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Delta hepatitis within the Veterans Affairs medical system in the United States: Prevalence, risk factors, and outcomes

Tatyana Kushner[1], Marina Serper[1,2], David E. Kaplan[1,2,*]

[1]*Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA, United States*; [2]*Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, United States*

Background & Aims: Low hepatitis delta prevalence estimates in the United States are likely biased due to low testing rates. The objectives of this study were to quantify the prevalence of testing and identify factors associated with hepatitis D positive status among chronic hepatitis B patients in the Veterans Health Administration.

Methods: We performed a nationwide retrospective study of all veterans who tested positive for HBsAg from October 1999 to December 2013. Hepatitis D antibody testing results were used to stratify patients into three groups: HDV-positive, HDV-negative, and HDV-not tested. Demographics, comorbidities, additional laboratory data and clinical outcomes were compared across these groups of patients using standard statistical approaches.

Results: Among 25,603 patients with a positive hepatitis B surface antigen, 2175 (8.5%) were tested for HDV; 73 (3.4%) patients tested positive. Receiving HDV testing was associated with receipt of testing for HBV, HIV, and HCV. Predictors of positive HDV results included substance abuse and cirrhosis. Fitting a predefined high-risk profile (abnormal ALT with suppressed HBV DNA titers) was strongly associated with testing positive for HDV (OR 3.2, 95%CI 1.4–7.5). Most (59%) of HDV-positive patients were HCV co-infected. HDV-positive subjects had higher risks of all-cause mortality. Incidence rates of HCC were 2.9 fold higher in HDV-positive relative to HDV-negative individuals ($p = 0.002$). In adjusted analyses, HDV was independently associated with HCC (OR 2.1, 95%CI 1.1–3.9).

Conclusions: Testing rates for hepatitis delta in chronic hepatitis B patients in the United States are inappropriately low. Approaches to increase testing for HDV particularly in high-risk subsets should be explored.

Introduction

Hepatitis Delta virus (HDV) is an incomplete human RNA virus that requires chronic hepatitis B (HBV) infection for replication [1,2]. Super-infection of individuals with chronic HBV with HDV frequently results in chronic delta hepatitis, which has been associated with accelerated fibrosis progression and increased risk of HCC relative to hepatitis B mono-infection [3,4]. The prevalence of chronic delta hepatitis in the United States is thought to be rising due to increased sexual transmission and increasing prevalence in certain urban injection drug using populations [2,5]. To date, however, no study has examined the prevalence, risk factors, and clinical outcomes in HDV among a national US cohort.

The objectives of this study were to report on the prevalence of HDV testing, HDV co-infection and associated adverse clinical outcomes such as HCC and hepatic decompensation among a national cohort of U.S. Veterans. We additionally examined factors associated with HDV testing, HDV-positive status, and adverse clinical outcomes.

Patients and methods

Data source

This was a retrospective cohort study from October 1999 to December 31, 2013 using the VA Corporate Data Warehouse (CDW), a national data repository updated with daily demographic information, laboratory results, prescription fills, and claims information (e.g. diagnosis codes) from all outpatient and inpatient encounters from the Veterans Health Administration, which serves 8.76 million US veterans each year at over 1700 sites. The CDW is a relational database that has been utilized extensively for epidemiology studies in chronic viral hepatitis studies [6–8]. In a cohort of HBsAg-positive individuals, the following demographic and laboratory data were extracted: age, gender, race/ethnicity, presence and results of anti-HDV antibody (HDVAb), HDV RNA, HBeAg, HBeAb, HBV DNA titers, HBcIgM, HIV antibody (HIVAb), Hepatitis C antibody (HCVAb), alanine aminotransferase (ALT), total bilirubin, and international normalized ratio (INR). We also report the proportion of patients that ever had a positive HCV RNA.

Keywords: Hepatitis D; Hepatitis B; Hepatocellular carcinoma; Database.
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* Corresponding author. Address: 415 Curie Blvd., BRB II/III 9th Floor, Philadelphia, PA 19104, United States. Tel.: +1 (215) 823 5800x6729; fax: +1 (215) 823 4289.
E-mail address: dakaplan@mail.med.upenn.edu (D.E. Kaplan).

