



Hepatitis delta-associated mortality in HIV/HBV-coinfected patients

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Background & Aims: Hepatitis delta virus (HDV) infection accelerates the progression of hepatitis B virus (HBV)-related liver disease. We assessed the epidemiological characteristics of HDV infection in the nationwide Swiss HIV Cohort Study and evaluated its impact on clinical outcomes.

Methods: All HIV-infected patients with a positive hepatitis B surface antigen test were considered and tested for anti-HDV antibodies. HDV amplification and sequencing were performed in anti-HDV-positive patients. Demographic and clinical characteristics at initiation of antiretroviral therapy, as well as causes of death were compared between HDV-positive and HDV-negative individuals using descriptive statistics. Kaplan-Meier and multivariable Cox regression analyses were used to evaluate the association between HDV infection and overall mortality, liver-related mortality as well as incidence of hepatocellular carcinoma (HCC).

Results: Of 818 patients with a positive hepatitis B surface antigen tests, 771 (94%) had a stored serum sample available and were included. The prevalence of HDV infection was 15.4% (119/771, 95% CI: 12.9–18.0) and the proportion of HDV-positive patients with HDV replication 62.9% (73/116). HDV-infected patients were more likely to be persons who inject drugs (60.6% vs. 9.1%) and to have a positive hepatitis C virus (HCV) serology (73.1% vs. 17.8%) compared to HDV-uninfected ones. HDV infection was strongly associated with overall death (adjusted hazard ratio 2.33, 95% CI 1.41–3.84), liver-related death

(7.71, 3.13–18.97) and with the occurrence of HCC (9.30, 3.03–28.61). Results were similar when persons who inject drugs or HCV-coinfected patients were excluded from the analyses.

Conclusions: The prevalence of HDV in hepatitis B surface antigen-positive patients in the Swiss HIV Cohort Study (SHCS) is high and HDV infection is independently associated with mortality and liver-related events, including HCC.

Lay summary: Hepatitis delta virus (HDV) infection accelerates the progression of hepatitis B virus (HBV)-related liver disease. In a nationwide cohort of HIV-infected individuals in Switzerland, 15% of HBV-coinfected patients had antibodies to HDV infection, of which a majority had active HDV replication. HDV-infected individuals were 2.5 times more likely to die, eight times more likely to die from a liver-related cause and nine times more likely to develop liver cancer compared to HDV-uninfected ones. Our results emphasize the need for prevention programs (including HBV vaccination), the systematic screening of at risk populations as well as close monitoring, and underline the importance of developing new treatments for chronic HDV infection.

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Introduction

Worldwide, 15–20 million people are infected with hepatitis delta virus (HDV), with the highest prevalence reported in regions endemic for hepatitis B virus (HBV) infection, such as Eastern and Mediterranean Europe, Sub-Saharan Africa (SSA) and parts of Asia [1,2]. It is estimated that 5–20% of HBV-infected individuals have serological evidence of exposure to HDV [3]. However, data on the prevalence of HDV in HIV/HBV-coinfected patients are scarce. Of a selected sample of 422 hepatitis B surface antigen (HBsAg) carriers in the EuroSIDA collaboration, 61 (14%) were coinfecting with HDV [4]. The

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prevalence of anti-HDV antibodies is even higher in HIV/HBV-coinfected patients from SSA, reaching 25% in Guinea-Bissau [5]. Although the prevalence of HDV infection may be decreasing in some regions, probably due to HBV preventive measures [6], this is not the case in Northern Europe. Most cases from this region are now diagnosed in young migrants from other endemic regions [2].

HDV accelerates the course of HBV-related liver disease, including the progression to liver cirrhosis, hepatic decompensation and possibly hepatocellular carcinoma (HCC) [7,8]. In HIV-infected patients, the presence of HDV-coinfection has been associated with a higher incidence of hepatic flares and decompensation as well as an increased mortality [9,10]. However, most studies assessing the impact of HDV on long-term outcomes in HIV/HBV-coinfected individuals have been limited by small sample sizes, highly selected study populations, short follow-up periods or by a retrospective design. Although most HIV/HBV/HDV-coinfected patients now experience HBV virological suppression on tenofovir disoproxil fumarate (TDF)-containing antiretroviral therapy (ART), its impact on HDV replication remains controversial [11,12].

