Received: 8 July 2022 | Revised: 20 November 2022 | Accepted: 4 January 2023

DOI: 10.1111/liv.15519

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Hepatitis delta infection among persons living with HIV in Europe

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Funding information
NEAT-ID Foundation; European Union's Seventh Framework Programme for Research; EuroCoord, Grant/Award Number: 260694; ViiV Healthcare LLC; GlaxoSmithKline R&D Limited; Janssen Scientific Affairs; Janssen R&D; Bristol-Myers Squibb Company; Merck Sharp and Dohme; Gilead Sciences; Swiss National Science Foundation, Grant/Award Number: PP00P3_211025 and 201369

Handling Editor: Alessio Aghemo

Abstract

Background and Aims: A high prevalence of hepatitis delta virus (HDV) infection, the most severe form of viral hepatitis, has been reported among persons living with HIV (PLWH) in Europe. We analysed data from a large HIV cohort collaboration to characterize HDV epidemiological trends across Europe, as well as its impact on clinical outcomes.

Methods: All PLWH with a positive hepatitis B surface antigen (HBsAg) in the Swiss HIV Cohort Study and EuroSIDA between 1988 and 2019 were tested for anti-HDV antibodies and, if positive, for HDV RNA. Demographic and clinical characteristics at initiation of antiretroviral therapy were compared between HDV-positive and HDV-negative individuals using descriptive statistics. The associations between HDV infection and overall mortality, liver-related mortality as well as hepatocellular carcinoma (HCC) were assessed using cumulative incidence plots and cause-specific multivariable Cox regression.

Results: Of 2793 HBsAg-positive participants, 1556 (56%) had stored serum available and were included. The prevalence of HDV coinfection was 15.2% (237/1556, 95%

*EuroSIDA and SHCS groups listed in acknowledgments.

confidence interval [CI]: 13.5%–17.1%) and 66% (132/200) of HDV-positive individuals had active HDV replication. Among persons who inject drugs (PWID), the prevalence of HDV coinfection was 50.5% (182/360, 95% CI: 45.3%–55.7%), with similar estimates across Europe, compared to 4.7% (52/1109, 95% CI: 3.5%–5.9%) among other participants. During a median follow-up of 10.8 years (interquartile range 5.6–17.8), 82 (34.6%) HDV-positive and 265 (20.1%) HDV-negative individuals died. 41.5% (34/82) of deaths were liver-related in HDV-positive individuals compared to 17.7% (47/265) in HDV-negative individuals. HDV infection was associated with overall mortality (adjusted hazard ratio 1.6; 95% CI 1.2–2.1), liver-related death (2.9, 1.6–5.0) and HCC (6.3, 2.5–16.0).

Conclusion: We found a very high prevalence of hepatitis delta among PWID across Europe. Among PLWH who do not inject drugs, the prevalence was similar to that reported from populations without HIV. HDV coinfection was associated with liver-related mortality and HCC incidence.

KEYWORDS
HCC, Hepatitis Delta, HIV, PLWH, prevalence

1 | INTRODUCTION

Approximately 5%–10% of individuals with hepatitis B surface antigen (HBsAg) are coinfected with the hepatitis delta virus (HDV), totalling 15–30 million people worldwide.[1] The prevalence of HDV coinfection varies considerably across clinical settings, geographic areas and the constellation of risk factors within study populations.[2] However, epidemiological data on HDV infection among persons living with HIV (PLWH) remain limited as the uptake of routine testing is generally suboptimal due to the lack of awareness, issues with standardizing diagnostic techniques and limited treatment options.[3–5] Despite the large-scale implementation of hepatitis B virus (HBV) vaccination programs, the prevalence of HDV infections has yet to decrease in Europe, with most new cases being diagnosed in migrants from highly endemic regions.[6] In HIV/HBV-coinfected persons, the prevalence of HDV infection seems to be higher than among HBV-monoinfected populations. Ten years ago, Soriano and colleagues reported a prevalence of 14% in a selected sample of 422 individuals with HIV and HBsAg across Europe, and even higher estimates were reported in sub-Saharan Africa (SSA), reaching, for example, 25% in Guinea Bissau.[7,8]

Hepatitis delta is the most severe form of viral hepatitis: a faster progression to liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) has been described in populations with and without HIV.[9,10] Whereas the magnitude of HDV replication seems to be an important driver of morbidity, few studies have assessed the impact of clinical and virological characteristics on mortality and liver-related outcomes in large and representative cohort studies.[11,12] We aimed to describe the main epidemiological characteristics of HDV coinfection in a large European HIV cohort collaboration and to evaluate its impact on clinical outcomes.