Abbreviations: HDV, Hepatitis D; HDV Ab, Hepatitis D antibody; CDW, VA corporate data warehouse; HBV, Hepatitis B; HCV, Hepatitis C; HBcIgM, Hepatitis B core IgM antibody; HBeAg, Hepatitis B e antigen; HBeAb, Hepatitis B e antibody; HIV, Human immunodeficiency virus; ALT, Alanine aminotransferase; INR, International normalized ratio; AFP, Alpha-fetoprotein; HCC, Hepatocellular carcinoma.

The presence of chronic confirmed HBV was defined as having a second positive HBsAg, second positive HBeAg, or positive HBV DNA more than six months following the original positive HBsAg result. We predefined a "high-risk for HDV" laboratory profile of suppressed HBV DNA titers (<2000 IU/ml) and elevated ALT ($\geqslant 2 \times$ ULN, 62 U/ml) for specific analyses. The number of prescriptions and dates of interferon and oral nucleos(t)ide antivirals was obtained from outpatient pharmacy data. Patients were considered to have received interferon or oral nucleos(t)ides (lamivudine, telbivudine, adefovir, entecavir, or tenofovir) if they filled at least one outpatient prescription. Hepatic decompensation was defined using a previously validated algorithm including International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for ascites, variceal hemorrhage, and spontaneous bacterial peritonitis [9]. Cirrhosis was ascertained using ICD-9-CM codes using previously validated methodology [10]. Significant alcohol use was defined as having a score of $\geqslant 5$ on the Alcohol Use Disorders Identification Test (AUDIT-C) [11]. Drug abuse was identified using ICD-9-CM codes. We classified patients as having had specialty care if they had at least one appointment with a gastroenterology (GI) or infectious disease (ID) specialist within two years of the index HBsAg+ result. Death events were identified using the Vital Status File [12] censored as of 12/31/2013.

Statistical analysis

Descriptive statistics such as means, standard deviations, medians and interquartile ranges were calculated. Medians for continuous variables were compared using the Kruskal-Wallis test and proportions for categorical variables were compared using the chi squared test. Univariate and multivariable logistic regression was used to evaluate factors associated with the outcomes of HDV testing and positive HDV status. For logistic regression models, goodness of fit was evaluated with the Hosmer-Lemeshow goodness of fit test. Incidence rates (cases per 1000 person-years) and incidence rate ratios were calculated for the outcomes of HCC, hepatic decompensation, and death. Multivariable Cox proportional hazards models were conducted for the outcome of HCC. For the outcome of HCC, two models were constructed: model 1 included all covariates with a p <0.05 on univariate analyses of association with HCC development; model 2 was a parsimonious model including only covariates found to be statistically significant in multivariable analysis. The proportional hazards assumption was tested using Schoenfeld residuals. All analyses were conducted with Stata 12.1 (StataCorp, College Station, Texas). To account for possible misclassification bias due to low rates of HDV testing, we conducted sensitivity analyses to assess clinical outcomes such as HCC, hepatic decompensation, and death among patients not tested for HDV, but meeting a high-risk profile (ALT $\geqslant 2$ ULN and HBV DNA <2000 IU/ml).

Results

Characteristics of the HBsAg+ study cohort and HDV testing rates

A total of 25,603 HBsAg+ patients were identified from the VA Corporate Data Warehouse. Of these, 8159 (32%) of patients were confirmed to have chronic HBV infection with subsequent virologic and serologic testing. However, given the low rates of serologic testing and low prevalence of HDV, analyses were performed among the entire cohort. The patient population was predominantly male and non-Asian (33% African American, 40% white). Two-thousand and eight (7.8%) of all HBsAg+ patients were tested for HDV and 73 (3.6%) were HDV seropositive (HDV-positive) (Table 1). The average age of the cohort was 52 (SD = 12) and did not vary by testing status. HDV-positive patients were more likely to have documented alcohol abuse and substance abuse than HDV-negative patients. The prevalence of HCV, HIV co-infection and cirrhosis was higher among HDV-positive patients. The majority of HDV-positive patients (64%) did not have HBV DNA testing performed within the VA system, however, among those tested 88% (23 of 26) had HBV DNA <2000 IU/ml. Peak ALT and total bilirubin were significantly higher in tested individuals (p <0.001). Among the 5935 patients with available data, 1468 (25%) met the high-risk HDV profile defined by HBV DNA <2000 IU/ml and ALT $\geqslant 2$ ULN; the percentage of patients with the high-risk profile in the HDV-positive group was more than twice that of the HDV-negative group (62% *vs.* 28%).