In this study, we aimed to describe the main epidemiological characteristics of HDV infection and to evaluate its impact on clinical outcomes in the Swiss HIV Cohort Study (SHCS) [13]. The systematic ascertainment of causes of death and liver-related complications in the SHCS allowed us to perform a detailed assessment of liver-related outcomes in a nationwide representative cohort of HIV/HBV-coinfected individuals.

Patients and methods

Swiss HIV Cohort Study

The SHCS (www.shcs.ch) is a prospective cohort study with ongoing enrollment of HIV-infected adults in Switzerland since 1988 [13]. It includes 73% of all diagnosed HIV-infections in Switzerland [14]. Representation has remained stable throughout the study duration. Detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events, coinfections, and treatment is collected using a standard protocol at registration and at intervals of 6 months. Plasma samples are collected every 6–12 months in all study participants. Local ethical committees of all participating study sites approved the study and written consent was obtained from all participants.

Inclusion criteria, definitions and outcomes

All HIV-infected adults with a positive HBsAg test between January 1988 and December 2014 were considered. We performed a screening HDV serology in all patients without information on HDV infection in the database and excluded patients without available stored samples from our analysis. This measurement was performed on the stored serum samples drawn closest to the diagnosis of HBV infection. In all individuals with a positive HDV serology, we quantitatively assessed HDV RNA in the same sample, or the first available sample after the positive HDV serology. To rule out false-positive HDV screening results, we performed a second anti-HDV serology test in all patients with negative HDV RNA. Patients with false-positive HDV screening results were re-classified as HDV-negative.

Our primary outcome was overall mortality after the initiation of ART. Individual follow-up started at initiation of ART and ended on the date of death, loss to follow-up or database closure (31.12.2014), whichever occurred first. The secondary outcomes were: development of i) HCC and ii) liver-related death, which included death from chronic viral hepatitis, cirrhosis, HCC, acute liver failure and variceal bleeding, as coded in ICD-10. In the SHCS, data on causes of death are collected on standardized case-report forms, using reports from medical hospitalizations to inform and validate the diagnosis (<http://shcs.ch/user->

[files/file/documents/CODE.pdf](#)). Patients who did not initiate ART, defined as a combination of at least three antiretroviral drugs, were excluded from the longitudinal analyses.

Laboratory analyses

A competition ELISA test (ETI-AB-DELTA-2™, Diasorin, Saluggia, Italy) 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 µl plasma (Qiagen EZ1 DSP kit) and cDNA (High Capacity cDNA Reverse Transcription Kit, Applied Biosystems™) 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. The HDV genotype was assessed by sequencing and phylogenetic analysis of a 260-base-pair cDNA fragment encompassing the 3' end of the hepatitis D antigen coding region. A second serological ELISA test with a sensitivity and specificity >98% (HDV-Ab™ kit, Diapro, Milan, Italy, performed with an ETI-Max [DiaSorin] platform) was used to confirm the anti-HDV screening results from all samples with a positive screening serology but negative HDV RNA. A result was considered negative when the ratio (threshold/OD) was <0.9. Plasma samples were diluted 1:1 with plasma and HBV 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. HBV Genotyping was performed by PCR amplification, Sanger sequencing and subsequent *in silico* analysis by the geno2pheno tool (<http://hbv.geno2pheno.org/index.php>) as described by Hirzel *et al.* [16]. The quantitative determination of HBsAg was analyzed with a fully automated chemiluminescent microparticle immunoassay (Architect, Abbott Diagnostics, USA). The Architect HBs Ag Assay has a sensitivity of ≤0.05 IU/ml.