Key points

- Close to 50% of PWID had anti-HDV antibodies, of whom 65% had active replication. Among other participants, the prevalence of HDV infection was close to estimates reported in populations without HIV, with the highest estimates observed in southern Europe.
- Over a median of 10.8 years, HDV-infected individuals were 1.6 times more likely to die, this excess mortality being driven by liver-related deaths in individuals with active HDV replication.
- HDV-infected individuals were also six times more likely to develop HCC compared to HDV-negative ones.
- These results highlight the importance of HDV screening of all HIV/HBV-coinfected patients, emphasize the need for the close monitoring of HDV-infected patients and underline the importance of developing and evaluating new treatments for chronic hepatitis delta.

2 | PARTICIPANTS AND METHODS

2.1 | Study population

Two large prospective cohort studies contributed to this work. All participants from the Swiss HIV Cohort Study (SHCS) and EuroSIDA with a positive HBsAg test between January 1988 and December 2019 were considered. The SHCS (www.shcs.ch) is an ongoing nationally representative cohort study established in 1988.[13] It

includes >21 000 participants, close to 80% of all PLWH receiving antiretroviral therapy (ART) who are followed in one of the five university hospitals, two regional hospitals, 15 affiliated hospitals or by one of 36 private physicians in Switzerland. The EuroSIDA study is a prospective observational cohort of almost 23 000 PLWH who were enrolled from 1994 onwards and followed across 100 hospitals in 35 European countries plus Israel and Argentina (https://www.chip.dk/Portals/0/files/Eurosida/EuroSIDA/EuroSIDA_Protocol_v4_2019JULI05.pdf?ver=2019-10-02-145631-730).[14] Laboratory values, socio-demographic and clinical data are prospectively recorded at registration, and every 6–12 months thereafter using standardized protocols (http://shcs.ch/292-instructions) (http://www.chip.dk/Ongoing-Studies/EuroSIDA/About). Local and/or national ethical committees approved the cohort studies, and all participants provided written informed consent.

2.2 | Definitions and outcomes

Our main outcome was the prevalence of HDV infection in different parts of Europe (Northern/Western, Southern and Eastern Europe). We defined infection by anti-HDV-positive serology. For individuals with data on HDV infection, we used the most recent test to define infection status. For individuals without data on HDV infection, we screened for HDV antibodies in the last available stored serum sample, which was used to define infection status. We assumed that all individuals had the same infection status during follow-up. We excluded individuals without data on HDV infection or stored samples from analysis. In individuals with a positive HDV serology, we quantitatively assessed HDV RNA from the same sample, or the first available sample after anti-HDV antibodies were detected.

We estimated the rates of the following long-term clinical outcomes: (i) overall mortality (ii) HCC and (iii) liver-related deaths. The latter included deaths from chronic viral hepatitis, cirrhosis, HCC, acute liver failure and variceal bleeding, as coded in ICD-10. In the SHCS and EuroSIDA, data on causes of death are collected on standardized case-report forms, using reports from medical hospitalizations to inform and validate the diagnosis.

2.3 | Laboratory analyses

A competition ELISA test (ETI-AB-DELTA-2TM, Diasorin) was used to screen for anti-HDV antibodies in all HBsAg-positive individuals. All analyses were performed according to the manufacturer's instructions and the results were considered positive when the optical density (OD) was <0.9. For HDV amplification, total nucleic acids were purified from 200 LL plasma (Qiagen EZ1 DSP kit) and cDNA (High Capacity cDNA Reverse Transcription Kit, Applied BiosystemsTM) was subjected to real-time polymerase chain reaction (PCR) according to Ferns et al., with minor modifications.[15] The detection limit of HDV real-time PCR was 1000 genome equivalents per ml of plasma. HBV-DNA was quantified with the COBAS_ TaqMan_ HBV Test v2.0 on the COBAS AmpliPrep/TaqMan48 system (Roche Diagnostics International AG, Rotkreuz, Switzerland) according to the manufacturer's protocol.

