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ORIGINAL ARTICLE

Determinants of worse liver-related outcome according to HDV infection among HBsAg positive persons living with HIV: Data from the ICONA cohort

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Abstract

Objectives: We aimed to study hepatitis D virus (HDV) prevalence and risk of progression to severe liver-related events (SLRE) in HBsAg positive people living with HIV (PLWH) in Italy; role of HDV-RNA copy levels, HCV coinfection and nadir CD4 counts were also investigated.

Methods: People living with HIV (PLWH) from Italian Foundation cohort Naïve antiretrovirals (ICONA) with available HBsAg and HDV Ab were enrolled. HBsAg,

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; ART, antiretroviral therapy; ARV, antiretroviral; aSHR, adjusted sub-hazard ratio; CI, confidence interval; CIF, comulative inceidence function; ESLD, end stage liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MSM, men who have sex with men; Neg, negative; PI, protease inhibitors; PLWH, people living with HIV; pos, positive; PWID, persons who inject drugs; PYFU, patient year follow-up; SHR, sub-hazard ratio; SLRE, severe liver related events.

Antonella d'Arminio Monforte and Alessandro Tavelli contributed equally to the manuscript.

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HDV Ab, HDV-RNA and HDV genotypes were tested. Primary end-point: time from first HDV screening to Severe Liver Related Events (SLRE: decompensated cirrhosis, liver transplantation, HCC). Fine-grey regression models were used to evaluate the association of HDV Ab, HDV-RNA, HDV/HCV coinfection, CD4 nadir and outcome. Secondary end-points: time to SLRE or death; HDV Ab and HDV-RNA prevalence.

Results: A total of 152/809 (18.8%) HBsAg positive PLWH showed HDV Ab reactivity; 63/93 (67.7%) were HDV-RNA positive. Being male, persons who inject drugs (PWID), HCV Ab positive, with FIB-4 > 3.25 were independent factors of HDV Ab positivity. In a median follow-up of 5 years, 37 PLWH (4.1% at 5-year) developed SLRE and 97 (12.0%) reached the SLRE or death end-point. HDV-RNA positive (independently from HDV-RNA copy level) PLWH had a 4.6-fold (95%CI 2.0–10.5) higher risk of SLRE than HDV negatives. PLWH positive for both HCV Ab and HDV Ab showed the highest independent risk of SLRE (ASHR: 11.9, 95%CI: 4.6–30.9 vs. HCV neg/HDV neg). Nadir CD4 < 200/mL was associated with SLRE (ASHR: 3.9, 95% 1.0–14.5).

Conclusions: One-fifth of the HBsAg positive PLWH harbour HDV infection, and are at high risk of progression to advanced liver disease. HCV contributes to worse outcomes. This population needs urgently effective treatments.

KEYWORDS
death, Delta infection, HBV infection, HCV infection, HIV infection, immunodepression, severe liver disease

1 | INTRODUCTION

Hepatitis delta virus (HDV) is a small defective RNA virus, needing hepatitis B virus (HBV) to generate the complete transmission of HDV virion. Indeed, HDV exploits the HBV surface proteins (collectively defined as HBsAg) for the release of its progeny and de novo entry into hepatocytes.[1] HDV superinfection results in severe chronic hepatitis in a high proportion of chronic HBsAg carriers, while individuals coinfected with HBV and HDV at the same time (HDV–HBV coinfections) experience severe acute hepatitis, but a low rate of evolution to chronicity.[2] The prevalence of HDV superinfection in Italy is estimated to be around 9% of HBV chronically infected individuals.[3] Wide variations of HDV prevalence in the different reports can largely be attributed to HBV vaccination policies according to geographical areas and to the tested setting. Migrants are, therefore, the most affected group among HIV-negative individuals, while persons who inject drugs (PWID) are at higher risk among persons living with HIV (PLWH).[4]

The burden and the determinants of natural history of HDV hepatitis in the HIV population have not been well examined. The rates of Delta antibodies (HDV Ab) screening in HBsAg positive PLWH is very low and even lower is the rate of HDV-RNA screening in HDV Ab positive PLWH. Further, HDV-RNA screening is rarely repeated over time.[5,6] In a recent study including the EuroSIDA and the Swiss HIV cohorts, the overall prevalence of HDV Ab among chronic HBsAg carriers was around 15%, with the highest prevalence, of 50%, among HBsAg positive PWID.[6] HDV-related liver disease is shown to progress faster in PLWH as compared to HIV-uninfected individuals.[7] Indeed, hepatitis delta is a major determinant of decompensated cirrhosis, hepatocellular carcinoma (HCC) and poor survival in this population, especially after the availability of antiviral suppressive therapy for HBV and cure for HCV.[7,8] Actually, in a cohort of 1187 PLWH with viral hepatitis followed for a decade in Spain the 17 patients with active HDV infection had the poorest survival.[9]

