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## Prevalence and Determinants of Hepatitis Delta Virus Infection Among HIV/Hepatitis B-Coinfected Adults in Care in the United States

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### Author Contributions

N Ferrante and V Lo Re contributed to the conceptualization of the study. N Ferrante, D Bhattacharya, HN Kim, J Martin, and V Lo Re contributed to the study design. M Kallan performed the statistical analyses. N Ferrante and M Kallan prepared the figures and tables. S Sukkestad, M Kodani, T Hayden, and S Kamili performed the laboratory testing of serum/plasma samples and assisted with data acquisition. N Ferrante, D Bhattacharya, J Martin, HN Kim, V Lo Re, S Sukkestad, M Kodani, T Hayden, and S Kamili interpreted the study results. N Ferrante drafted the manuscript. All authors participated in manuscript review and approved of the final manuscript.

**Conflicts of Interest:** Nothing to report

### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.

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## Abstract

Hepatitis delta virus (HDV) infection increases the risk of liver complications compared to hepatitis B virus (HBV) alone, particularly among persons with human immunodeficiency virus (HIV). However, no studies have evaluated the prevalence or determinants of HDV infection among people with HIV/HBV in the US. We performed a cross-sectional study among adults with HIV/HBV coinfection receiving care at eight sites within the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) between 1996–2019. Among patients with available serum/plasma specimens, we selected the first specimen on or after their initial HBV qualifying test. All samples were tested for HDV IgG antibody and HDV RNA. Multivariable log-binomial generalized linear models were used to estimate prevalence ratios (PRs) with 95% CIs of HDV IgG antibody-positivity associated with determinants of interest (age, injection drug use [IDU], high-risk sexual behavior). Among 597 adults with HIV/HBV coinfection in CNICS and available serum/plasma samples (median age, 43 years; 89.9% male; 52.8% Black; 42.4% White), 24/597 (4.0%; 95% CI, 2.4–5.6%) were HDV IgG antibody-positive, and 10/596 (1.7%; 95% CI, 0.6–2.7%) had detectable HDV RNA. In multivariable analysis, IDU was associated with exposure to HDV infection (adjusted PR=2.50; 95% CI, 1.09–5.74). Among a sample of adults with HIV/HBV coinfection in care in the US, 4.0% were HDV IgG antibody-positive, among whom 41.7% had detectable HDV RNA. History of IDU was associated with exposure to HDV infection. These findings emphasize the importance of HDV testing among persons with HIV/HBV coinfection, especially those with a history of IDU.

## Keywords

Hepatitis delta virus; Hepatitis B virus; HIV HBV and HDV coinfection; Epidemiology; Prevalence

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Coinfection with hepatitis B virus (HBV) and hepatitis delta virus (HDV) is associated with more severe hepatitis and higher rates of hepatic decompensation, hepatocellular carcinoma, and death compared to infection with chronic HBV alone.<sup>1–6</sup> HDV infection has been reported to occur in 5–10% of patients with chronic HBV, affecting 12–25 million people worldwide, but accurate estimates of HDV prevalence have been limited by the availability of standardized assays and lack of universal screening.<sup>1,7–9</sup> The prevalence of HDV infection varies geographically, with high prevalence estimates being reported in Central and Western Africa, Southeast Asia, Eastern Europe, the Middle East, and the Amazon Basin.<sup>9,10</sup> HDV prevalence may be increasing in certain parts of the world, which has been primarily attributed to the immigration of people from areas of high to low HDV endemicity.<sup>8,11–13</sup> Although HDV testing is recommended among high-risk subgroups of chronic HBV-infected patients, including those with human immunodeficiency virus (HIV)

coinfection,<sup>14</sup> screening for HDV infection occurs infrequently in clinical practice among persons with chronic HBV infection, especially in the United States (US).<sup>15,16</sup>

HIV/HBV coinfection is common due to shared routes of transmission, particularly parenteral and sexual transmission.<sup>17</sup> Coinfection with HBV occurs in 6–14% of people with HIV (PWH) in North America and Europe and 10–20% in Asia and Africa.<sup>6,18–21</sup> The prevalence of HDV antibody-positivity among PWH with HBV coinfection has been reported to be 15% in European cohorts, and as high as 25% in a cohort from Guinea-Bissau Africa.<sup>2,22–24</sup> People with HIV/HBV/HDV in these settings were more likely to have used injection drugs, have hepatitis C virus (HCV) coinfection, and develop cirrhosis or hepatic decompensation compared to those with HIV/HBV coinfection.<sup>2,5,22,24,25</sup>

Despite the adverse clinical impact of HDV infection in the setting of HIV/HBV coinfection, there is a paucity of data on the prevalence and determinants of HDV among PWH with HBV coinfection in the US. If the prevalence of HDV infection is high among people with HIV/HBV coinfection, or certain subgroups, routine testing for HDV infection would be further supported to identify chronically HDV-infected persons and prompt early initiation of HDV therapy, especially considering novel HDV therapies on the horizon.<sup>26–28</sup> Moreover, knowledge of the factors associated with HDV infection could identify subgroups of PWH with HBV coinfection who might be at increased risk of developing HDV infection and warrant close monitoring for liver complications.