2.4 | Statistical analyses

Demographic and clinical characteristics at initiation of ART were described using proportions for categorical data, medians and interquartile ranges (IQR) for continuous data and were compared between HIV/HBV- and HIV/HBV/HDV-coinfected participants using Chi-square test (or variations thereof) or the Mann–Whitney U test. The prevalence of HDV infection was given with a 95% confidence interval (CI) and reported for the three different European regions and across different HIV transmission groups (men having sex with men [MSM], persons who inject drugs [PWID] and heterosexuals). Individual follow-up started at date of ART initiation and ended on the date of death, loss to follow-up or database closure (31.12.2019), whichever occurred first. Plots of the Kaplan–Meier and Aalen-Johansen (competing risk) estimators, along with the associated log rank and Grey's test, respectively, were used to compare the survival functions for overall and liver-related mortality, as well as for HCC-free survival between groups. For the endpoints HCC and liver-related mortality, non–liver-related mortality was treated as a competing risk. Furthermore, the association between HDV infection and the main outcomes was explored using a multivariable Cox proportional hazards (CPH) model, adjusted for baseline age, sex, CD4 cell count, person having an AIDS defining disease (prior to or at baseline), most likely source of HIV transmission and geographical origin. We fitted cause-specific models in which non–liver-related mortality was handled as a censoring event for the endpoints HCC and liver-related mortality. We performed several supplementary analyses, including the comparison of demographic and clinical characteristics, between individuals tested in routine clinical care or on samples, as well as the comparison of outcomes between HDV RNA-positive individuals with the rest of the cohort (i.e. HDV-negative and those HDV-positive but with undetectable HDV RNA). Unlike other analyses in EuroSIDA for which follow-up started at cohort inclusion, we used ART initiation as baseline date because this allowed harmonization across cohorts and consideration of maximal observation time. However, as this type of left-truncation could introduce immortal time bias, we repeated our main analyses using cohort entry as baseline date for longitudinal analyses. All statistical analyses were performed using R version 3.6.1.

3 | RESULTS

3.1 | HDV Prevalence

Of 2793 HBsAg-positive participants, 1556 (56%) had either been tested during routine care or had a stored serum available for HDV serology and were included. Demographic characteristics where similar in participants included and those not included in the analysis

(Table S1). The overall prevalence of anti-HDV positivity was 15.2% (237/1556, 95% CI 13.5%–17.1%) and was similar in the SHCS (15%) and EuroSIDA (15.5%). Anti-HDV antibody positive prevalence was 50.5% (182/360, 95% CI: 45.3%–55.7%) among persons who inject drugs (PWID, 48.9% [95% CI 42.5%–55.3%] in North-western Europe, 50.1% [95% CI: 37.5%–64.4%] in Southern Europe and 55.6% [95% CI 44.0%–67.0%] in Eastern Europe, p = 0.6), and 4.7% (52/1109, 95% CI 3.5%–5.9%) among other participants (4.5% [95% CI 3.2%–5.8%] in North-western Europe, 8.1% [95% CI 1.3%–14.8%] in Southern Europe and 3.7% [95% CI 0.0%–8.7%] in Eastern Europe, p = 0.4, Figure 1). Overall, 66% (132/200) of anti-HDV-positive participants with available data had active HDV replication. The proportion of HDV-positive participants with HDV replication was similar in PWID (65.5%, 95% CI 58.2%–73.3%) and those other than PWID (64.4%, 95% CI 50.5%–78.4%).

In the SHCS 494/829 (59.6%) of the participants were tested in routine clinical care (Table S2). The prevalence of anti-HDV positivity was similar in those tested in routine clinical care (14.6%) compared to those tested retrospectively in samples (15.5%), and the proportion with HDV replication was also similar, with, respectively, 60% and 56%.

3.2 | Demographic and clinical characteristics

Table 1 summarizes the main characteristics of the study population at ART initiation, by HDV infection status. HDV-positive individuals were slightly younger (median 33 vs. 36 years), more likely to be PWID (76.8% vs. 14.3%) and to have a positive HCV serology (75.5% vs. 24.3%) compared to HDV-negative ones, whereas sex distribution was similar among both groups. The median alanine aminotransferase (ALT) level was higher (50 vs. 32 IU/L) and the thrombocyte count lower (147 vs. 196 G/L), in HDV-infected people. Among individuals with a positive HCV serology, only 40.5% (51/126) in the HDV-positive group had detectable HCV RNA compared to 69.4% (179/258) in the HDV uninfected group.