Factors associated with HDV testing

In order to address differences between patients who were tested and those who were not tested, we compared these two cohorts of patients (Table 2). We found that age was similar across groups (p = 0.49). White (OR 1.2, 95%CI 1.1–1.3) and male subjects (OR 1.8, 95%CI 1.4–2.3) were more like to be tested. Patients who also underwent testing for HBeAg, HBeAb, HBV DNA, HBcIgM, HCV, and HIV serologies were more likely to be HDV tested, suggesting that diagnostic work-up for ALT flares, which were more prevalent in the tested group, frequently prompted appropriate HDV testing. Notably, HBeAg and HBeAb testing were associated with the highest odds ratios for HDV testing among the variables studied (12.3 and 8.9, respectively), likely reflecting increased testing for HDV in setting of concern for change in HBV infection phase and disease activity. Not surprisingly, patients with outpatient visits with gastroenterology or infectious disease specialists were more than three times more likely to undergo HDV testing (OR 3.3, 95%CI 3.0–3.6). Patients with the high-risk profile for HDV were indeed more likely to be HDV tested (RR 1.3, p <0.001) yet despite this, 1181 of 1468 (80%) subjects with the high-risk profile in the cohort were not HDV tested (Table 1). HDV tested patients were more likely to be exposed to interferon or nucleoside therapy (ORs 3.1 and 2.4, respectively), possibly due to higher rates of active hepatitis in these individuals. By contrast, HCV co-infection and alcohol abuse were associated with reduced HDV testing (OR = 0.86, p <0.001 and OR = 0.50, p <0.001, respectively) possibly due to attribution of abnormal liver associated enzymes to chronic HCV or alcohol abuse in these individuals. In summary, patients who underwent more comprehensive HBV testing were also more likely to be HDV tested. Together, these data suggest that coordination of testing by specialists with expertise in HBV resulted in higher testing of HDV.

Factors associated with a positive HDV result

When comparing patients who tested positive *vs.* those who tested negative for HDV among those tested (Table 3), strikingly, HBV/HCV-co-infected individuals were significantly more likely to test positive for HDV (OR 7.1, 95%CI 4.4–11.5), possibly related to common routes of exposure of HCV and HDV. Not unexpectedly, HBcIgM+ and HBeAg+ patients conversely were much less likely to test positive for HDV (OR 0.21, p = 0.009 and OR 0.39, p = 0.002, respectively) as ALT elevations and higher disease activity in these individuals would be more consistent with hepatitis B mono-infection-related flares. Other factors positively associated with an HDV-positive result included alcohol abuse (OR 1.8, 95%CI 1.1–2.8) and expectedly substance abuse (OR 3.4, 95%CI 2.1–5.4). ICD9-coded cirrhosis was also positively associated with HDV-positivity (OR 2.4, 95%CI 1.5–4.1), likely related to the known more aggressive progression of fibrosis associated with HDV. The predefined high-risk profile (high ALT, low HBV DNA) was strongly associated with testing positive for HDV (OR 4.2, 95%CI 1.9–9.3). Finally, interferon therapy was associated with HDV-positive results, an association that could

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Table 1. Patient demographics and clinical characteristics stratified by HDV status.

