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ORIGINAL ARTICLE

The Delta Delta: Gaps in screening and patient assessment for hepatitis D virus infection

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Abstract

Hepatitis D virus (HDV) infection is highly prevalent in patients with chronic hepatitis B (CHB). AASLD guidelines recommend a risk-based screening approach. Our aim was to ascertain if the risk-based approach leads to appropriate HDV screening, identify targets to improve screening rates, and study HDV clinical burden. CHB patients screened for HDV from 01/2016 to 12/2021 were identified. Level of training and specialty of providers ordering HDV screening tests were determined. HDV seropositive (HDV+) patient charts were reviewed for the presence of individual risk factors per the AASLD guidelines to determine if they met screening criteria. The severity of liver disease at the time of HDV screening was compared between the HDV+ group and a matched (based on age, hepatitis B e antigen status, BMI and sex) HDV seronegative (HDV−) group. During the study period, 1444/11,190 CHB patients were screened for HDV. Most screening tests were ordered by gastroenterology (90.2%) specialists and attending physicians (80.5%). HDV+ rate was 88/1444 (6%), and 72 HDV+ patients had complete information for analysis. 18% of HDV+ patients would be missed by a risk-based screening approach due to unreported or negative risk factors (see Table). A significantly higher number of HDV+ patients had developed significant fibrosis ($p = 0.001$) and cirrhosis ($p < 0.01$) by the time of screening than HDV− ($n = 67$) patients. In conclusion, targeted interventions are needed towards trainees and primary care clinics to improve screening rates. Current risk-based criteria do not appropriately screen for HDV. It is time for universal screening of HDV in CHB patients.

KEYWORDS
delta virus, HDV, hepatology, liver, viral hepatitis

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, Alanine transaminase; APASL, Asian Pacific Association for the Study of the Liver; AST, Aspartate aminotransferase; AUROC, Area under receiver operating characteristic curve; BMI, Body mass index; CDC, Centers for Disease Control and Prevention; CHB, chronic hepatitis B; CHD, Chronic hepatitis D; D4FS, delta 4 fibrosis score; DNA, Deoxyribo Nucleic Acid; EASL, European Association for the Study of the Liver; EMR, Electronic medical records; FDA, Food and Drug Administration; FIB-4, Fibrosis 4; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B Virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HDV, Hepatitis D Virus; HEC, Hepatitis D virus Endemic Country; HIPAA, Health Insurance Portability and Accountability Act; IRB, Institutional Review Board; IVDU, intravenous drug use; LT, Liver transplant; MSM, Men who have Sex with Men; NHANES, National Health and Nutrition Examination Survey; RNA, Ribonucleic acid; STI, Sexually Transmitted Infection; US, United States; VA, Veterans Affairs.

1 | INTRODUCTION

Hepatitis D virus (HDV) is a small defective RNA virus that can propagate only in individuals infected with the Hepatitis B Virus (HBV). This infection can either be concurrent coinfection with HBV or superinfection in a patient with chronic hepatitis B (CHB).[1] Chronic HDV infection is the most severe form of chronic viral hepatitis and is associated with increased progression to liver cirrhosis, hepatocellular carcinoma (HCC), mortality from liver failure, and the need for liver transplant (LT).[2–4] Despite its discovery almost 45 years ago in 1977 by Rizzetto et al,[5] the global burden of HDV infection remains poorly defined. A recent study estimated the prevalence of HDV seropositivity to be about 4.5% in hepatitis B surface antigen (HBsAg)-positive patients.[6] The actual number of cases may be much higher due to underscreening and underreporting of HDV cases in both high- and low-income countries.