To address these knowledge gaps, we identified a subset of PWH with HBV coinfection from across the US in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) who had stored serum or plasma available to permit testing for HDV IgG antibody and HDV RNA. We determined the prevalence of HDV infection in this sample and evaluated the determinants of HDV antibody-positivity.

## Material and Methods

### Study Design and Data Source

We conducted a cross-sectional study using clinical data and banked serum/plasma specimens from PWH with HBV coinfection who were in care in CNICS between January 1, 1996 and December 31, 2019. CNICS is a dynamic cohort of PWH across eight CFARs, including the University of Alabama (UAB), University of Washington (UW), University of California San Diego (UCSD), University of California San Francisco (UCSF), Case Western Reserve University (CWRU), Johns Hopkins University (JHU), Fenway Health/Harvard (Harvard), and the University of North Carolina (UNC).<sup>29</sup> CNICS collects data on demographics, medical diagnoses, laboratory results, and antiretroviral therapy (ART) use. A subset of CNICS participants contributed plasma/serum samples across one or more dates to a specimen repository located at each site. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee and was deemed exempt by the University of Pennsylvania Institutional Review Board.

## Study Patients

PWH in CNICS were eligible for inclusion if they had: 1) 18 years of age, 2) active HBV infection (defined by positive HBV surface antigen, positive HBV e antigen [HBeAg], or detectable HBV DNA), 3) a 0.5 mL serum or plasma specimen available for testing on or after their qualifying HBV test, and 4) absence of a positive hepatitis B surface antibody (anti-HBs) after their qualifying HBV test.<sup>30</sup> To minimize the likelihood of including individuals with acute HBV infection, we excluded patients who had an alanine aminotransferase level (ALT) or aspartate aminotransferase (AST) >1,000 U/L on or within 180 days after their qualifying HBV test. If a participant had more than one serum/plasma sample available, the first sample collected on or after the qualifying HBV test was selected for analysis of HDV antibody and HDV RNA.

## Study Measurements

**Laboratory Data**—The primary outcome was a positive anti-HDV IgG test. Serum/plasma samples were tested for anti-HDV IgG via the Luminex Magpix bead-based assay (97% sensitivity and 97% specificity versus ETI-AB-DELTA-2 enzyme immunoassay [Diasorin, Italy]) by the Division of Viral Hepatitis Laboratory at the US Centers for Disease Control and Prevention. Samples with detectable HDV RNA but negative anti-HDV IgG by MagPix were confirmed with automated Western blot (Protein Simple; 97% sensitivity 97% specificity). Both assays use the hepatitis delta antigen as a capture molecule. A sample was considered to be positive for anti-HDV IgG via automated Western blot if it had a band of 57–59 kDa.

For detection of HDV RNA, all serum/plasma samples were tested for HDV RNA. Total nucleic acid (TNA) was extracted from 200 µL of each sample, which was performed using the MagNA Pure 96 automated platform with the DNA and Viral NA Small Volume Kit according to the manufacturer's instructions (Roche, Indianapolis, IN). Extracted nucleic acid was eluted in a final volume of 50 µL. All serum/plasma TNA extracts were tested for HDV RNA with quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) using the protocol by Kodani et al. (2013) with minor modifications.<sup>31</sup> This assay was performed on the LightCycler 480 II (Roche, Indianapolis, IN) using the SuperScript III Platinum One-Step qRT-PCR Kit (Thermo Fisher Scientific, Waltham, MA) and targeted a sequence slightly upstream of the large delta antigen.