Variable, N (%)	Total (n = 25,603)	HDV not tested (n = 23,595)	HDV negative (n = 1935)	HDV positive (n = 73)	*p* value*
Age (M, SD)	52 (12)	52 (12)	52 (12)	51 (10)	0.52
Male	24,140 (94)	22,202 (94)	1867 (96)	71 (97)	<0.001
Race					<0.001
Black	8313 (33)	7638 (32)	649 (34)	26 (36)	
White	10,339 (40)	9332 (39)	970 (50)	37 (51)	
Asian	1149 (4.5)	1045 (4.4)	100 (5.2)	4 (5.5)	
Indian/Hawaiian/PI	484 (1.9)	449 (1.9)	34 (1.8)	1 (1.4)	
Unknown/refused	5380 (21)	5192 (22)	183 (9.5)	5 (6.7)	
Alcohol abuse	13,917 (54)	13,145 (56)	734 (38)	38 (52)	<0.001
Substance abuse	5397 (21)	4927 (21)	434 (22)	36 (49)	<0.001
HCV Ab positive	4331 (17)	3964 (17)	324 (17)	43 (59)	<0.001
HCV RNA positive	2728 (11)	2501 (11)	206 (11)	21 (29)	<0.001
HIV co-infection	1195 (4.7)	1053 (4.5)	135 (7.0)	7 (9.6)	<0.001
Cirrhosis	1937 (7.5)	1625 (6.9)	290 (15)	22 (30)	<0.001
HBV DNA					<0.001
<2000 IU/ml	3985 (16)	3400 (14)	562 (29)	23 (32)	
2000-20,000 IU/ml	512 (2.0)	425 (1.8)	87 (4.5)	0 (0)	
>20,000 IU/ml	1437 (5.6)	1104 (4.7)	330 (17)	3 (4.1)	
Not tested	19,669 (77)	18,666 (79)	956 (49)	47 (64)	
Peak ALT (median, IQR) (n = 16,569)	49 (29, 105)	47 (28, 96)	78 (38, 260)	84 (44,201)	<0.001
High risk profile*	1468 (25)	1181 (24)	271 (28)	16 (62)	<0.001
Peak total bilirubin (median, IQR) (n = 16,460)	0.8 (0.6, 1.2)	0.8 (0.6, 1.2)	1.0 (0.7, 1.8)	1 (0.6, 2.7)	<0.001
Peak INR (median, IQR) (n = 8719)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	0.09
Seen by specialist	5743 (22)	4719 (20)	988 (51)	36 (49)	<0.001
GI/hepatology	3904 (15)	3134 (13)	744 (38)	26 (36)	<0.001
Infectious disease	2172 (8.5)	1832 (7.8)	326 (17)	14 (19)	<0.001

M, mean; SD, standard deviation; ALT, alanine aminotransferase; INR, international normalized ratio; IQR, interquartile range.
Alcohol abuse/dependence, AUDIT-C score $\geqslant$5; Substance abuse/dependence, HIV and cirrhosis identified by ICD-9-CM codes.
*High-risk profile refers to patients with ALT $\geqslant$2 ULN and HBV DNA <2000 IU/ml, (data available for n = 5935).

reflect initiation of current standard of care therapy, but could also reflect the higher rates of HCV co-infection in HDV-positive individuals.

Confirmatory testing

A minority (n = 6, 8.2%) of HDV-positive subjects underwent confirmatory PCR testing. A total of 2% of patients who tested negative for HDV antibody were tested with PCR.

Antiviral therapy

Of the 73 HDV-positive patients, a total of seven (9.6%) were exposed to interferon-based therapy. Of interferon-treated patients, the median number of month-long fills 7 (IQR: 1–16). A total of 30 (41%) of HDV-positive patients received HBV-directed nucleos(t)ide therapy.

Clinical outcomes

Incidence rates per 1000 person-years for the outcomes of HCC, hepatic decompensation, and death are presented in Table 4. The overall incidence of HCC was 3.9 per 1000 person-years; 23.0 per 1000 person-years in HDV-positive individuals and 8.0 per 1000 person-years in HDV-negative individuals (IRR 2.9, 95%CI 1.5–5.4). The incidences of hepatic decompensation and death was 8.0 and 44.0 cases per 1000 person-years, respectively, rates were numerically higher for HDV-positive patients, approaching statistical significance for both outcomes.

We performed multivariable models for the outcome of HCC (Table 5). In both models, HDV-positive status, older age, significant alcohol use, and the presence of cirrhosis were independently associated with HCC. Not unexpectedly, increasing age, alcohol abuse, and cirrhosis were also independently associated with HCC. HCV status and nucleos(t)ide therapy was not significantly associated with the development of HCC.

Discussion

This is the first nationwide study in the U.S. examining testing rates for hepatitis D (HDV) and outcomes. Testing for HDV infection occurred in fewer than 8% of all HBsAg+ patients and in only 19% of patients with hepatitis not attributable to active hepatitis B replication. These low testing rates contrast significantly with testing rates internationally [13] and suggest a lack of awareness regarding importance of HDV testing in the United States. While practice within the Veterans Affairs medical system may not reflect all United States-based health systems, and certain academic centers may test more frequently [2], the authors suspect

Table 2. Factors associated with HDV testing in univariate analyses (n = 2009).