There are varied screening recommendations for HDV among major societies. Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of the Liver (EASL) recommend routine screening of all HBsAg-positive patients for HDV infection.[7,8] In contrast, 2018 American Association for the Study of Liver Diseases (AASLD) guidelines recommend a risk-based screening approach.[9]

The absence of safe and effective treatments for HDV has slowed the development of standardized tests (both HDV antibody and RNA tests). The only therapy currently recommended per the AASLD guidelines is interferon-alpha, which is associated with poor viral response rates, many side effects, and is not Food and Drug Administration (FDA) approved for this indication in the United States (US).[9]

Despite initial success in reducing HDV rates with HBV vaccination programmes, high-income countries are now seeing an uptrend in HDV infections due to increased immigration from HDV-endemic countries (HEC) and rising intravenous drug use (IVDU).[10–12] In addition, HDV was recently awarded "orphan disease" status creating much interest in the development of pharmacological interventions and effective disease awareness and recognition strategies. The virus entry inhibitor bulevirtide has been approved for the treatment of HDV infection in the European Union and is pending approval by the United States FDA, with several other pharmacological targets in phase 2 clinical trials.[13]

Given the significant health burden of this disease and the promise of novel therapeutics on the horizon, this study was conducted to ascertain if the risk-based screening approach leads to appropriate HDV screening, identify targets to improve screening rates, and to study HDV clinical burden.

2 | METHODOLOGY

This retrospective study was approved by the Mount Sinai Hospital Institutional Review Board (IRB) and was conducted in a Health Insurance Portability and Accountability Act (HIPAA) compliant manner. Electronic medical records (EMR) were reviewed to identify patients diagnosed with CHB infection in a tertiary health system in a multicultural urban area from January 2016 to December 2021.

CHB was defined by the sustained presence of positive hepatitis B surface antigen (HBsAg) based on two HBsAg tests at least 6 months apart. Patients screened for HDV infection were identified using a query for the presence of HDV antibody test in laboratory values. Characteristics of the provider ordering the screening test, including the level of training (attendings vs. trainees vs. advanced practice providers) and primary specialty (Internal Medicine vs. Infectious Disease vs. Gastroenterology), were evaluated.

Patients who had a positive HDV antibody test were considered as HDV seropositive (HDV+). To characterize this HDV+ group, we collected baseline demographic data, including age, sex, race, body mass index (BMI), and associated comorbidities. HDV+ patients were assessed for the presence of risk factors that would have made them eligible for HDV screening per AASLD guidelines (Table 1),[9] prior to when they were screened. Based on a chart review, each individual risk factor mentioned in the AASLD guidelines was classified as positive, negative, or unknown. Documentation of the presence of a risk factor was considered a positive risk factor, whereas documentation of its absence was considered a negative risk factor. Missing information on risk factors was assumed to be either due to under-eliciting of information by providers or underreporting by patients and was classified as unknown.

We hypothesized that there was a delay in HDV screening, and HDV− infected patients had already developed significant liver disease by the time of screening. To test this hypothesis, we compared the liver disease status of HDV+ patients to HDV seronegative (HDV−) patients at the time of HDV screening. We identified a matched cohort of HDV− patients using age, hepatitis B e antigen status, BMI and sex as matching factors in decreasing order of priority. The severity of liver disease at the time of HDV diagnosis was determined by Fibrosis 4 (FIB 4) scores and presence of cirrhosis. Patients with FIB 4 scores >=1.3 at the time of screening were considered as having clinically significant liver fibrosis (>=F2 stage).

TABLE 1 HBsAg-positive persons at high risk of HDV infection who should be screened[a]

Persons born in regions with reported high HDV endemicity • Africa (West Africa, horn of Africa) • Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan) • Pacific Islands (Kiribati, Nauru) • Middle East (all countries) • Eastern Europe (Eastern Mediterranean regions, Turkey) • South America (Amazonian basin) • Other (Greenland)
Persons who have ever injected drugs
Men who have sex with men
Individuals infected with HCV or HIV
Persons with multiple sexual partners or any history of sexually transmitted disease
Individuals with elevated ALT or AST with low or undetectable HBV DNA

[a]Table adopted from Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance.