Higher HDV-RNA levels have been shown to be associated with a higher risk of progression of liver disease in HIV-uninfected persons.[10] For these reasons, low HDV-RNA levels have been identified as a positive prognostic factor[11] and reaching HDV-RNA

Lay Summary

HDV infection is diagnosed in around 20% of HBsAg positive persons living with HIV (PLWH) in Italy and more than 2/3 of HBsAg positive/HDV Ab positive PLWH show replicating HDV in plasma, most of them males, infected through intravenous drug use and coinfected with HCV. HDV-RNA positive PLWH have a 4.9-fold dependent higher risk of severe liver-related events than HDV negatives. Coinfection HDV/HCV was an independent factor of worse liver-related outcome and low CD4 counts accelerate severe liver-related events in HBsAg positive and in HDV positive PLWH.

below 1000 copies/mL has been considered a surrogate marker of effective treatment in Delta hepatitis.[12] In PLWH the relationship between HDV-RNA levels and prognosis has never been assessed. Taking into account additional co-factors such as HIV-induced immune suppression and the high prevalence of HCV in this population, this relationship could be different than in persons without HIV infection.

Given these considerations, the aims of our study are to ascertain the prevalence and the factors associated with HDV infection among HBsAg positive PLWH enrolled in the ICONA cohort, and to evaluate in our real-world setting the liver-related clinical outcome of HDV infected PLWH, in viremic HDV and of those with triple hepatitis infection, with HBV, HDV and HCV. Finally, we aim to evaluate the role of CD4 at nadir on liver disease progression.

2 | METHODS

2.1 | Design of the study and setting

Observational study on the Italian Foundation cohort Naïve antiretrovirals (ICONA). ICONA is a multicentre Italian cohort including antiretroviral (ART) naïve PLWH from 60 infectious diseases centres. Details of the cohort are specified elsewhere.[13]

2.2 | Objectives

Primary

- to evaluate the role of HDV, HDV-RNA levels and triple hepatitis infection (HBV, HCV, HDV) on time to severe liver related events (SLRE)

Secondary

- to evaluate the prevalence and associated factors of HDV Ab among HBsAg positive PLWH
- to evaluate the prevalence and associated factors of HDV-RNA among HDV Ab positive PLWH
- to evaluate the role of HDV and HDV-RNA levels and triple hepatitis infection (HBV, HCV, HDV) on time to SLRE or death for any causes
- to evaluate the role of CD4 nadir on time to SLRE in HDV Ab positive PLWH

2.3 | End-points

Primary

- Hepatitis clinical progression defined as SLRE (decompensated cirrhosis, hepatocellular carcinoma, liver transplant)

Secondary

- positive HDV Ab
- positive HDV-RNA
- clinical progression defined as SLRE or death

2.4 | Inclusion criteria

PLWH enrolled in the ICONA cohort were included in the study when fulfilling the following criteria:

- available data of HBV serology or stored plasma samples available for testing
- available data of HDV serology or stored plasma samples available for testing

2.5 | Data collection

The ICONA database included the following data used for the study: age, sex, nation of birth, HIV transmission, alcohol intake; immunological and virological parameters (CD4 counts both at nadir and at baseline HDV screening); hepatitis markers (HBsAg, HDV Ab, HDV-RNA, HCV Ab, HCV-RNA), and clinical variables (ALT, FIB-4, AIDS). Decompensated cirrhosis (bleeding esophageal varices or ascites or hepatorenal syndrome or hepatic encephalopathy stage III or IV), hepatocellular carcinoma (HCC), liver transplant as well as death and causes of death were also collected.

The presence of metabolic syndrome has been defined as the presence of at least three among the following five conditions: (i) diagnosis of hypertension or anti-hypertensive treatment start; (ii) hyperglycaemia (fasting glucose ≥100 mg/dL) or start of hypoglycaemic agents; (iii) hypertriglyceridemia (≥150 mg/dL) or start of drug treatment for elevated triglycerides; (iv) low HDL cholesterol (40 mg/dL in male and 50 mg/dL in female) or start of drug treatment for low HDL cholesterol; (v) abdominal fat accumulation (waist circumference ≥102 cm for men or ≥88 cm for women). As waist circumference was reported only in a minority of patients, we used the formula proposed by De Socio et al.[14] to estimate it. The presence of each one of these conditions has been evaluated at every clinical visit; last observation carried forward method has been used in case of missing data between visits.