Variable	Unadjusted OR (95% CI)	*p* value
Age (per 1 year increase)	0.99 (0.99-1.00)	0.49
White	1.2 (1.1-1.3)	<0.001
Male	1.8 (1.4-2.3)	<0.001
HBeAg tested	12.3 (9.1-12.2)	<0.001
Anti-HBe tested	8.9 (7.8-10.0)	<0.001
HBV DNA tested	3.8 (3.5-4.2)	<0.001
HCV Ab tested	2.2 (1.9-2.5)	<0.001
HIV tested	2.6 (2.3-2.8)	<0.001
HBcIgM tested	2.1 (1.9-2.3)	<0.001
HBcIgM$^+$	3.0 (2.6-3.5)	<0.001
HBeAg$^+$	1.7 (1.6-1.9)	<0.001
HCV Ab$^+$	0.86 (0.76-0.97)	0.014
Alcohol abuse	0.50 (0.45-0.55)	<0.001
Substance abuse	1.2 (1.0-1.3)	0.007
Cirrhosis	2.5 (2.2-2.8)	<0.001
High risk profile*	1.3 (1.1-1.5)	0.002
Oral nucleoside therapy	3.1 (2.9-3.4)	<0.001
Interferon therapy	2.4 (1.9-3.1)	<0.001
Specialty care (GI/ID)	3.3 (3.0-3.6)	<0.001
Gastroenterology/hepatology	4.0 (3.7-4.5)	<0.001
Infectious disease	2.4 (2.1-2.7)	<0.001

OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B e antigen.
Anti-HBe, hepatitis B antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.
Substance abuse, cirrhosis obtained using ICD-9-CM codes.
Alcohol abuse, score of ⩾5 on AUDIT-C questionnaire.
Specialty care, at least one outpatient visit with gastroenterology or infectious disease specialist within two years of initial HBV diagnosis.
*High-risk profile refers to patients with ALT ⩾2 ULN and HBV DNA <2000 IU/ml.

that the testing rates identified are similar to if not greater than national rates due to frequent affiliation of large urban VA hospitals with neighboring academic centers. Prompt referral to a gastroenterologist/ hepatologist or infectious disease specialist was strongly associated with HDV testing. Outpatient visits with gastroenterology/hepatology were more strongly associated with testing than visits with infectious disease specialists. However, this finding should be interpreted with caution as we are unaware of the indications for the outpatient visits and some patients saw both specialists. We hypothesize that low testing rates reflect relative inexperience with HDV, inadequate education of providers regarding high-risk groups, infrequent referral rates to appropriate specialists, and poor access to HDV testing modalities [1]. Further studies are needed to confirm these hypotheses.

As expected, testing was more common in individuals with elevated ALT levels and patients likely being evaluated for hepatitis flares with concomitant HBcIgM and HBeAg testing. However, patients predefined by a "high-risk" serologic profile of suppressed HBV DNA and elevated ALT were rarely tested (~20% of cases), though among those tested with that profile, greater than half of patients were HDV-positive. Small racial differences in testing rates were identified, but these differences are of unclear significance. The 3.4% seropositive prevalence rate of HDVAb in HBsAg-positive U.S. veterans remains relatively low compared to rates seen in endemic regions such as the Mediterranean basis (overall 14.8% [14], up to 45.5% in eastern Turkey [15,16], 44% in Tunisia [17]), south Asia (17% in Iran [18], 16.6% in Pakistan [19], 8.6% in Saudi Arabia [20]), Amazon Basin [21], and Mongolia (56–66%) [22] and is similar to rates seen in western Europe [13,23–25]. Importantly, as testing rates are quite low, it is difficult to draw conclusions about actual HDV prevalence in the US. Further studies with improved testing for high-risk populations will need to be performed to characterize prevalence. In a recent study from Northern California, a relatively high frequency of HDV-positive individuals were of Asian descent [2]. In our cohort, only four Asian-Americans tested positive for HDV; this may reflect the low prevalence of Asian veterans within the VHA. These patients did not have co-existent HCV, HIV, or substance abuse, perhaps implying that Asian descent was a risk factor for HDV infection rather than for drug use. However, conclusions are difficult to draw from this limited sample size. The majority of the veterans in our cohort who tested positive for HDV served in the military during the Vietnam War era but exact service locations are unavailable, limiting inferences about the geography of HDV exposures in the cohort.