Patients were determined to have cirrhosis either histologically or by imaging features of a liver with nodular contours and one or more signs of portal hypertension (i.e., thrombocytopenia [platelet count <150 × 109/L], collaterals, splenomegaly, varices, or ascites). We also collected data regarding treatment status for HBV and HBV viral suppression at the time of HDV diagnosis.

For a supplemental analysis, we assessed the outcomes of HDV+ patients compared to the matched HDV− group. Outcomes of interest included mortality, development of liver decompensation events (defined by the development of ascites, jaundice, portosystemic encephalopathy, or bleeding oesophageal varices), hepatocellular carcinoma, and need for liver transplantation.

Continuous variables were compared using means and their standard deviations. No tests of statistically significant differences between HDV+ and HDV− groups were performed because all continuous variables were used in the matching process. Categorical variables were studied by comparing the proportions in each group. To test the statistical significance of differences between the groups for categorical variables, chi-squared tests (for large samples) or Fisher's exact tests (for small samples) were performed.

3 | RESULTS

3.1 | HDV screening

Of 11,190 CHB patients in our database, 1444 patients were screened for HDV during the study period. Most patients were screened by attending physicians (80.5%), with only the minority being screened by physician trainees (2.7%) or advanced practice providers (16.6%). In addition, most patients were screened by gastroenterologists and/or hepatologists (90.2%) rather than an infectious disease (5.5%) or internal medicine (2.7%) physician.

Among the screened patients, 88 patients (6%) were HDV+, of which 72 patients had complete data available for analysis. Of the 72 HDV+ patients, 58 (80.5%) underwent confirmatory HDV RNA PCR testing, of whom 27 (46.6%) patients had detectable HDV RNA. Among the HDV+ group, HEC of origin was the most common risk factor (36 patients, 50%), followed by elevated transaminase levels despite negative HBV DNA levels (23 patients, 32%). Intravenous drug use was the least common risk factor and was reported negative in 53 patients (74%). More than half of the patients were negative for HIV (51 patients, 71%) and HCV (46 patients, 64%). The history of high-risk sexual behaviour/prior history of STIs was not elicited in half of the patients (36 patients, 50%). Table 2 includes a detailed analysis of the presence of each of the risk factors mentioned in the AASLD practice guidance.

Crucially, 13 HDV+ patients (18%) did not meet any of the criteria for HDV screening based on the AASLD Hepatitis B practice guidance either due to the risk factors being negative or unknown.

3.2 | Baseline demographics and liver disease status of HDV+ and HDV− patients at the time of screening

The mean age at the time of diagnosis for patients that were HDV+ was 48 years (SD ± 13.5 years); most patients were male (45 patients, 62.5%) with a mean BMI of 27.2 kg/m^2 (SD ± 5.2). Hepatitis B e antigen was positive in 7 patients (9.7%). The characteristics of the matched cohort of HDV− patients are presented in Table 3.

Coinfection with Hepatitis C virus (HCV) was seen in 8 HDV+ patients (11.1%) compared to only 1 HDV− patient (1.5%). HIV coinfection was present in 6 HDV+ patients (8.3%) compared with 8 HDV− patients (11.9%). Table 3 includes detailed information on the presence of other comorbidities among the two groups.

At the time of screening, there was a higher proportion of HDV+ patients with cirrhosis compared to the HDV− group (55.5% vs. 16.4%, $p < 0.01$). Based on FIB-4 scores, clinically significant fibrosis (>=F2) was present in 68% of HDV+ compared to 40% of HDV− ($p = 0.001$). The HDV+ patients were more likely to be on HBV treatment (73.6% in HDV+, 20.9% in HDV−, p-value <0.01) and had a higher incidence of HBV viral suppression (68.1% in HDV− positive, 38.8% in control, p-value <0.01).