Statistical analyses

The prevalence of HDV infection among all HIV/HBV-coinfected individuals was estimated after the re-classification of false-positive results and given with a 95% confidence interval (CI). Demographic and clinical characteristics at initiation of ART were described using absolute numbers and proportions, or medians and interquartile ranges (IQR), and compared between HIV/HBV- and HIV/HBV/HDV-coinfected patients using Chi-square, Fisher's exact or Mann-Whitney *U* test, where appropriate. Kaplan-Meier analyses and the rank-sum tests were used to compare overall and liver-related mortality as well as HCC-free survival between study groups. The association between HDV infection and the main outcomes was further explored using multivariable Cox regression analyses adjusted for age, sex, CD4 cell count, stage of HIV infection, most likely source of HIV transmission and hepatitis C virus (HCV) coinfection.

We performed several sensitivity analyses and repeated the main analysis, comparing HIV/HBV/HDV RNA negative and HIV/HBV/HDV RNA positive patients. The association between HDV infection and the main outcomes after the exclusion of persons who inject drugs (PWID) and patients with a positive HCV serology was evaluated. As these two categories of patients are more likely to have multiple comorbidities and to die during follow-up, their over-representation in the HDV-positive group could have had an important impact on our results. TDF treatment was used as a proxy for HBV suppression, as longitudinal data on HBV replication were lacking. The association between HDV infection and the main outcomes, after the exclusion of persons who had never been treated with TDF, was evaluated. All statistical analyses were performed using Stata version 13.1. (StataCorp 2012, Stata Statistical Software, College Station, TX, USA).

Results

HDV prevalence

Of 818 patients with a positive HBsAg, 771 (94%) had an HDV serology performed, either during routine care (422/771) or from a stored serum sample (349/771) (Fig. 1). Overall, 139 patients (18%) had a positive HDV screening serology, of which 122 had a sample available for amplification. Seventy-three patients (59%) examined by PCR had a detectable HDV RNA. After the

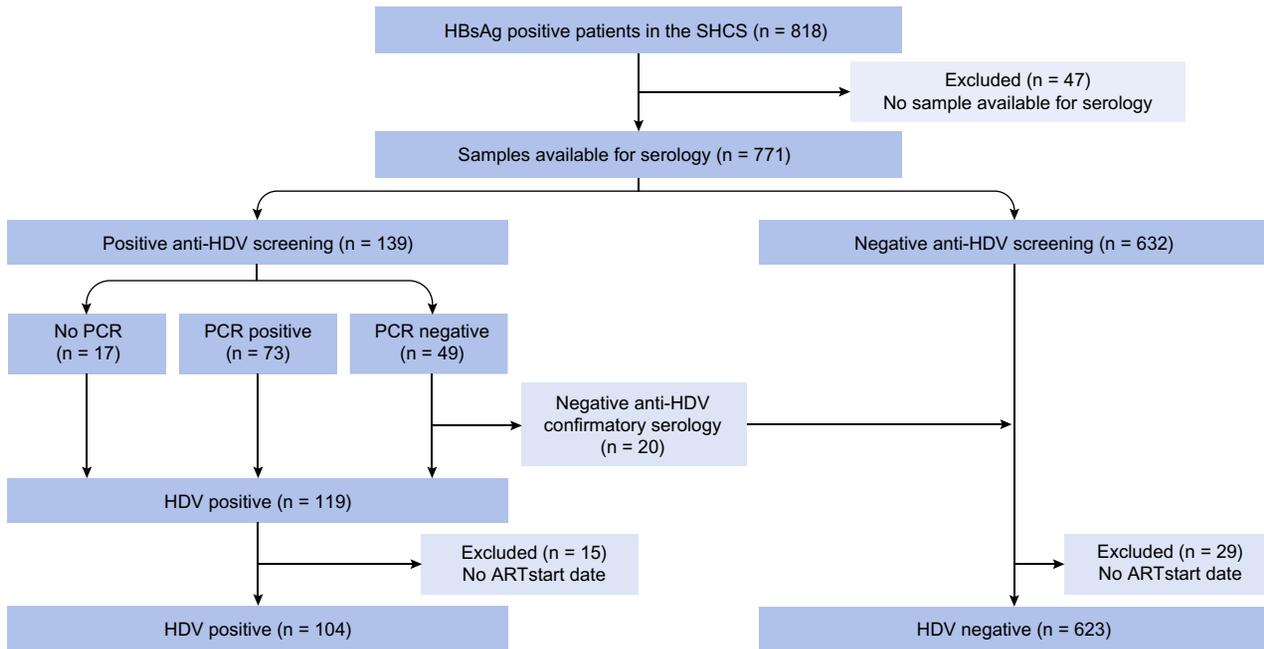


Fig. 1. Patient flowchart. HDV, hepatitis D virus; PCR, polymerase chain reaction; ART, antiretroviral therapy.