All samples with detectable HDV RNA were genotyped for HDV by bidirectional sequencing using the BigDye Terminator v3.1 Sequencing Kit (Thermo Fisher Scientific). Partial delta antigen amplicons were generated using a semi-nested amplification protocol with primers and thermal cycling conditions adapted from Le Gal et al. (2006).<sup>32</sup> In addition, anti-HDV IgG antibody and/or HDV RNA positive samples with sufficient HBV DNA were genotyped for HBV by bidirectional sequencing using the BigDye Terminator v3.1 Sequencing Kit (Thermo Fisher Scientific) in the S gene region on the ABI Genetic Analyzer (SeqStudio and 3500 xL, Thermo Fisher Scientific).<sup>33</sup> All consensus sequences were assembled and trimmed in SeqMan Pro 17 (DNASTAR, Inc., Madison, WI). Genotypes were determined by multiple alignment using fast Fourier transform (MAFFT) algorithms in MegAlign 17 using 46 reference sequences representing all eight HDV

genotypes for HDV genotyping and 23 reference sequences representing HBV genotypes A-H for HBV genotyping.<sup>34</sup> A maximum likelihood phylogeny with 1,000 bootstrap iterations was generated in MEGA 11 using the general time reversible model with a gamma distribution and invariant sites for HDV and the Kimura 2-parameter model with gamma distribution for HBV.<sup>35</sup>

Laboratory data obtained within 365 days before and 30 days after the date of serum/plasma collection date included HCV-related tests (i.e., HCV antibody, RNA, genotype), HIV RNA, absolute CD4+ cell count, serum ALT, serum AST, and platelet count. If multiple laboratory results were available during this period, the result closest to the specimen collection date was used. HCV infection was defined by: 1) positive HCV antibody, or 2) detectable HCV RNA or genotype. We also determined ever positive HBeAg status on or prior to the specimen collection date. The degree of liver fibrosis was estimated by calculating the Fibrosis-4 Index for Liver Fibrosis (FIB-4) score using AST, ALT, platelet count, and age as follows:  $(\text{age [years]} \times \text{AST [U/L]}) / (\text{platelet count [10}^9\text{/L]} \times (\text{ALT [U/L]}^{1/2}))$ .<sup>36,37</sup> FIB-4 >3.25 indicates advanced hepatic fibrosis/cirrhosis (METAVIR stages F3-F4).

**Sociodemographic Data**—We collected birth year, sex at birth, race, and ethnicity. Age was estimated by the date of serum/plasma sample collection minus July 1<sup>st</sup> of the birth year, since exact birthdates were unable to be collected due to data restrictions.

**Clinical Data**—Clinical data obtained from dates on or prior to the serum/plasma collection date included history of diabetes mellitus, hazardous alcohol use, injection drug use (IDU), and man who has sex with men (MSM) status. Diabetes was defined by: 1) hemoglobin A1c  $\geq 6.5\%$ , 2) prescription of anti-diabetic medication, 3) International Classification of Diseases, Ninth or Tenth Revision [ICD-9/–10] diagnosis of diabetes plus prescription of diabetes-related medication, or 4) diabetes diagnosis plus at least two random glucose results  $\geq 200$  mg/dL.<sup>38</sup> Hazardous alcohol use was defined by the presence of at least one ICD-9/–10 diagnosis for alcohol abuse/dependence. IDU and MSM status were determined from self-reported risk factors for HIV transmission at the time of CNICS enrollment.

We also collected use of ART (defined as use of three antiretrovirals from at least two drug classes), HBV-active antiretroviral medications (i.e., lamivudine, emtricitabine, tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF]), and entecavir at the time of specimen collection.<sup>39</sup>

### Statistical Analysis

We determined the prevalence and 95% confidence interval (CI; exact interval) of HDV IgG antibody-positivity within the study sample, overall and by CNICS site. We also measured the prevalence and 95% CI of HDV viremia within the study sample. We described the characteristics of patients by anti-HDV IgG status using Chi-square tests for categorical data and Wilcoxon rank-sum tests for continuous data.

Multivariable log binomial generalized linear models were used to estimate prevalence ratios (PRs) with 95% CIs of HDV IgG antibody-positivity associated with determinants

of interest. We used the literature and expert consultation to identify relevant determinants of HDV IgG antibody-positivity to create a directed acyclic graph (DAG; Figure 1).<sup>40</sup> We utilized a DAG-informed approach, and results from our unadjusted analyses, to determine the covariates for inclusion in the final multivariable model. We ensured that there were at least 8 outcomes of positive anti-HDV IgG for each covariate included in the final multivariable model to avoid overfitting. Data were analyzed using SAS, version 9.4 (Cary, North Carolina).

## Results

### Characteristics of Study Population

Among 2,265 PWH with active HBV infection in CNICS between January 1, 1996 and December 31, 2019, 602 (26.6%) met our inclusion criteria; 597 persons with serum/plasma samples were submitted for analysis (UCSD: 114; UAB: 88; UCSF: 19; CWRU: 58; UW: 60; Fenway: 20; UNC: 162; JHU: 76). Five samples were requested but not received. Of the samples received, 54.9% were collected between November 1996 and December 2009 and 45.1% between January 2010 and August 2019. There were 1,648 PWH with HBV coinfection in CNICS who did not have an available sample. Compared to those with available samples, those without a sample demonstrated a lower prevalence of hazardous alcohol use (20.6% versus 27.5%) and use of at least one antiretroviral (34.0% versus 74.7%) and a higher prevalence of HCV infection (10.9% versus 7.2%) and IDU (20.6% versus 16.9%; Supplementary Table 1). Otherwise, characteristics of persons with and without a serum/plasma sample were generally similar.