3.3 | Mortality and liver-related outcomes

During a median follow-up time of 10.8 years (IQR 5.6–17.8), 82 (34.6%) HDV-positive participants and 265 (20.1%) HDV-negative individuals died (log rank test, $p < .001$, Figure S1A). 41.5% (34/82) of the deaths were liver-related in HDV-positive individuals, compared to 17.7% (47/265) in HDV-negative individuals (Figure S1B). Fourteen (5.9%) HDV-positive individuals developed HCC compared to only 21 (1.6%) in those without HDV coinfection (Figure S1C). Treating non–liver-related death as a competing risk, the 10-year cumulative incidence of liver-related death was 0.12 (95% CI 0.07–0.17) in HDV-positive and 0.02 (95% CI 0.01–0.03) in HDV-negative individuals (Grey's test $p < .001$; Figure 2A,B), whereas the overall survival at 10 years was not significantly different between both groups (Grey's test $p = .3$). Cumulative incidence of HCC at 10 years was 0.04 (95% CI 0.01–0.07) in HDV-positive and 0.007 (95% CI

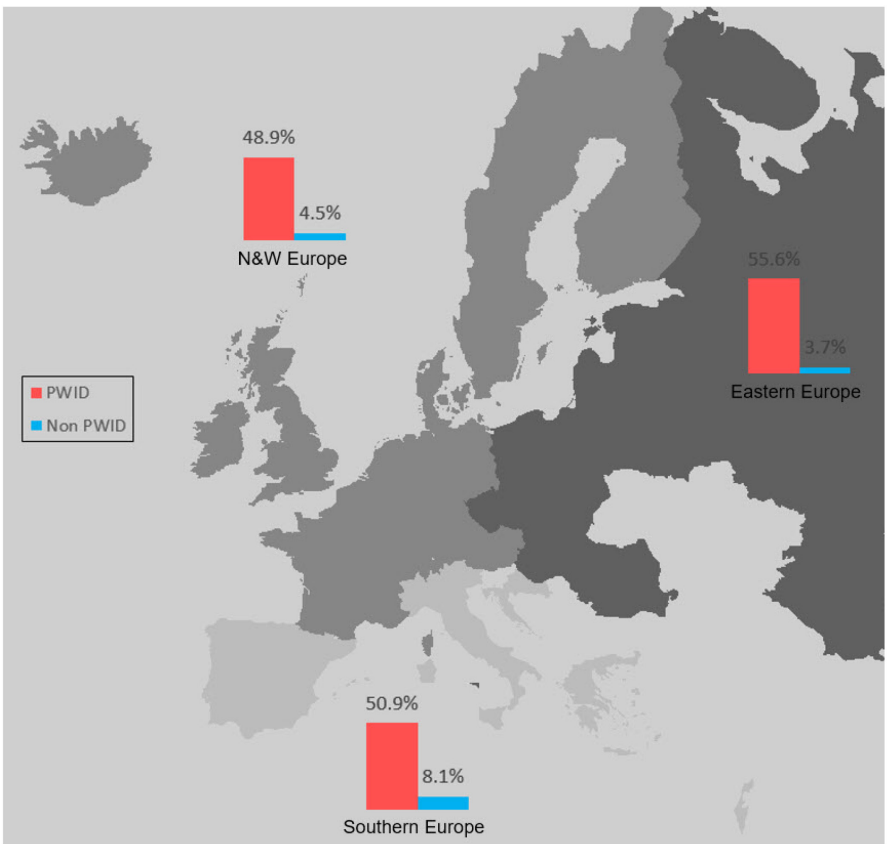

FIGURE 1 Prevalence of HDV among PLWH across the different European regions and according to HIV transmission group. Southern Europe: Croatia, Greece, Israel, Italy, Portugal, Spain; Eastern Europe: Belarus, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovakia; North-western Europe: Austria, Belgium, Switzerland, Denmark, Finland, France, Germany, Iceland, Ireland, Luxembourg, Netherlands, Sweden, United Kingdom.

TABLE 1 Demographic and clinical characteristics of participants at ART initiation, by HDV status