re-classification of 20 patients with a positive HDV screening test but negative viral load and negative confirmation anti-HDV tests, the prevalence of HDV infection was 15.4% (119/771, 95% CI: 12.9–18.0) and the proportion of HDV-positive patients with HDV replication 62.9% (73/116). Of 70 patients with available results from HDV sequencing, 66 (94.3%) were infected with genotype 1 and four (5.7%) with genotype 5.

Characteristics of HDV infection

Fifteen (12.6%) patients from the HDV-positive group and 29 (4.5%) from the HDV-negative group never started ART during follow-up and were excluded from the longitudinal analyses. **Table 1** summarizes the main characteristics of the study population at ART initiation, by HDV infection status. Whereas age and sex distribution were similar across both groups, HDV-positive individuals were more likely to be PWID (60.6% vs. 9.1%) and to have a positive HCV serology (73.1% vs. 17.8%) compared to HDV-uninfected ones. Among individuals with a positive HCV serology, only 15/76 (20%) in the HDV-positive group had detectable HCV RNA compared to 67/111 (60%) in the HDV-uninfected group. In HIV/HDV/HDV-coinfected patients with replicating HDV, HCV RNA was suppressed in 90% of patients. Of the anti-HDV-positive patients, 34/74 (46%) had suppressed HBV DNA at the time of measurement and 75% of them were under an ART with at least one drug active against HBV. Compared to HDV-negative patients, patients coinfecting with HDV were more likely to have genotype D HBV infection. HDV RNA-positive patients were more likely to have a replicating HBV DNA and had higher quantitative HBsAg than HDV RNA-negative patients (**Supplementary Table 1**). The median CD4 cell count as well as the relative CD4 value were lower in HDV-infected (180 vs. 248 cells/ μ L and 19% vs. 24%) and the median alanine aminotransferase (ALT) level higher (61 vs. 33 IU/L) than in HDV-negative patients.

Mortality and liver-related outcomes

Thirty-six (34.6%) HDV-infected patients and 96 (15.4%) HDV-uninfected individuals died during 6718 patient-years (py) of follow-up. Median follow-up was 8.71 years (interquartile range [IQR]: 5.01–13.78) in the HDV-positive and 9.75 years (IQR: 4.71–15.27) in the HDV-negative group. Causes of death by HDV status are summarized in **Fig. 2**. One half of the deaths were liver-related (18/36) in HDV-infected patients (8 deaths from HCC and ten from decompensated liver disease), compared to 24.0% (23/96) in HDV-uninfected individuals (12 deaths from HCC and 11 from decompensated liver disease). Overall mortality was higher in HDV-infected patients (3.62 deaths per 100 py, 95% CI 2.59–5.07) compared to uninfected ones (1.49 per 100 py, 95% CI 1.20–1.84). Kaplan-Meier cumulative survival probability was significantly higher among HDV-negative patients ($p < 0.001$; **Fig. 3A**). The cumulative probability of liver-related deaths as well as HCC were significantly higher in HDV-positive patients compared to HDV-negative ones (both $p < 0.001$; **Fig. 3B, C**).

