Epidemiologic Burden of Hepatitis D Virus in the United States

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Introduction

Infection with Hepatitis D virus (HDV) is a potential complication of Hepatitis B virus (HBV) infection and a major global health concern. HDV infection can be acquired simultaneously with HBV as a coinfection or as a superinfection with chronic hepatitis B. HDV is estimated to affect approximately 4.5% of people globally who have a chronic infection with hepatitis B (**Figure 1**).[1]

HDV seroprevalence studies of the US population are limited, and reported infection rates vary depending on the study population. To increase HDV detection, universal HDV testing of hepatitis B surface antigen (HBsAg)-positive specimens has been proposed.[2]

The objective of this study was to estimate the epidemiological prevalence of HDV infection within the United States using HBsAg-positive specimen remnants obtained from routine clinician requests received at a national laboratory network.

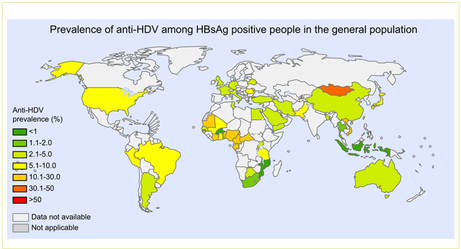


Figure 1. Global prevalence of HDV. Reproduced from Stockdale et al, Journal of Hepatology 2020 73:523-532 DOI: (10.1016/j.jhep.2020.04.008) under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/).

Methods

- Specimen Collection: For Phase 1 of this retrospective study, 2,646 consecutive unique remnant HBsAg positive patient specimens, originally submitted for clinical testing at Quest Diagnostics, and representing each of the ten Health and Human Services (HHS) regions, were included. Regional sampling was relative to the 2022 US Census population size. Specimen remnants that were insufficient for HDV antibody testing were excluded.
- HDV Testing: Study specimens were deidentified and tested using a CLIA laboratory-developed HDV Total Antibody, immunoassay. Antibody(+) specimens were reflexed to a CLIA laboratory-developed HDV RNA, Quantitative Real-Time PCR assay.
- Data Analysis: Positivity rates for HDV antibody and HDV RNA were determined and further evaluated according to select demographics and HHS regions.

Results

- A total of 2,646 specimens were included in Phase I of the study, drawn from ten HHS geographic regions (**Figure 2, Table 2**). The overall cohort was 54.5% male with a mean age of 49.7 years (48.9 years female, 50.4 years male) (**Table 1**). There were no significant differences in the proportions of male and female study patients between the HHS regions (**Figure 3**) and patient ages were similar for all regions (**Figure 4**).
- Overall, 43 specimens were positive for HDV antibodies resulting in a seroprevalence of 1.6% (95% CI: 1.1%-2.1%). Seroprevalence rates were not significantly different (*P*>.05) between sex or mean age (**Table 1**).

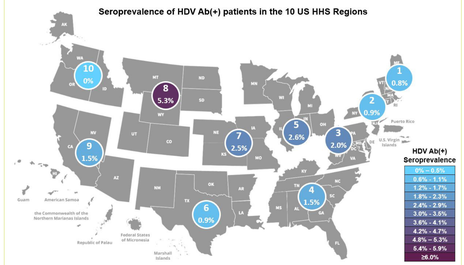


Figure 2. HDV Ab seroprevalence rates by HHS region. HBsAg-positive specimen remnant sampling from each region was relative to the 2022 US Census population size. Ab, antibody; HDV, hepatitis D virus; HHS, US Department of Health and Human Services.

Table 1. Patient Sex and Age According to HDV Serostatus[a,b]

	HDV Ab Serostatus	
	NEGATIVE	POSITIVE
Female % (N)	98.6 (1,179)	1.4 (17)
Male % (N)	98.2 (1,401)	1.8 (26)
Age Mean (sd)	49.7 (14.4)	48.8 (15.9)

[a] The percent of males and females in the 43 HDV Ab(+) was not significantly different (*P*>.05).
[b] The mean ages of HDV Ab(-) and Ab(+) patients were not significantly different (*P*>.05).

Results (continued)

Table 2. HDV Seropositivity by HHS Region[a]

HHS region	Specimens, N		HDV Ab positivity (95% CI)
	Total	HDV Ab–positive	
1	121	1	0.008 (0.00-0.024)
2	235	2	0.009 (0.00-0.020)
3	249	5	0.020 (0.003-0.038)
4	548	8	0.015 (0.005-0.025)
5	423	11	0.026 (0.011-041)
6	348	3	0.009 (0.00-0.002)
7	118	3	0.025 (0.00-0.054)
8	76	4	0.053 (0.002-0.10)
9	408	6	0.015 (0.003-0.026)
10	120	0	0
Total	**2,646**	**43**	**0.016 (0.011-0.021)**

Ab, antibody; CI, confidence interval; HDV, hepatitis D virus; HHS, US Department of Health and Human Services.
[a] Positivity rates are shown as proportions. HHS regions are shown in Figure 2.