	HDV-positive	HDV-negative	*p*-value
N (%)	237 (15.2%)	1319 (84.8%)	—
Cohort			
Eurosida	113 (47.7)	614 (46.6)	
SHCS	124 (52.3)	705 (53.4)	
Age, median (IQR)	33 [28, 37]	36 [30, 43]	<.001
Female (%)	53 (22.4%)	243 (18.4%)	.2
HIV transmission group (%)			<.001
MSM	17 (7.2%)	681 (51.6%)	
PWID	182 (76.8%)	188 (14.3%)	
HET	32 (13.5%)	354 (26.8%)	
Other	3 (1.3%)	36 (2.7%)	
missing	3 (1.3%)	60 (4.5%)	
Geographical origin			<.001
Africa	21 (8.9)	208 (15.8)	
Asia	2 (0.8)	59 (4.5)	
Europe	211 (89.0)	940 (71.3)	
Latin America	0 (0.0)	66 (5.0)	
North Africa and the Middle East	1 (0.4)	16 (1.2)	
missing	*2 (0.8)*	*30 (2.3)*	
HIV RNA in $\log_{10}$ cp/ml, median (IQR)	4.3 [3.0, 5.0]	4.4 [2.9, 5.1]	.4
missing	8 (3.4%)	30 (2.3%)	
Prior AIDS (%)	71 (30.0%)	476 (36.1%)	.08
CD4 count, cells/μl, median (IQR)	218 [113, 338]	240 [105, 365]	.4
missing	2 (0.8%)	1 (0.1%)	
Median creatinine in μmol/L (IQR)	74.0 [65.7, 84.5]	79.0 [68.0, 90.0]	.001
missing	46 (19.4%)	192 (14.6%)	
Median thrombocyte count in G/L (IQR)	147.5 [106.0, 202.5]	196.0 [153.8, 247.0]	<.001
missing	13 (5.5%)	135 (10.2%)	
Median ALT in U/L (IQR)	50.0 [26.5, 89.0]	32.0 [19.0, 54.0]	<.001
missing	38 (16.0%)	125 (9.5%)	
Anti-HCV Ab positive (%)	179 (75.5%)	321 (24.3%)	<.001
Median HBV-DNA (IQR)	0 [0, 1210]	207 [0, 75712]	.002
missing	81 (34.0%)	391 (29.6%)	
HBV-DNA category (%)			.01
HBV-DNA <20 IU/mL	88 (37.1%)	427 (32.4%)	
HBV-DNA 20–2000 IU/mL	32 (13.5%)	174 (13.2%)	
HBV-DNA >2000 IU/mL	36 (14.2%)	327 (24.8%)	
missing	81 (34.2%)	391 (29.6%)	
HBV-active ART at time of HBV-DNA measurement (%)			
XTC	103 (43.5%)	711 (53.9%)	.004
TDF	54 (22.8%)	322 (24.4%)	.7
XTC + TDF	41 (17.3%)	275 (20.8%)	.3

Abbreviations: Ab, antibody; AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HET, heterosexual; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; PWID, persons who inject drugs; TDF, tenofovir disoproxil fumarate; XTC, lamivudine/emtricitabine.

0.002–0.011) in HDV-negative ($p < .001$, Figure 2C,D). In multivariable cause-specific Cox PH analyses, HDV infection was associated with overall mortality (adjusted hazard ratio [aHR] 1.8, 95% CI 1.3–2.5), liver-related death (aHR 3.1, 1.7–5.7) and the occurrence of hepatocellular carcinoma (aHR 6.3, 2.5–16.0, Figure 3 with details in Table S3a–c). In sensitivity analyses, results were similar after excluding PWID (Figure 3), or if baseline date was set at inclusion into the cohort instead of ART initiation.

Among HDV-positive individuals, 73% (52/63) of those who died, 84% (26/31) of those who died from liver-related death and 92% (12/13) of those who developed HCC had active HDV replication. In analyses comparing HDV RNA-positive individuals with the rest of the cohort (i.e. HDV-negative and those HDV-positive but with undetectable HDV RNA), the 10-year cumulative probability for both liver-related death (0.15, 95% CI 0.08–0.20) and HCC (0.06, 95% CI 0.01–0.11) were higher in HDV RNA-positive individuals. In multivariable analyses, active HDV replication was associated with overall mortality (aHR 1.8, 1.3–2.5), liver-related death (aHR 3.1, 1.7–5.7) and HCC occurrence (aHR 8.3, 3.0–22.7), similarly to the main analyses.

4 | DISCUSSION

In this large European cohort study of >1500 participants with HIV and HBV coinfection, close to 50% of PWID had anti-HDV