Among the 597 who underwent HDV antibody and RNA testing, the median age was 43 (IQR: 37–49) years, 89.9% were male, 52.8% were Black, 42.4% were White, and 6.4% were Hispanic (Table 1). Diabetes (19.9%), hazardous alcohol use (27.5%), and HCV infection (17.9%) were common among those in the sample; 44.6% had detectable HIV RNA and 27.3% had a CD4+ cell count  $\geq 200$  cells/mm<sup>3</sup>. A total of 254 (42.7%) had HBeAg tested on or before specimen collection, of whom 159 (62.6%) were HBeAg-positive.

A total of 424 (71.0%) patients were on ART at the time that their serum/plasma sample was collected. Of these, 109 (18.3%) received an HBV-active antiretroviral agent (66 [60.6%] with lamivudine or emtricitabine alone; 26 [23.9%] with TDF or TAF plus either emtricitabine or lamivudine; 17 [15.6%] with TDF or TAF alone [Table 1]). Fourteen (2.3%) patients received entecavir.

### Prevalence of HDV Coinfection

Among the 597 PWH with HBV coinfection who were tested for anti-HDV IgG, 24 (4.0%; 95% CI, 2.4–5.6%) were HDV IgG antibody-positive. The prevalence of HDV antibody-positivity ranged between 0–8.8% by CNICS site (Supplementary Table 2).

Among the 596 samples tested for HDV RNA (one sample had insufficient volume for RNA testing), 10 (1.7%; 95% CI, 0.6–2.7%) had detectable HDV RNA, representing 41.7% (10/24) of those who were HDV IgG antibody-positive. One person with detectable HDV RNA was HDV IgG antibody-negative on the MagPix assay but HDV IgG antibody-positive

when retested on the automated Western Blot anti-HDV assay. Otherwise, none of the other HDV IgG antibody-negative persons had detectable HDV RNA. The median HDV RNA level was 476,000 (IQR, 69,900–1,560,000) IU/mL, and all ten (100%) HDV viremic persons were infected with HDV genotype 1. Six of the ten HDV viremic patients were able to be sequenced for HBV, of whom four (66.7%) were HBV genotype D, and two (33.3%) were HBV genotype H. Five of the fourteen HDV IgG antibody-positive/HDV RNA-negative individuals were able to be sequenced for HBV, of whom three (60%) were HBV genotype A and two (40%) were HBV genotype G.

### Determinants of HDV Coinfection

The prevalence of HDV IgG antibody-positivity among those with and without a history of IDU was 8.9% and 3.0%, respectively, and 6.3% and 3.3% among those with and without a history of HCV infection, respectively (Table 2). In unadjusted analyses, HDV IgG antibody-positivity was associated with history of hazardous alcohol use (PR=2.23; 95% CI, 1.02–4.89) and IDU (PR=2.95; 95% CI, 1.33–6.55; Table 2). In multivariable analysis adjusting for hazardous alcohol use, a history of IDU remained associated with HDV IgG antibody-positivity (adjusted PR=2.50; 95% CI, 1.09–5.74; Table 2).

### Discussion

In this cross-sectional study, we found that 24 of 597 (4.0%) adults with HIV/HBV coinfection in the CNICS cohort were HDV IgG antibody-positive, and 10 of 597 (1.7%) had detectable HDV RNA. Among those who were HDV IgG antibody-positive, 10 of 24 (41.7%) had detectable HDV RNA. Lastly, we found that a history of IDU was associated with an increased prevalence of HDV antibody-positivity.

The prevalence of HDV infection among PWH with HBV coinfection in this US sample was lower than estimates reported from European cohorts of persons with HIV/HBV coinfection. In 2011, the EuroSIDA study group reported a 14.5% prevalence of HDV infection among a sample of 422 PWH with HBV coinfection tested for HDV antibody, of whom 87% had detectable HDV RNA.<sup>22</sup> In 2016, the Swiss HIV Cohort Study reported a 15.4% prevalence of HDV infection among a sample of 771 PWH with HBV coinfection, of whom 62% had HDV RNA.<sup>2</sup> More recently, the ICONA study group reported a 19% prevalence of HDV infection among 617 PWH with HBV coinfection in Italy.<sup>41</sup> The lower prevalence of HDV infection in our cohort may have been due to inclusion of fewer persons from countries of high HDV endemicity within CNICS, a lower prevalence of HDV-associated behaviors (e.g., IDU), and/or selection bias as a result of the inability to test a proportion of HBV-infected patients due to lack of sample availability. Among our sample of PWH with HBV coinfection who underwent HDV testing, 16.9% had a history of IDU in our sample as compared to 24.6% in the EuroSIDA cohort and 16.5% in the Swiss HIV Cohort Study.