3.3 | Clinical outcomes

Over a mean follow-up period of 5.1 years, there was a non-statistically significant trend towards an increase in HCC among HDV+ patients compared to HDV− (11 cases, 15.2% vs 4 cases, 5.9%, $p = 0.07$). Liver decompensation events were seen in 16

TABLE 2 Presence of high-risk features as per the American Association for the Study of Liver Diseases Guidelines in cases ($n = 72$)

	HEC	IVDU	MSM[a]	HIV	HCV	High-risk sexual practice or STI history	Negative HBV DNA with elevated transaminases	Presence of any 1 risk factor
Risk Factor absent (%)	13(18)	53(74)	23(51.1)	51(71)	46(64)	31(43)	49(68)	**13 (18)**
Risk Factor present (%)	36(50)	5(7)	3(6.7)	6(8)	12(17)	5(7)	23 (32)	**59 (82)**
Unknown (%)	23(32)	14(19)	19(42.2)	15(21)	14(19)	36(50)	0	0

Abbreviations: HBV DNA, Hepatitis B virus deoxyribonucleoprotein; HCV, Hepatitis C virus; HEC, HDV endemic country; HIV, Human immunodeficiency virus; IVDU, Intravenous Drug User; MSM, Men who have sex with men; STI, Sexually transmitted infection.

[a]$n = 45$ (HDV+ male) for history of men who have sex with men.

TABLE 3 Demographics and degree of liver disease at the time of HDV antibody testing

	HDV−Positive $n = 72$	HDV−negative $n = 67$	p value
Mean Age at diagnosis in years (SD)	48 (13.5)	48 (14)	(matched)
Male (%)	45 (62.5)	45 (67.2)	(matched)
Mean BMI at diagnosis in kg.m^2 (SD)	27.2 (5.2)	26.8 (4.5)	(matched)
Hepatitis B e antigen-positive (%)	7 (9.7)	6 (8.9)	(matched)
Comorbidities (%)	HCV 8 (11.1)	HCV 1 (1.5)	
	HIV 6 (8.3)	HIV 8 (11.9)	
	NAFLD 5 (6.9)	NAFLD 5 (7)	
	HLD 10 (13.9)	HLD 5 (7.4)	
	HTN 10 (13.9)	HTN 10 (14.9)	
	DM 7 (9.7)	DM 11 (16.4)	
Cirrhosis (%) at the time of HDV diagnosis	40 (55.5)	11 (16.4)	<0.01
HBV (%) suppressed	49 (68.05)	26 (38.8)	<0.01
On HBV treatment	53 (73.6)	14 (20.9)	<0.01
Significant fibrosis by FIB-4 score calculation	68%	40%	0.001

Abbreviations: BMI, body mass index; DM, diabetes mellitus; FIB 4, fibrosis 4; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation.

TABLE 4 Difference in outcomes HDV+ vs HDV−

	HDV−Positive $n = 72$	HDV−negative $n = 67$	p value
Liver decompensation events – Ascites, HE, jaundice, bleeding oesophageal varices (%)	16(22.22)	6 (8.95)	0.054
Developed HCC	11 (15.2)	4 (5.9)	0.07
Needed LT	15 (20.8)	0	0.002
Death	2	2	0.94

Abbreviations: HCC, Hepatocellular carcinoma; HE, Hepatic encephalopathy; LT, Liver transplantation.

HDV+patients (22%) vs. 6 HDV− patients (9%) without clinically significant difference ($p = 0.056$). Development of ascites was the most common decompensation event in both HDV+ (12 cases, 80%) as well as HDV− (6 cases, 9%). There was a statistically significant difference ($p = 0.002$) in need for liver transplantation in the HDV+ group (15 patients, 20.8%) vs. HDV− group (0 patients). No difference in mortality was seen between the two groups (2 cases in HDV+ vs. 2 cases in HDV− group, $p = 0.94$) (Table 4).