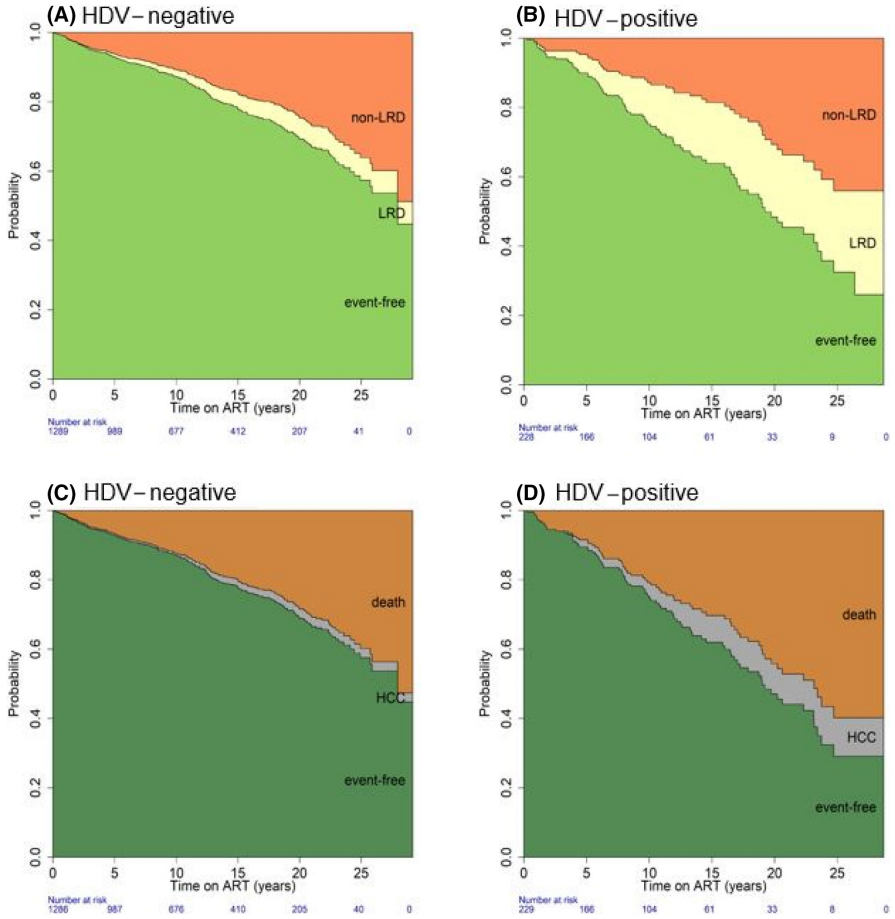

FIGURE 2 Aalen-Johansen-Meier survival analyses treating death as a competing risk, stratified by hepatitis D virus serological status: death and liver–related death (A, B) and death and hepatocellular carcinoma (C, D); number of patients at risk beneath the x-axis. ART, antiretroviral therapy; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; LRD, liver-related death.

antibodies, of whom 65% had active replication. Among other participants, the prevalence of HDV infection was close to estimates reported in populations without HIV, with the highest estimates observed in southern Europe. Over a median of 10.8 years, HDV-infected individuals were 1.6 times more likely to die, this excess mortality being driven by liver-related deaths in individuals with active HDV replication. HDV-infected individuals were also six times more likely to develop HCC compared to HDV-negative ones. Our results underline the importance of the systematic assessment of HDV infection among HBsAg-positive individuals and highlight the urgent need for improving treatment strategies to reduce the risk for HDV-related complications.

In our study, the prevalence of HDV infection among HIV/HBV-coinfected individuals in Europe was around 15%, in line with the results from a recently published meta-analysis.[16] Based on our results, HIV/HBV-coinfected individuals should be classified as a high-risk group for HDV infection, as suggested previously.[17] The high prevalence of HDV infection in our study was mainly driven by HIV/HBV-coinfected individuals who inject drugs, a sub-population in which more than one out of two persons are HDV-infected across Europe. In contrast, the prevalence of HDV coinfection in HIV/HBV-coinfected individuals who do not inject drugs was much lower, and thus much closer to the global estimated anti-HDV prevalence among HBsAg-positive individuals without HIV.[1,16] Injection drug use is a well-known route of transmission for HDV and probably the main one in high-income countries.[2,18] However, in countries with a substantial uptake of prevention programs, including HBV vaccination and needle and syringe exchange programs, the importance of injection drug use as a driver of HDV infection seems to be decreasing.[19] Other routes of transmission remain less clear, with specific sexual behaviours being suggested as one in a recent meta-analysis.[2] Data from Asia indicated an increased risk of HDV infection among commercial sex workers, whereas few studies showed a high prevalence in MSM.[19–22] However, data on sexual transmission are scarce and should be interpreted with caution.[1,23] In our study, the prevalence of HDV infection among PLWH who did not report to inject drugs was highest in southern Europe, in line with previous reports from Italy and Spain.[1]