HDV RNA was detected in 10 of 597 (1.7%) HIV/HBV-coinfected adults, which represented 41.7% of HDV IgG antibody-positive patients. All ten individuals with detectable HDV RNA in our study were infected with HDV genotype 1. HDV genotype 1 is the most common HDV genotype overall and in North America and Europe.<sup>9,42</sup> Genotypes 2 and 4 are predominantly seen in Asia, genotype 3 in South America, and genotypes 5–8 in



Africa.<sup>1</sup> Severe forms of HDV infection have been reported with genotype 3 in the Amazon Basin.<sup>43–45</sup>

We found that IDU was strongly associated with exposure to HDV. In EuroSIDA and the Swiss HIV Cohort Study, PWH with HBV coinfection were more likely to have used injection drugs and have HCV coinfection, with up to 60% of HDV antibody-positive individuals in the Swiss HIV Cohort Study reporting a history of IDU.<sup>2,22</sup> In our study, 37.5% of HDV-infected patients reported a history of IDU compared to 16% without HDV infection. To explore the association between HCV infection and HDV antibody-positivity, we used two different definitions of HCV exposure based on either anti-HCV antibody-positivity or detectable HCV RNA/genotype. In univariable and multivariable analyses adjusting for IDU history, HCV infection was not associated with anti-HDV positivity. Our study might have been underpowered to detect an independent association between HCV infection and HDV antibody-positivity. It is also possible that HCV infection and IDU are collinear, such that HCV infection serves as a proxy for IDU. Although we did not find a significant association between HCV infection and anti-HDV positivity, our findings bolster existing evidence of IDU as a risk factor for contraction of HDV.

In the context of HIV/HBV, HDV coinfection has been associated with worse clinical outcomes including high rates of liver-related death, liver decompensation, and hepatocellular carcinoma.<sup>1–6</sup> While routine HDV testing is not currently recommended for all persons with chronic HBV infection in the US, the American Association for the Study of Liver Diseases recommends risk-based HDV screening, which includes PWH, people who inject drugs, and persons from countries of high HDV endemicity.<sup>14</sup> In the US, screening for HDV infection occurs infrequently in clinical practice among persons with chronic HBV infection.<sup>15,16</sup> Benefits to earlier HDV screening and detection include earlier initiation of HDV therapy and closer monitoring for liver-related complications, which may improve clinical outcomes. With the advent of novel HDV therapies on the horizon, our findings emphasize the importance of HDV serological screening and reflex RNA testing among PWH and HBV coinfection, especially those with a history of IDU.<sup>26–28</sup>

Our study has several potential limitations. First, selection bias is possible since only patients who had an available serum/plasma sample on or after their initial HBV test were included. When compared to those with an available sample, those without a sample were more likely to have HCV infection and a history of IDU, and less likely to be on ART and have HIV RNA suppression, suggesting poorer health care engagement. This potential sample selection bias may have resulted in a lower estimated prevalence of HDV infection. Second, there is the potential for misclassification of some variables due to recall bias, since IDU and hazardous alcohol use were self-reported and potentially underreported. Third, the cross-sectional nature of our study does not allow us to determine whether potential determinants preceded HDV infection; thus, causality cannot be inferred. We were also unable to estimate the association between HDV coinfection and clinical outcomes. Fourth, it is possible that our study was underpowered to detect associations between hypothesized determinants and HDV antibody-positivity given the paucity of outcomes. Fifth, we were unable to assess the association between HDV infection and country of origin, since this information is not collected by CNICS. Sixth, we were unable to determine

the proportion who underwent HDV testing in clinical practice, since reporting of HDV testing to CNICS is incomplete. Lastly, our sample consisted of PWH with active HBV infection who are engaged in clinical care across eight clinical sites in CNICS. Therefore, our study findings may not be representative of all PWH with HBV coinfection or those with occult HBV (defined as detectable HBV DNA in the absence of positive HBsAg); however, the prevalence of occult HBV is low in the US.<sup>46</sup>

