, 15.5%	Adults with positive HBsAg	Referral bias
Wong et al[22]	Below 5%	Persons with chronic HBV	Generalizable across the US population
All-Payer Claims Database (Gish et al[21])	4.6%	Patients with HBV infection	Generalizable across the US population
Ferrante et al[23]	4.0%	People with HIV and chronic HBV	Generalizable across the US population
Polaris Observatory Collaborators[11]	3%	HBsAg-positive patients	Generalizable across the US population
Quest Diagnostics (Marlowe et al)[12]	1.6%	Persons with HBsAg	Generalizable across the US population

people with HIV and chronic HBV infection engaged in HIV care, HDV seroprevalence was recently reported to be 4.0%.[23] New data from the All-Payer Claims Database also found a low prevalence (4.6%) of HDV infections among patients with HBV infection.[21] Thus, HDV seroprevalence in the United States is likely much lower than reported in the paper by Patel et al.

In a study published in 2021, Da et al[24] retrospectively evaluated 652 adults with positive HBsAg seen at the National Institutes of Health (NIH) Clinical Center from January 2019 through April 2020. Of 588 individuals with positive HBsAg tested for HDV, anti-HDV prevalence was 19.2% and viremic HDV prevalence was 15.5%. However, the investigators themselves acknowledged in their limitations section that "… the true prevalence of HDV in the US *should not be interpreted from this study* and still requires further investigation." Thus, this paper should not be part of a general population HDV prevalence estimate.

The only other recent study that has recorded a high anti-HDV seroprevalence rate (41.2%), specifically among the high-risk population of Mongolian-Americans in Southern California, does not represent the general risk or prevalence in the United States of HBV-infected people.[25]

Recently, the Polaris Observatory, an initiative of the non-profit Center for Disease Analysis (CDA) Foundation,[26] published the adjusted estimate of the prevalence of HDV in 25 countries.[11] According to the Polaris Observatory expert panel, the overall anti-HDV prevalence in the United States is 3% of all people testing positive for HBsAg. Based on the most recent data from the Polaris Observatory in 2022, which reports 1.65 million patients who are HBsAg-positive in the United States, this prevalence translates to an estimated 49,500 individuals with HDV in 2023.[11]

CONCLUSIONS

HDV infection leads to significant morbidity and mortality, and for the first time, there is a robust therapeutic pipeline for this serious disease. People living with HDV need better treatment options, and the drug development pipeline needs to be supported to maximize the chance of seeing FDA-approved treatments in the near future. The majority of recent studies to assess the epidemiology of HDV in the United States confirm that while there are pockets of infection that coincide with geographic and demographic risks, overall, the HDV prevalence rates indicate that there are $<200{,}000$ HDV-infected people in the United States. Standardization and validation of HDV testing are urgently needed. Until then, the more conservative and reproducible lower prevalence estimates should be used. Thus, the authors believe the Office of Orphan Products Development should use the totality of the data from recent studies and a conservative estimate (1%–5% of patients with HBV) for HDV active infection prevalence in the United States.

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