In multivariable analyses, HDV infection was strongly associated with overall death (adjusted hazard ratio [aHR] 2.33; 95% CI 1.41–3.84), with liver-related mortality (aHR 7.71; 95% CI 3.13–18.97), and with the occurrence of HCC (aHR 9.30; 95% CI 3.03–28.61, **Fig. 4** and **Supplementary Table 2**). The risk for non-liver-related deaths did not differ significantly between HDV-positive and -negative patients (aHR 1.36; 95% CI 0.72–2.57). In analyses comparing HDV RNA-negative and HDV RNA-positive patients, we found that the cumulative probability for overall death, liver-related death and HCC were significantly higher in HDV RNA-positive patients (**Fig. 3D–F**; **Supplementary Table 3**). In multivariable analyses, HDV replication was strongly associated with overall death (adjusted hazard ratio [aHR] 7.14; 95% CI 1.60–31.85), liver-related mortality and the occurrence of HCC. There were no liver-related deaths and no HCC in patients

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Table 1. Demographic and clinical characteristics of patients at ART initiation, by HDV status.

Characteristics	HDV-positive (N = 104)	HDV-negative (N = 623)	p value
Age, median (IQR)	34 (29–37)	36 (30–43)	<0.001
Male sex (%)	79 (76.0)	487 (78.2)	0.25
Region of origin (%)			0.01
Northwestern Europe	74 (71.1)	344 (55.2)	
Central and Eastern Europe	2 (1.9)	18 (2.9)	
Southern Europe (Mediterranean)	14 (13.5)	64 (10.3)	
Sub-Saharan Africa	13 (12.5)	131 (21)	
Southeast Asia	1 (1)	38 (6.1)	
Other	0 (0)	28 (4.5)	
Education level (%)			<0.001
No or low	49 (47.1)	187 (30)	
Medium	35 (33.6)	255 (40.9)	
High	7 (6.7)	150 (24.1)	
No information	13 (12.5)	31 (5)	
HIV transmission group (%)			<0.001
MSM	10 (9.6)	300 (48.1)	
PWID	63 (60.6)	57 (9.1)	
HET	17 (16.3)	217 (34.8)	
Other	14 (13.5)	49 (7.9)	
Median HIV RNA in log cp/ml (IQR)	4.6 (3.2–5.1)	4.7 (3.3–5.2)	0.70
CDC stage C (%)	34 (32.7)	191 (30.7)	0.17
Median CD4 count in cells/ μ L (IQR)	180 (96–314)	248 (120–358)	0.03
CD4 cell count category in cells/ μ L (%)			0.07
1–200	52 (50.5)	242 (40)	
201–350	33 (32)	201 (33.2)	
>350	18 (17.5)	162 (26.8)	
Median creatinine in μ mol/L (IQR)	71.5 (67–84)	75 (65–90)	0.68
eGFR in ml/min (IQR) [†]	103 (94–123)	109 (93–126)	0.80
Median hemoglobin in g/L (IQR)	13.8 (12.4–14.2)	14.1 (12.7–15.2)	0.11
Anemia (%) ^{**}			0.66
No	72 (75.8)	415 (76.4)	
Mild	16 (16.8)	100 (18.4)	
Moderate-severe	7 (7.4)	28 (5.2)	
Median thrombocytes in g/L (IQR)	158 (113–212)	206 (161–246)	<0.001
Median ALT in IU/L (IQR)	61 (36–90)	33 (23–59)	0.04
Anti-HCV positive (%)	76 (73.1)	111 (17.8)	<0.001

ART, antiretroviral therapy; HDV, hepatitis D virus; HBV, hepatitis B virus; IQR, interquartile range; HIV, human immunodeficiency virus; MSM, men who have sex with men; PWID, people who inject drugs; HET, heterosexual; CDC: Centers for Diseases Control; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; aspartate aminotransferase (AST), aspartate aminotransferase; HCV, hepatitis C virus; Ab: antibody; APRI: AST-to-platelet ratio index.

[†] eGFR: calculated with the CKD-EPI formula.

^{**} Anemia defined as follows: Mild: hemoglobin <13 g/L in males and <12 g/L in females. Moderate-severe: hemoglobin <11 g/L in males and <10 g/L in females.

that were HDV RNA-negative. Results were similar when PWID or HCV-infected individuals were excluded from the analyses (Fig. 4, Supplementary Fig. 1). In analyses stratified by viral hepatitis coinfection sub-group (HIV/HBV, HIV/HBV/HDV, HIV/HBV/HCV and HIV/HBV/HDV/HCV), overall survival was lowest in the two groups of HDV-infected individuals, independently of anti-HCV antibody status or replicating HCV infection (Supplementary Figs. 2 and 3). In analyses restricted to patients who had received TDF (77%), the point estimate of the association between HDV infection and overall death remained similar (aHR 2.03; 95% CI 0.80–5.15).