## Conclusions

In conclusion, we found that the prevalence of HDV infection among a sample of PWH with HBV coinfection in care in CNICS was low. History of IDU was the strongest determinant of HDV antibody-positivity. Our findings emphasize the importance of HDV testing among PWH with HBV coinfection, especially those with a history of IDU, since earlier detection would allow for earlier treatment initiation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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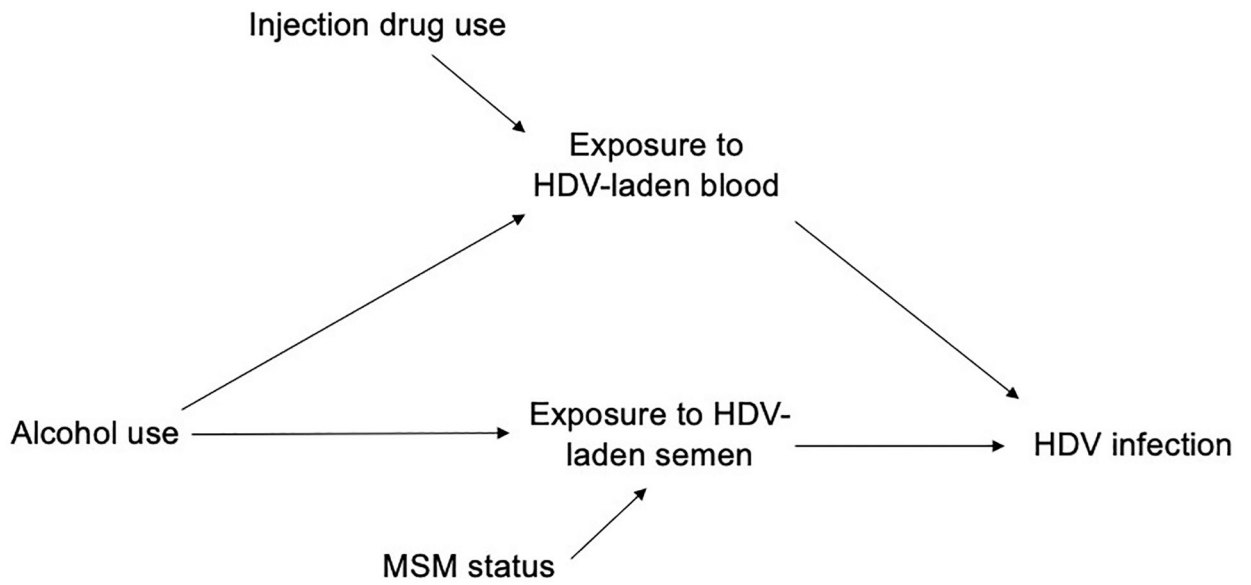
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**Figure 1.** Directed acyclic graph demonstrating hypothesized determinants of hepatitis delta virus seropositivity. Abbreviations: HDV=Hepatitis delta virus; MSM=man who has sex with men.

**Table 1.** Characteristics of persons included in the study sample, overall and by hepatitis D virus IgG antibody status.

	<b>HDV-Ab Positive (n=24)</b>	<b>HDV-Ab Negative (n=573)</b>	<b>Total (n=597)</b>
<b>Age (n, %)</b>			
Median (years, IQR)	45.5 (37.5–51.5)	43 (37–49)	43 (37–49)
<40 years	8 (33.3)	203 (35.4)	211 (35.3)
40–49 years	8 (33.3)	239 (41.7)	247 (41.4)
50 years	8 (33.3)	131 (22.9)	139 (23.3)
<b>Male sex (n, %)</b>	23 (95.8)	514 (89.7)	537 (89.9)
<b>Race (n, %)</b>			
White	14 (58.3)	239 (41.7)	253 (42.4)
Black or African American	9 (37.5)	306 (53.4)	315 (52.8)
Asian/Pacific Islander	0 (0.0)	11 (1.9)	11 (1.8)
Other or unknown	1 (4.2)	17 (3.0)	18 (3.0)
<b>Hispanic/Latino (n, %)</b>	2 (8.3)	36 (6.3)	38 (6.4)
<b>Hazardous alcohol use<sup>7</sup>(n, %)</b>	11 (45.8)	153 (26.7)	164 (27.5)
<b>HIV transmission risk factors<sup>7</sup>(n, %)</b>			
Men who have sex with men	13 (56.5)	383 (74.5)	396 (73.7)
History of injection drug use	9 (37.5)	92 (16.1)	101 (16.9)
Heterosexual contact	4 (16.7)	198 (34.6)	202 (33.8)
<b>Diabetes mellitus<sup>8</sup>(n, %)</b>	5 (20.8)	114 (19.9)	119 (19.9)
<b>Hepatitis C virus infection status<sup>8</sup>(n, %)</b>			
None	16 (66.7)	474 (82.7)	490 (82.1)
+ HCV Antibody, - HCV RNA and – HCV genotype	4 (16.7)	39 (6.8)	43 (7.2)
+ HCV RNA or + HCV genotype	4 (16.7)	60 (10.5)	64 (10.7)
<b>Quantitative HBV DNA (n, %)</b>			
Median HBV DNA (log <sub>10</sub> IU/mL, IQR)	35 (20–1605)	160 (20–13359)	160 (20–12300)
200 IU/mL	8 (33.3)	155 (27.1)	163 (27.3)
201–2,000 IU/mL	1 (4.2)	34 (5.9)	35 (5.9)
>2,000 IU/mL	3 (12.5)	89 (15.5)	92 (15.4)
No result within –365/+30 days of index date	12 (50.0)	295 (51.5)	307 (51.4)