4 | DISCUSSION

Our findings show a disappointingly poor practice of HDV screening among CHB patients in a large tertiary care centre in the United States. Nonetheless, many of the screened patients were found to be HDV+, and a sizable portion of HDV+ patients would have been missed by current AALSD screening guidelines.[9]

The global estimate of HDV seroprevalence among CHB patients varies widely among studies. A meta-analysis by Chen et al estimated the prevalence of HDV as high as 14.57% in HBsAg-positive populations whereas Stockdale et al estimated this prevalence to be only 4.5%.[6,14] In the US, HDV awareness remains low and prevalence data is limited. While a study from Northern California showed a prevalence of 8% among 1191 CHB patients,[15] in a recent population-based study by Patel et al using National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2016, a striking 42% of HBsAg carriers were positive for HDV antibody.[11] A reason for the wide prevalence range could be assay variability and differences in the populations that were sampled. To get a true representation of disease prevalence in the US, it would be prudent to make HDV a disease reportable to the Centers for Disease Control (CDC), standardized testing assays and have nationwide prevalence studies.

Only 1444 patients had been screened for HDV antibody over the course of almost 6 years in our study. We were unable to determine the screening rates in our study as CHB patients may have been screened prior to the study period or at the time of diagnosis, however, given the large volume of patients in a large tertiary

care centre, these numbers reflect inadequate screening. In a study by Kushner et al to assess the prevalence of HDV–positive status in the VA (Veterans Affairs) system in the United States, only 8.5% of more than 25,000 people with CHB had been screened for HDV antibodies.[16]

The EASL and APASL guidelines recommend routine HDV testing among all HBsAg carriers,[7,8] while the AASLD guidance restricts screening to only those perceived to be at an increased risk.[9] Risk-factor-based screening has been abandoned for HCV due to high rates of missed infections attributed to patient underreporting and provider reluctance to elicit risk factor information.[17] In our review of HBV high-risk features, we found that information on sexual history was missing in up to 50% of HDV+ patients. More than 50% of HDV+ patients did not have co-infection with HIV or HCV, reflecting that a sizeable portion of HDV+ patients does not meet traditionally identified risk factors.

Heterogeneity in the geographic distribution of HDV infection has been well described, with particularly high prevalence in Mongolia, the Republic of Moldova, and regions of Africa, central Asia and the Middle East.[9] The regions of endemicity in the AASLD guidelines are based on population studies, however, as many countries under-test and under-report HDV infections, this may be based on incomplete data. To this end, a recent study in a North American cohort showed that patient origination from an HEC was a strong risk factor for HDV seropositivity.[18] Similarly, in our cohort 50% of the HDV− positive patients were from an HEC. However, provider familiarity with countries having high HDV prevalence is poor, and the AASLD guidelines recommend erring on the side of screening in cases of uncertainty.

If risk-factor screening alone was strictly applied to our cohort, 18% of our HDV patients would not have met the criteria for screening, and therefore, the diagnosis of HDV would have been missed (Table 2). This emphasizes the detriment of risk-factor-based screening and the importance of adopting a universal screening protocol nationwide.

HDV+ patients had higher rates of clinically significant fibrosis (>=F2) by FIB4 score calculation and cirrhosis by the time they were screened despite being on HBV suppression therapy, indicating faster disease progression and the need for earlier screening. FIB 4 scores have been shown to have an AUROC of 0.7 for detecting significant fibrosis (F2) and 0.83 for detecting cirrhosis in patients with HDV infection.[19] While other noninvasive methods to detect fibrosis have not been well studied in patients with HDV, the delta 4 fibrosis score (D4FS) has now been developed specifically for HDV but needs further validation before it can be widely used.[20]

Multiple prior studies have showed an increased morbidity and mortality associated with chronic hepatitis D virus infection.[2–4] We similarly noticed a statistically significant increase in need for liver transplantation among the HDV+ group. While our study was underpowered to detect a statistically significant difference in outcomes due to small numbers, we noticed a trend towards the development of HCC and liver decompensation events. We did not notice a similar trend in mortality. Apart from a small number of patients, this could be explained at least in part by the availability of liver transplantation at our facility.