Discussion

The prevalence of HDV infection was high among HIV/HBV-coinfected individuals in Switzerland: 15% were antibody-

positive and 63% of them had detectable viral replication. Over nine years of individual follow-up on ART, HDV-infected patients were twice as likely to die as HDV-uninfected ones. The excess mortality in HDV-positive patients was driven by liver-related deaths: HDV-positive individuals were eight times more likely to die from liver disease and nine times more likely to develop an HCC compared to HDV-negative patients. These associations were robust, remaining similar in all sensitivity analyses.

The prevalence of HDV infection in our cohort was similar to the findings from the EuroSIDA collaboration but slightly higher than the estimate reported in cohort studies from France and North America [17,18]. As false-positive HDV screening results seem to be frequent in the setting of HIV-infection [19], we performed a confirmatory serology in all patients with a negative HDV RNA in order to strengthen our HDV prevalence estimate. In our study, 14% of positive HDV screening tests were false-positive. After the exclusion of these patients, 63% of

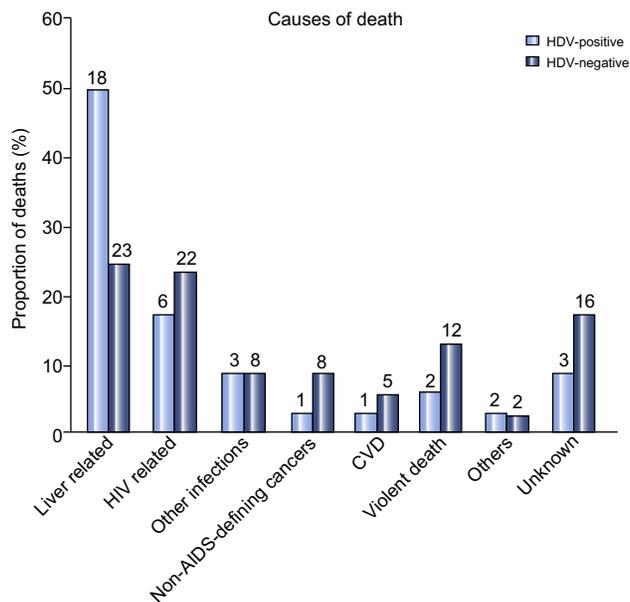


Fig. 2. Main cause of death, by hepatitis D virus (HDV) status. Absolute numbers of death are shown at the top of the bars. HIV, human immunodeficiency virus; CVD cardiovascular disease; HDV, hepatitis delta virus.

HDV-positive patients had a detectable HDV viral load, which was lower than the proportion found in the EuroSIDA study [4]. Although the main reason for this difference remains unclear,

the unselected nature of our study population, in which all patients were screened for HBV and HDV infection independently of clinical manifestations or laboratory abnormalities, might have played an important role. HDV-infected individuals were predominantly PWID of Western European origin, which explains the high proportion of HDV genotype 1 found in our cohort. As all remaining patients (6%) were HDV genotype 5-infected migrants from SSA diagnosed during the last five years, our results suggest a changing pattern in HDV epidemiology in Switzerland [2,20,21]. Injection drug use being the most probable route of HDV transmission for the majority of patients included in our study, HCV infection was also present in many of them. The complex interplay between HBV, HCV and HDV has been described in several previous reports which generally showed HDV to be the dominant virus, often leading to the suppression of HBV as well as HCV [17,22,23]. In line with these findings, only 20% of HIV/HBV/HDV-coinfected patients and 10% of HIV/HBV/HDV-coinfected patients with replicating HDV in our cohort had a replicating HCV infection compared to 60% of HDV-negative individuals. HCV-coinfection had no impact on overall survival in our study. Almost one half of HDV-positive patients had a suppressed HBV-viremia. Those with a replicating HDV were more likely to also have a replicating HBV as well as higher HBsAg titers.