HDV-positive individuals were 1.6 times more likely to die during follow-up than uninfected ones. This excess mortality was driven by liver-related deaths in individuals with active HDV replication. In HDV-positive individuals, 41.5% of the deaths were liver-related, compared to only 17.7% in HDV-negative individuals, resulting in a 3-fold risk increase. Whereas all studies tend to show a higher mortality in HBV/HDV-coinfected individuals compared to those only infected with HBV, data are still limited among PLWH.[7,11] Sheng and colleagues found that HBV/HDV-coinfected individuals were 5 times more likely to die than HBV-infected ones in a case–control with 26 HDV-infected individuals.[24] Fernandez-Montero and colleagues found that individuals with HDV coinfection were 7.5 times

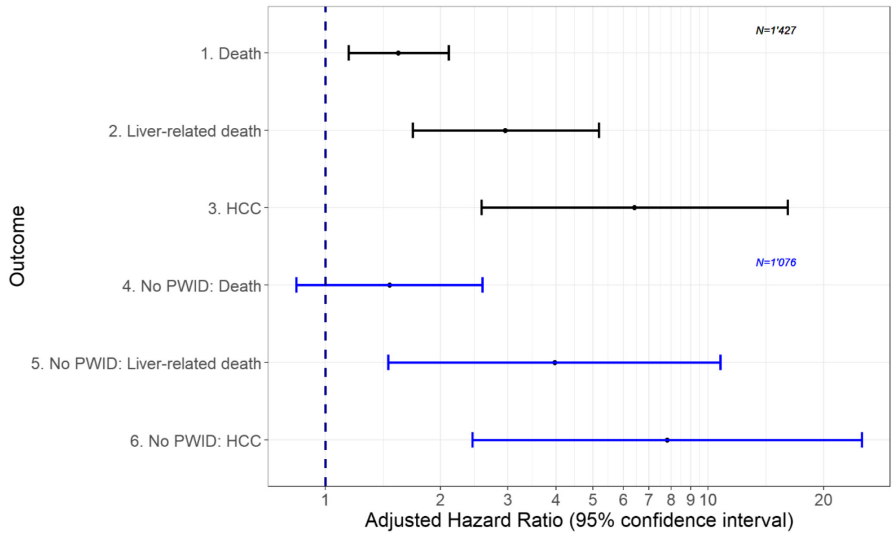

FIGURE 3 Forest plot of hazard ratios (HDV-positives compared to HDV-negatives) for the main outcomes; adjusted for age, sex, CD4 cell count, prior AIDS infection, stage of HIV infection, most likely source of HIV transmission and geographical origin; all participants (outcomes 1, 2, 3) and without PWID (outcome 4, 5, 6).[4–6] HCC hepatocellular carcinoma; HR hazard ratio; LRD liver-related death; PWID people who inject drugs. Univariable and multivariable estimates for death, LRD and HCC - refer to Table S4; subgroup analysis excluding PWID ('no PWID'): Death (univariable HR 1.69, 95% confidence interval [0.98, 2.91], $p = .06$/adjusted HR (aHR) 1.47 [0.84, 2.57], $p = .2$), LRD (aHR 3.56 [1.38, 9.15], $p = .008$/aHR 3.97 [1.46, 10.76], $p = .007$); HCC (HR 5.62 [1.87, 16.84], $p = .002$/aHR 7.80 [2.42, 25.19], $p < .001$).

more likely to develop liver decompensation or die.[10] These high estimates could be explained by the small and selected samples size in the first study and by the composite endpoint of decompensation and death in the second one.[3,25]

It has been postulated that the strong associations between HDV infection and adverse outcomes in studies from PLWH could be partially explained by the high proportion of individuals on HBV-active ART. Nucleoside analogues efficiently suppress HBV replication and reduce the risk of liver-related complications among HIV/HBV-coinfected individuals without delta infection, whereas they probably have no effect on HDV replication, thus increasing the gap in clinical events between the two groups.[26] Recently, Kamal and colleagues confirmed the impact of HDV viremia on liver-related outcomes and found that liver-related events were 3.8 more likely to occur in HIV-uninfected individuals with active HDV replication compared to those without replication.[12] In our study, two thirds of HDV-positive individuals had HDV replication, in line with several previous studies among PLWH, and there was no significant difference between PWID and the rest of the population. Our HDV replication estimates are also concordant with findings among HIV-uninfected populations, as shown in recent studies from Sweden and Spain.[12,27] Among HDV-positive individuals who died from a liver-related cause, 84% had active HDV replication. The 10-year cumulative probability of liver-related death in patients with HDV replication was 15% compared to only 2% in the rest of the individuals. We did not have data on liver decompensation but found that patient with replicating HDV were 3.8 times more likely to experience liver-related death, reflecting an even higher liver-related mortality in our study.