Outcomes of HDV-positive individuals were markedly poorer relative to HDV-negative individuals with nearly three-fold higher rates of HCC. Even after adjusting for chronic hepatitis C, cirrhosis and alcohol use, which could increase either the prevalence or detection of liver cancer, HDV remained an independent

Table 3. Factors associated with HDV-positive status.

Variable	Unadjusted (OR, 95% CI)	*p* value	Adjusted (OR, 95% CI)	*p* value
HCV Ab$^+$	7.1 (4.4-11.5)	<0.001	3.2 (1.4-7.6)	0.007
Alcohol abuse	1.8 (1.1-2.8)	0.016	3.2 (1.4-7.8)	0.009
Cirrhosis	2.4 (1.5-4.1)	0.001	3.5 (1.4-8.5)	0.006
High risk profile*	4.2 (1.9-9.3)	<0.001	3.2 (1.4-7.5)	0.007
HBcIgM$^+$	0.21 (0.07-0.68)	0.009	0.18 (0.02-1.5)	0.107
HBeAg$^+$	0.39 (0.21-070)	0.002	0.50 (0.17-1.4)	0.182
Substance abuse	3.4 (2.1-5.4)	<0.001	2.0 (0.83-5.0)	0.119
Interferon therapy	2.7 (1.2-6.1)	0.016	1.4 (0.27-7.1)	0.693

HBcIgM, hepatitis b core IgM; HCV hepatitis c virus.
Substance abuse, cirrhosis obtained using ICD-9-CM codes.
Alcohol abuse, score of ⩾5 on AUDIT-C questionnaire.
*High-risk profile refers to patients with ALT ⩾2 ULN and HBV DNA <2000 IU/ml.

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Table 4. Incidence rates of hepatocellular carcinoma and decompensation stratified by HDV status.

Variable	HDV not tested (n = 23,595)	HDV negative (n = 1935)	HDV positive (n = 73)	IRR (95% CI) (HDV-positive versus HDV-negative)	*p* value
HCC	3.9	8.0	23	2.9 (1.4-5.4)	0.002
Hepatic decompensation	8.0	22	33	1.5 (0.8-2.6)	0.063
Death	44	38	52	1.4 (0.9-2.1)	0.059

HCC, hepatocellular carcinoma.
Incidence rates reported as cases per 1000 person-years.

Table 5. Multivariable models for the outcome of hepatocellular carcinoma.

Variable	Model 1			Model 2		
	HR	95% CI	*p* value	HR	95% CI	*p* value
HDV positive	1.9	1.1-3.7	0.044	2.1	1.1-3.9	0.025
Age (per one year increase)	1.06	1.04-1.08	<0.001	1.05	1.03-1.08	<0.001
Significant alcohol use	2.7	1.8-4.0	<0.001	2.5	1.7-3.7	<0.001
Cirrhosis	4.8	3.2-7.2	<0.001	5.2	3.5-7.8	<0.001
HCV positive	1.2	0.72-1.9	0.523	---	---	---
Nucleos(t)ide therapy	1.4	0.94-2.2	0.093	---	---	---

Adjusted IRR adjusted for black race, alcohol abuse, gender, age, HCV and HIV status.

predictor of HCC with a strong trend toward association with hepatic decompensation. Further, overall unadjusted survival was lower in HDV-positive veterans highlighting the importance of testing and potential treatment.

The American Association for the Study of Liver Diseases' most recent hepatitis B guidelines from 2009 recommend testing for hepatitis D in patients with a history of injection drug use or from countries with high HDV seroprevalence [26]. The recommendation to limit testing to individuals with history of injection drug use could be ineffective at identifying prevalent cases due to significant underreporting of remote illicit drug use in the past [27]. Furthermore, focusing testing on just patients from the Mediterranean basin and the developing world may be inappropriate in the United States due to significant prevalence (8% in one study from California) [2] in non-Mediterranean Caucasian and Asian populations. Overall adherence to testing recommended by the AASLD HBV guidelines has been shown to be poor [28,29] and thus our finding of low HDV testing rates even among high-risk subgroups in the U.S. is not unexpected.