HDV-positive individuals were 2.3 times more likely to die during follow-up on ART than uninfected ones. A detailed analysis of causes of death showed that this finding was driven by the excess liver-related mortality seen in HDV-positive individuals: 50% of HDV-positive patients died of liver disease, resulting in an 8-fold risk increase compared to HDV-negative patients. The

Analysis by HDV serological status



Analysis by HDV-RNA status in anti-HDV seropositive patients

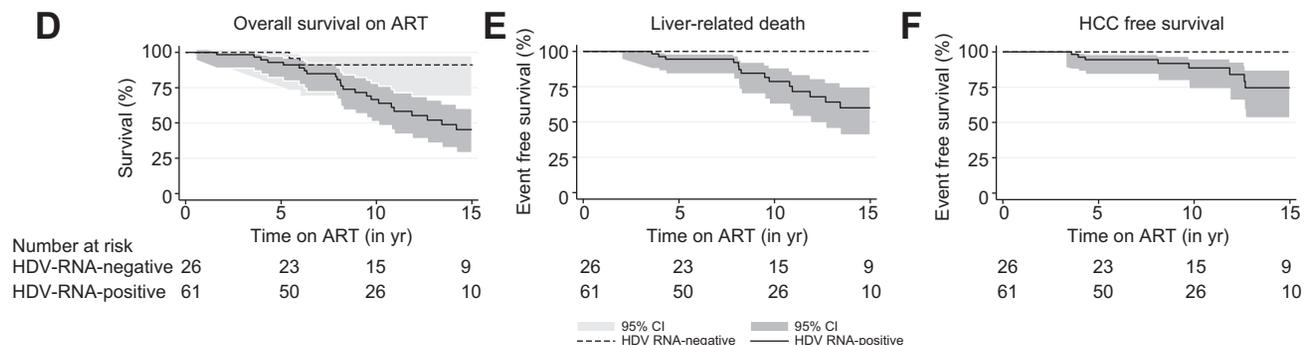


Fig. 3. Kaplan-Meier survival analyses. Data from hepatitis D virus (HDV) serological and replication status for overall survival (A, D), liver-related mortality (B, E) and hepatocellular carcinoma (HCC) free survival (C, F). ART, antiretroviral therapy; HDV, hepatitis D virus; CI, confidence interval; HCC, hepatocellular carcinoma.

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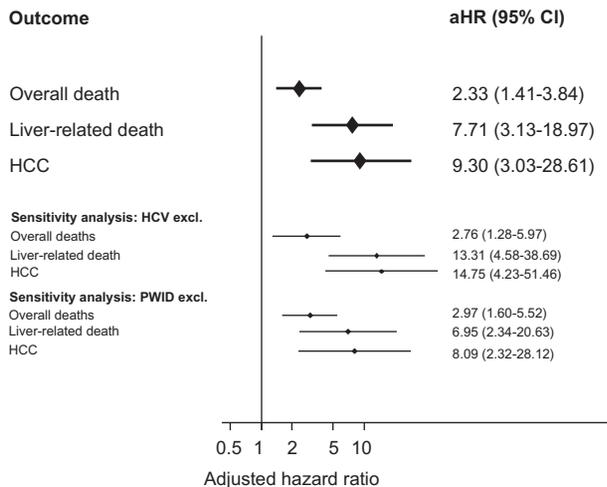


Fig. 4. Forest plot of hazard ratios (HDV-positives compared to HDV-negatives) for the main outcomes. Adjusted for age, sex, CD4 cell count, stage of HIV infection, most likely source of HIV transmission and hepatitis C virus (HCV) coinfection. aHR, adjusted hazard ratio; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PWID, people who inject drugs.

impact of HDV on overall and liver-related mortality was further demonstrated by the similar estimates obtained after the exclusion of HCV-infected patients and in analyses limited to patients with optimal HBV-therapy. In a case-control study among HIV-infected patients in Taiwan, Sheng *et al.* found that HBV/HDV-coinfected individuals were five times more likely to die than HBV-infected ones [10]. More recently, Fernandez-Montero *et al.* confirmed this finding and described an increase in liver-related mortality in HDV-positive individuals comparable to the estimate of the present study [9]. In our study the hazard of death, liver-related death and HCC was mainly driven by HDV RNA-positive patients. However, due to the low number of HDV-infected patients included in previous studies of HIV-positive individuals, data on the impact of HDV replication on liver-related outcomes and mortality are scarce.