	HDV-Ab Positive (n=24)	HDV-Ab Negative (n=573)	Total (n=597)
<b>Ever HBeAg positive<sup>†</sup>(n, %)</b>			
Yes	7 (29.2)	152 (26.5)	159 (26.6)
No	8 (33.3)	88 (15.4)	96 (16.1)
No result prior to index date	9 (37.5)	333 (58.1)	342 (57.3)
<b>ALT level (median, IQR)</b>			
No result within -365/+30 days of index date	37 (26-79)	38 (24-61.5)	38 (24-62.5)
No result within -365/+30 days of index date	0 (0.0)	13 (2.3)	13 (2.2)
<b>HIV RNA<sup>‡</sup>(n, %)</b>			
Median (cells/mm <sup>3</sup> , IQR)	163.5 (48-74700)	367 (48-25868)	269 (48-28167)
500 copies/mL	14 (58.3)	297 (51.8)	311 (52.1)
>500 copies/mL	10 (41.7)	256 (44.7)	266 (44.6)
No result within -365/+30 days of index date	0 (0.0)	20 (3.5)	20 (3.4)
<b>CD4+ cell count<sup>§</sup>(n, %)</b>			
Median (cells/mm <sup>3</sup> , IQR)	278.5 (109-396)	310 (140-525)	309 (137-524)
500 cells/mm <sup>3</sup>	4 (16.7)	157 (27.4)	161 (27.0)
200-499 cells/mm <sup>3</sup>	12 (50.0)	201 (35.1)	213 (35.7)
<200 cells/mm <sup>3</sup>	8 (33.3)	187 (32.6)	195 (32.7)
No result within -365/+30 days of index date	0 (0.0)	28 (4.9)	28 (4.7)
<b>Platelet count<sup>¶</sup>(n, %)</b>			
<150,000/ $\mu$ L	8 (33.3)	142 (24.8)	150 (25.1)
150,000/ $\mu$ L	16 (66.7)	418 (72.9)	434 (72.7)
No result within -365/+30 days of index date	0 (0.0)	13 (2.3)	13 (2.2)
<b>On ART<sup>‡</sup>(n, %)</b>			
17 (70.8)	407 (71.0)	424 (71.0)	
<b>Receiving HBV-active antiretroviral<sup>‡</sup>(n, %)</b>			
4 (16.7)	105 (18.3)	109 (18.3)	
<b>Specific HBV-active antiretroviral(s)<sup>‡</sup>(n, %)</b>			
Lamivudine or Emtricitabine alone	3 (75.0)	63 (60.0)	66 (60.6)
Tenofovir alone	0 (0.0)	17 (16.2)	17 (15.6)
Tenofovir + (Lamivudine or Emtricitabine)	1 (25.0)	25 (23.8)	26 (23.9)
<b>On entecavir<sup>‡</sup>(n, %)</b>			
1 (4.2)	13 (2.3)	14 (2.3)	
<b>FIB-4 score<sup>°</sup></b>			



	HDV-Ab Positive (n=24)	HDV-Ab Negative (n=573)	Total (n=597)
<1.45 (no cirrhosis)	10 (41.7)	310 (54.1)	320 (53.6)
1.45–3.25 (inconclusive)	10 (41.7)	177 (30.9)	187 (31.3)
>3.25 (cirrhosis/advanced fibrosis)	4 (16.7)	68 (11.9)	72 (12.1)
No result within –365/+30 days of index date	0 (0.0)	18 (3.1)	18 (3.0)
<b>Sample collection year (n, %)</b>			
Between 1996–2009	14 (58.3)	314 (54.8)	328 (54.9)
Between 2010–2019	10 (41.7)	259 (45.2)	269 (45.1)

Abbreviations: Anti-HDV=HDV antibody; ART=antiretroviral therapy; FIB-4=fibrosis 4; HBeAg=hepatitis B e antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IQR=interquartile range; U=international units; mL=milliliter; RNA=ribonucleic acid; µL=microliter.