The cumulative incidence of HCC in our study was 10 times higher in HDV-positive compared to HDV-negative individuals and all but one HDV-infected patient who had HCC had active HDV replication. Fattovich and colleagues found a 3-fold increase in HCC incidence among HDV-coinfected individuals among HBV cirrhotics.[25] In non-HIV infected individuals, Romeo and colleagues and more recently, Kamal and colleagues showed a higher risk of developing HCC in individuals with ongoing HDV replication compared to HBV-monoinfected or HBV/HDV-coinfected individuals without replication.[9,12] Whether HDV has a direct carcinogenic activity or increases the risk of developing HCC though faster progression to liver cirrhosis is still debated.[28] This is partly due to the fact that most studies on HDV are retrospective, had short follow-up periods and few participants.[29,30]

We analysed the prevalence of HDV infection in PLWH in Europe and studied its impact on clinical outcomes in one of the largest cohort of HIV/HBV-coinfected individuals with optimal ascertainment of causes of death and clinical events. Although the Eastern European region was under-represented, we provide some of the first data on HDV infection among a sample population representative of the whole of Europe, including data on viral replication. As we only performed HDV serology and viral loads at one time-point we were not able to calculate the incidence of new infections and to describe epidemiological trends. HDV RNA measurement was only available in 66% of anti-HDV-positive participants and we had no data on HDV specific treatment. Based on previous studies we assumed that participants were infected with HBV/HDV prior to HIV; however, we cannot exclude incident HDV infections, which could have led to an underestimation of the burden of HDV infection. Information on HBV viral load, as well as on HBV and HDV genotypes, were only available for a limited number of individuals and could, therefore, not be included in our analyses. We did not have

data on liver fibrosis progression over time and could, therefore, not assess the impact of baseline liver disease severity on liver-related outcomes.

In conclusion, we found a very high prevalence of hepatitis delta among HIV/HBV-coinfected individuals who inject drugs across Europe. In PLWH who do not inject drugs, the prevalence varied across regions and was similar to that of HIV-uninfected populations. Replicating HDV infection was associated with increased liver-related mortality and HCC, which highlights the importance of the systematic screening of HDV infection among HBsAg-positive PLWH. Individuals with ongoing HDV replication should be followed closely, including with HCC screening. Without improvements in the efficacy of HDV therapy, prevention strategies including HBV vaccination, needle exchange and opioid substitution programs remain the most important interventions for reducing the burden of liver disease related to HDV infection.

ACKNOWLEDGEMENTS

We thank all participants, physicians and nurses associated with the SHCS and EuroSIDA. Open access funding provided by Inselspital Universitatsspital Bern.

The SHCS: The members of the SHCS are Abela I., Aebi-Popp K., Anagnostopoulos A., Battegay M., Bernasconi E., Braun D. L., Bucher H. C., Calmy A., Cavassini M., Ciuffi A., Dollenmaier G., Egger M., Elzi L., Fehr J., Fellay J., Furrer H., Fux C. A., Günthard HF (President of the SHCS), Hachfeld A., Haerry D (deputy of 'Positive Council'), Hasse B., Hirsch H. H., Hoffmann M., Hösli I., Huber M., Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L., Keiser O., Klimkait T., Kouyos R. D., Kovari H., Kusejko K (Head of Data Centre), Martinetti G., Martinez de Tejada B., Marzolini C., Metzner K. J., Müller N., Nemeth J., Nicca D., Paioni P., Pantaleo G., Perreau M., Rauch A. (Chairman of the Scientific Board), Schmid P., Speck R., Stöckle M. (Chairman of the Clinical and Laboratory Committee), Tarr P., Trkola A., Wandeler G., Yerly S.

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FUNDING INFORMATION

Swiss National Science Foundation (SNF); NEAT-ID Foundation; European Union's Seventh Framework Programme for Research, technological development and demonstration under EuroCoord grant agreement no 260694; Unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp and Dohme, Gilead Sciences.

CONFLICT OF INTEREST

This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant #201369) and by the SHCS research foundation. EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement no 260694. Current support includes unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp and Dohme, Gilead Sciences. GW was supported by a Professorship from the Swiss National Science Foundation [PP00P3_211025]. CB was supported by the NEAT-ID Foundation. The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. They declared further conflicts of interest outside the submitted work using the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Béguelin C, Atkinson A, Boyd A, et al. Hepatitis delta infection among persons living with HIV in Europe. *Liver Int*. 2023;43:819-828. doi:10.1111/liv.15519