HCC was diagnosed in 23 patients of which 20 died during the study period. HDV-positive individuals were nine times more likely to develop HCC as compared to HDV-uninfected HBV positive persons. Chronic HBV infection is the single most important risk factor of HCC worldwide [24–26], and this risk has been shown to correlate with HBV replication [27]. However, the impact of HDV on liver carcinogenesis and its contribution to global HCC epidemiology remains unclear. In cirrhotic HBV-infected patients, Fattovich *et al.* found a 3-fold increase in HCC incidence among HDV-infected patients, whereas similar rates of HCC were found in HBV- and HBV/HDV-infected patients in a retrospective study from London [20,28]. In Italy, Romeo *et al.* showed that persistent HDV replication was strongly associated with the development of HCC but no HIV-infected individuals were included [8]. To our knowledge, our study is the first to be powered to detect a difference in HCC incidence between HDV-infected and -uninfected HIV-positive individuals and calls for other cohorts to confirm these results.

We studied the impact of HDV infection on clinical outcomes in one of the largest studies of HIV/HBV-coinfected patients to date. Long individual follow-up time as well as the systematic ascertainment of death and liver-related complications allowed

us to provide robust estimates of liver-related mortality and HCC. Only very few patients were excluded from our analyses: HDV serology results were available for 94% of HBsAg-positive patients and 88% of HDV-positive individuals had an assessment of viral replication. Furthermore, the probability of false-positive results was substantially reduced by using confirmatory serologic tests. Unfortunately, information on HBV viral load and genotypes was only available for a limited number of patients, precluding its use in the main analyses. As there is a clear link between HBV viral load and liver-related outcomes such as HCC, our analyses do not provide the full picture of risk factors for liver disease. However, analyses which were restricted to patients on TDF, a good proxy for HBV suppression, showed results which were comparable to the main analyses. Although Su *et al.* showed worse outcomes in HBV genotype C than B in Taiwan, our results are unlikely to be affected by the HBV genotype distribution, as only 5% of our patients were of Asian origin [29]. The large difference in the proportion of PWID and HCV infections across both study groups was another limitation of our study, as these characteristics are known risk factors for mortality and liver-related morbidity. Again, sensitivity analyses showed that the association between HDV infection and the main outcomes were independent of these two cofactors. Finally, we only had information on HDV viral replication at one time-point for each patient and, as a consequence, might have misclassified patients as HDV RNA-negative despite potential subsequently detectable replication.

In conclusion, we found a high prevalence of hepatitis delta in HIV/HBV-coinfected individuals in Switzerland. The strong association between HDV infection and mortality as well as liver-related events, including HCC, highlights the importance of HDV screening of all HIV/HBV-coinfected patients. Our results emphasize the need for systematic screening for HDV infection, the close monitoring of HDV-infected patients and underline the importance of developing and evaluating new treatments for chronic hepatitis D. As potent treatment options for HDV are still lacking, preventing infections through the implementation of efficient HBV vaccination programs remains a cornerstone of the prevention of HDV infection. In persons with HDV-coinfection and end-stage liver disease (ESLD) or HCC, liver transplantation from an HBsAg-negative donor should be considered.

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Conflict of interest

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.

Authors' contributions

CB, AR and GW conceived and designed the study. CB and GW performed the statistical analyses. CB, AR and GW wrote the first draft of the manuscript. RS performed the molecular HDV analyses. All authors contributed to the acquisition and the interpretation of the data, critically revised the paper and approved its final version.

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The data from this study were gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in <http://www.shcs.ch/180-health-care-providers>). *Members of the Swiss HIV Cohort Study*. Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Weber R, Yerly S.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jhep.2016.10.007>.

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