- The highest number (n=11) of HDV Ab-positive specimens were identified in HHS region 5, which includes Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin (**Figure 2**). The highest proportions of HDV Ab(+) specimens were found in regions 8 (5.3%), 5 (2.6%) 7 (2.5%) and 3 (2.0%) (**Table 2, Figure 2**).

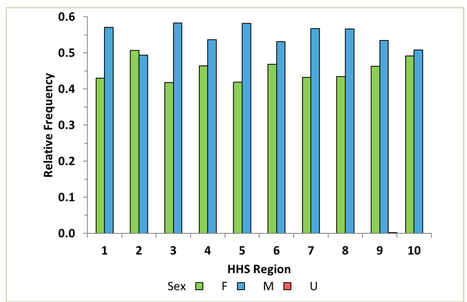


Figure 3. Relative frequency of male and female patients included in the study by HHS region. The proportions were not significantly different (*P*>.05) between regions. F, female; HHS, US Department of Health and Human Services; M, male; U, unknown.

Results (continued)

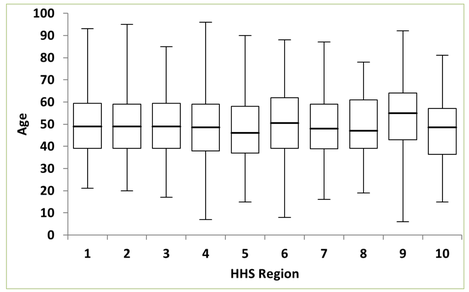


Figure 4. Age distribution of patients by HHS region. Ages were not significantly different (*P*>.05) between regions. HHS, US Department of Health and Human Services.

- HDV RNA testing was performed for 38/43 seropositive specimens. Five specimen remnants were insufficient for RNA testing. Of those tested, 39% (15/38) yielded a positive result (**Table 3**). Three RNA-positive specimens had detectable RNA levels below the limit of quantitation for the test. For the remaining RNA-positives (**Table 3**) the median viral load was 3.9 Logs and ranged from 198 IU/mL (1.97 Logs) to 7,480,000 IU/mL (6.87 Logs).

Table 3. HDV RNA Viral Loads for HDV Ab(+) Patients[a,b]

HDV RNA viral load	N (%)
Not detected	23 (61)
Detected[c]	15 (39)
<1.60 log IU/mL	3 (8)
<3 log IU/mL	3 (8)
3-4 log IU/mL	4 (11)
4-5 log IU/mL	3 (8)
5-6 log IU/mL	0 (0)
>6 log IU/mL	2 (5)
Total	**38 (100)**

[a] An HDV RNA quantitative test with an analytical measurement range of 1.6 to 7.0 Log IU/mL was used.
[b] Quantitative HDV RNA testing was performed on 38 of 43 HDV Ab(+) specimens.
[c] 40% (6/15) were in HHS region 5, 20% (3/15) were in region 8 and 13% (2/15) were in region 3.

Conclusions

- This is the first nationwide HDV seroprevalence study examining remnant HBsAg-positive samples collected from various regions across the United States. By testing all HBsAg (+) samples gathered from all regions across the US, the results offer an initial overview of the geographic prevalence of HDV.
- The overall HDV seroprevalence in this study was 1.6%, which is lower than reported in previous studies. Higher prevalences were noted in HHS regions 8 (5.3%), 5 (2.6%) 7 (2.5%) and 3 (2.0%), which is consistent with previous studies.[3,4]
- In the current study it was observed that 39.4% of HDV Ab(+) specimens were also positive for HDV RNA, supporting the use of confirmatory RNA testing to identify active infection.
- The current study was not influenced by clinician selection bias in ordering HDV antibody testing for patients with clinical suspicion of HDV, which may account for the lower proportions of HDV positive patients compared to prior studies that utilized insurance data or focused on specialized clinics for specimen testing selection.
- A limitation of this study is the relatively small number of HDV(+) specimens, however specimen collection is continuing in a second phase. Further HDV seroprevalence studies are needed to determine which specific US regions would obtain the greatest benefit from future potential HDV-related interventions.
- HDV infection is the most severe form of viral hepatitis. Given the serious nature of the disease and its relatively low prevalence as confirmed in this study, universal testing of HbsAg(+) specimens followed by HDV RNA testing would benefit patients with previously unrecognized HDV infection.[2]

References

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