Our data suggest that gastroenterologists and/or hepatologists are more likely to order HDV screening tests than primary care and infectious disease specialists. In addition, we identified poor anti-HDV screening rates among trainee clinics. The introduction of targeted quality improvement interventions in these settings, including EMR prompts and reflex HDV testing, may help improve screening rates, like established HCV screening initiatives.[21] Of the HBsAg-positive patients that were screened (n = 1444) in our cohort, 6% were positive for HDV. Considering similar baseline characteristics among the screened vs. not screened groups, if reflex HDV testing had been applied for not screened group at the time of HBsAg positivity, we could anticipate a similar proportion (6%) of these patients to be HDV+ leading to an increase in absolute numbers of HDV diagnosis. This would be a substantial number of new HDV+ cases given the large number of HBsAg-positive persons who were not screened. Similar results were obtained in a study by Palom et al after instituting reflex HDV antibody testing in all patients who tested positive for HBsAg.[22]

The conclusions of our study are compelling, yet there are certain limitations that are worth mentioning. Due to the study's retrospective nature, we were limited by the data available in our EMR, and a complete chart review was only available for 72 HDV− positive patients. In addition, it was not possible to distinguish between HDV superinfection vs. coinfection based on the chart review. HDV RNA levels were not available for all patients included in the study. However, as 90% of all HDV superinfections progress to chronic infections and HDV titres decline over time, most CHB patients with positive HDV antibodies can be assumed to have CHD infection. Since there is no standard HDV RNA assay, a negative test could indicate resolved hepatitis D, persistent infection with exceptionally low viremia, or a false-negative PCR test result. Another limitation of our study is that our findings are derived from a single healthcare system based in New York City, which has a high immigrant population, and these numbers may not be representative of the entire US population. As discussed above, we were limited by the small number of patients to detect statistically significant differences in outcomes.

Recently, bulevirtide has been approved by the European Medicines Agency (EMA) as a treatment for HDV and has shown itself to have promising results.[11] There are many other therapies currently in phase 2 clinical trials that are on the horizon.[23] Given the prospect of these new potentially effective therapies in the new future, it is important that we appropriately screen routinely for HDV antibodies and identify the disease early before the development of complications. Prevention of transmission of HBV and/or HDV infection remains the cornerstone in the management of HDV infections. This can be done most effectively through widespread immunization programmes against HBV infections. Other means to prevent the spread of HBV/HDV infection that have proved to be effective include the implementation of needle exchange programmes among high-risk groups like IVDUs.

In conclusion, HDV infection is associated with high morbidity and mortality. HDV is an independent risk factor for progressive and advanced liver disease, risk of HCC, and need for liver transplantation compared to those without HDV. Compared with patients without HDV infection, there is a higher incidence of liver decompensation events, HCC and the need for liver transplantation in patients with CHD. Larger multicentre studies are needed in the future.

To better understand the burden of HDV in the US, reporting HDV infections to the CDC (Centers for Disease Control) should be mandatory, and HDV antibody and RNA assays must be standardized to ensure uniformity in diagnosis. Prevention is the best way to tackle the dual devil of HBV and HDV infections. Widespread HBV vaccination programmes and the implementation of needle-sharing programmes are some examples of how this can be achieved. Most importantly, the current risk-based AASLD guidelines for HDV screening among HBsAg carriers are not an effective screening strategy. With newer treatments for HDV infection on the horizon, it is time to adopt universal HDV screening for all HBsAg carriers in the United States.

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CONFLITS OF INTEREST

Dr. Ilan Weisberg occasionally gives lectures at events sponsored by industry, but only if the events are free of any marketing purpose at i. Gilead Sciences, Inc. ii. Intercept Pharmaceuticals Inc. Dr. Amreen Dinani advises for and is on the speakers' bureau for Intercept Pharmaceuticals. She consults for Genfit and Expert Connect. She advises for Gilead Sciences, Inc. The remaining authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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