Strikingly, and confirming the findings of Gish *et al.* [2] and Kucirka *et al.* [5] our data show that HCV co-infection was present in the majority of HDV-positive patients suggesting a dominant role for high-risk behaviors such as injection drug use and high-risk sexual contact for transmission of HDV. We also found that the "high-risk profile" (indicating high ALT and low HBV DNA) was strongly associated with increased likelihood of HDV-positive status, however, only minimally associated with increased likelihood of HDV testing. We would propose that future iterations of U.S.-based HBV guidelines more strongly emphasize the need to test for HDV in patients at high-risk including those co-infected (HIV/HBV, HCV/HBV, HIV/HCV/HBV) and patients with active hepatitis despite suppressed HBV DNA titers, particularly those that are HBeAg-negative.

Among the 73 HDV-positive individuals in our study, only seven received current standard of care therapy with long-term interferon-alpha; five of those patients had HCV, leaving only two treated solely for HDV. In this cohort, few HDV-positive individuals received confirmatory HDV RNA testing by PCR, this most likely due to poor availability testing in the U.S. during this time-frame. When done in other series, confirmation of HDV RNA by PCR has ranged widely from 16% to 81% in HDVAb+ patients [15,30–32]. To date, the lack of highly effective, non-toxic therapy [33–37] for chronic HDV and lack of convenient testing services likely strongly contributed to the observed low testing and treatment rates. The recent clinical development of Lonafarnib, a farnesyl transferase inhibitor, which appears effective and safe in early clinical trials, [38] and other potential therapeutic approaches such as entry HBV inhibitors [39] may alter testing and treatment recommendations. It will be critical to improve access to validated and standardized HDV diagnostic tests to accompany HDV drug development in order to appropriately identify treatment candidates and monitor response.

Due to low testing rates for HDV, there is certainly some degree of misclassification bias, specifically that undiagnosed HDV-positive individuals might alter outcome rates in the HDV-not tested group. This could have two possible effects. First, due to less morbid illness in undiagnosed HDV+ individuals that event rates in diagnosed HDV-positive individuals are overestimated (i.e. the Will Rogers Effect). Second, contamination of events from undiagnosed HDV-positive individuals in the HDV-not tested group could falsely minimize real differences in adverse outcomes associated with HDV-positivity. Supporting the latter possibility, risks of HCC, decompensation and death in HDV-not tested individuals who met criteria for the "high-risk profile", which we found was strongly associated with HDV-positivity, were significantly higher than risks in individuals who did not meet the profile (Supplementary Table 1). Thus, event rates and differences in risk associated with HDV-positivity is most likely underestimated due to underdiagnosis of HDV infection in the cohort.

Several additional limitations of this work must be acknowledged. As a retrospective study, attribution of causation to the associations we identified is limited. Fewer than half of the study cohort met standard criteria for confirmed chronic HBV infection

(HBsAg or other marker of ongoing infection six months after initial testing). While we were unable to ascertain the exact proportion of patients with acute HBV, the relatively low median ALT (49 IU/ml; 75th percentile 105 IU/ml; 90th percentile 329 IU/ml) and low rates of HBcIgM+ suggest that the vast majority of the patients were indeed chronically infected. As with most VA-based studies, the predominant male gender and other features of the veteran population may limit generalizability. We did not have access to non-VA health records to account for non-VA testing and treatment. Data on substance abuse were administratively coded and subject to recall bias. Information on potential high-risk sex behaviors was also not available.

Conclusions

In a large cohort of U.S. veterans with chronic hepatitis B, testing rates for co-infection with hepatitis D were low. Among those tested, the prevalence was 3.4%. Testing appeared to be associated with evaluations for hepatitis flares and most often coordinated by gastroenterology or infectious disease specialists. HDV most commonly seen associated with HBV/HCV co-infection and epidemiologically linked to substance abuse disorders. HDV co-infection was associated with a higher likelihood of cirrhosis, decompensation, and most dramatically with increased HCC risk. Most HDV co-infected individuals did not receive effective antiviral therapy. Overall, our findings suggest that the need for updated national guidelines with specific recommendations for screening, treatment and follow-up among patients infected with chronic hepatitis B and hepatitis D are critically needed.

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Conflict of interest

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Author's contributions

Tatyana Kushner and David Kaplan worked on the study concept and design of the study in identifying relevant data, collecting the data, and analysis and interpretation of the data. Tatyana Kushner prepared the initial draft of the manuscript. David Kaplan and Marina Serper provided critical revisions of all aspects of the manuscript, from format to intellectual content. Tatyana Kushner, Marina Serper, and David Kaplan performed statistical analyses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2015.04.025.

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