Index date refers to the date of specimen collection.

Age was measured as the date of specimen collection minus July 1<sup>st</sup> of the birth year. Sex and race/ethnicity were collected upon enrollment into CNICS.

<sup>†</sup> Hazardous alcohol use was defined as ever having an inpatient or outpatient diagnosis of alcohol abuse/dependence based on the presence of at least one International Classification of Diseases code for alcohol abuse/dependence.

<sup>‡</sup> History of MSM status, intravenous drug use, and heterosexual contact were defined based on patient self-reporting of ever having engaged in the respective behavior. MSM status was determined from the subset of males. These risk factors are not mutually exclusive.

<sup>§</sup> Diabetes mellitus was defined as ever having at least one of the following: 1) hemoglobin A1c ≥6.5%, 2) use of 1+ diabetes-specific medications, 3) having 1 International Classification of Diseases 9<sup>th</sup> or 10<sup>th</sup> revision [ICD-9/10] code for a diabetes-related diagnosis and taking 1 diabetes-related medications, or 4) having 1 ICD-9/10 code for a diabetes-related diagnosis and at least two random glucose values ≥200 mg/dL.

<sup>§</sup> Hepatitis C virus infection status was defined as ever having either: 1) detectable HCV RNA or HCV genotype or 2) positive HCV antibody and undetectable HCV RNA and genotype

<sup>¶</sup> HBeAg status was determined as ever having a positive HBeAg on or prior to the specimen collection date.

<sup>¶</sup> Laboratory data were collected within 365 days prior and 30 days after the specimen collection date. If multiple laboratory results were available within –365/+30 days of the specimen collection date, the lab value closest to the specimen collection date was used.

<sup>¶</sup> ART was measured as a combination of 3 antiretroviral agents from at least two drug classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen. ART and HBV-active antiretroviral therapy use was determined based on the reported ART regimen documented at the time of specimen collection.

<sup>°</sup> FIB-4 score was by: (age [years] × AST [U/L]) / (platelet count [10<sup>9</sup>/L] × (ALT [U/L])<sup>1/2</sup>) using laboratory values

Relationship between patient characteristics (exposures) and hepatitis delta virus (HDV) IgG antibody-positivity (outcome) among HIV/hepatitis B virus-coinfected patients (n=597).

**Table 2.**

Characteristic	Percent HDV antibody positive (95% CI)	Prevalence difference (95% CI)	Prevalence ratio	
			Unadjusted (95% CI)	Adjusted 95% CI
Age				
Age ≥ 50 years	5.8% (1.9–9.6%)	2.3% (–2.0 to 6.5%)	1.65 (0.72–3.77)	-
Age < 50 years	3.5% (1.8–5.2%)		Reference	-
Age (per 1 year increase)	-		1.02 (0.98–1.06)	-
Hazardous alcohol use <sup>‡</sup>				
History of hazardous alcohol use	6.7% (2.9–10.5%)	3.7% (–0.4 to 7.9%)	2.23 (1.02–4.89)	1.81 (0.80–4.07)
No history of hazardous alcohol use	3.0% (1.4–4.6%)		Reference	Reference
Injection drug use (IDU) <sup>§</sup>				
History of IDU	8.9% (3.4–14.5%)	5.9% (0.1 to 11.6%)	2.95 (1.33–6.55)	2.50 (1.09–5.74)
No history of IDU	3.0% (1.5–4.5%)		Reference	Reference
Man who has sex with men <sup>§</sup>				
MSM	3.3% (1.5–5.0%)	–3.8% (–8.4 to 0.8%)	0.46 (0.21–1.03)	-
Not MSM	7.1% (2.9–11.3%)		Reference	-
HCV infection status				
Detectable HCV RNA or genotype	6.3% (0.3–12.2%)	3.0% (–4.4 to 10.3%)	1.91 (0.66–5.55)	-
Detectable HCV antibody only	9.3% (0.6–18.0%)	6.0% (–4.5 to 16.6%)	2.85 (0.997–8.14)	-
No history of chronic HCV infection	3.3% (1.7–4.8%)		Reference	-

Abbreviations: CI=Confidence interval; HCV=Hepatitis C virus; HDV=Hepatitis delta virus; MSM=Man who has sex with men

<sup>‡</sup> Hazardous alcohol use was defined as ever having an inpatient or outpatient diagnosis of alcohol abuse/dependence based on the presence of at least one International Classification of Diseases code for alcohol abuse/dependence.

<sup>§</sup> History of MSM status and intravenous drug use were defined based on patient self-reporting of ever having engaged in the respective behavior.