Missing HBsAg, HDV Ab, HDV-RNA and HDV genotype were tested in case a sample of plasma was stored and available for testing in the ICONA biobank.

We then collected from the ICONA database demographic and clinical data of the included PLWH, comparing:

- HBsAg positive/HDV Ab negative versus HBsAg positive /HDV Ab positive.
- HDV Ab positive/HDV-RNA negative versus HDV Ab positive / HDV-RNA positive.

2.6 | Viral markers detection

HDV Ab titre determination was performed using the Liaison XL Murex Anti-HDV assay (Diasorin) with a lower limit of detection of 1 AU/mL while HBsAg determination was performed by Liaison XL Murex assay (Diasorin) with a cut-off for sample positivity of .05 IU/mL. HDV-RNA quantification was performed by the Robogene v.2 assay with a lower limit of quantification of 6 IU/mL.[15]

3 | RESULTS

3.1 | Prevalence of HDV markers among HBsAg positive PLWH in ICONA

A total of 1025 out of 18 285 PLWH (5.6%) displayed at least 1 HBsAg positive test (5.8% of ever tested). Of these, 809/1025 (78.7%) have been screened for HDV Ab; 152/809 HBsAg positive PLWH (18.8%, 95%CI 16.1–21.6) showed HDV Ab reactivity (see Figure 1 for the flowchart of the study). HDV screening was done at enrolment in the cohort for 53.5% ($n=433$) of patients, or after a median of 21.9 months (Interquartile Range [IQR]: 7.1–52.6) from enrolment in 46.5%. HDV tested PLWH were younger, more frequently males, Italians, persons with injected drugs (PWID), enrolled in ICONA in later years, more frequently HCV coinfected and with FIB-4 > 3.25 (Supplemental Table S1A).

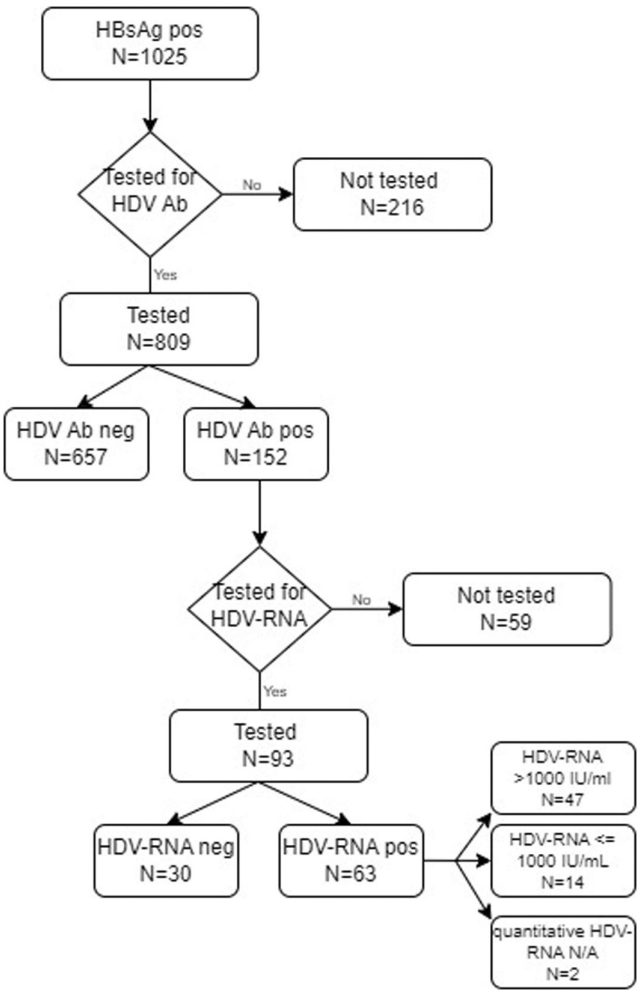

FIGURE 1 Flowchart of ICONA people living with HIV (PLWH) included in the study.

Among the tested PLWH, HDV Ab positive individuals were younger (median age 37 vs. 39 years), less frequently female (7.9% vs. 18.1%), more frequently PWID (67.1% vs. 15.8%), more frequently HCV Ab positive (71% vs. 21.5%), enrolled in earlier years (1998 vs. 2009) and more frequently showed FIB-4 > 3.25 (23.7% vs. 10.5%) (Table 1A). In the multivariable logistic regression model, male sex, PWID, HCV coinfection, FIB-4 > 3.25 and earlier year of enrolment were confirmed to be independent factors associated with HDV Ab positive status (Supplemental Table S2A).

A total of 93 out of 152 (61.2%) had stored plasma available to test for HDV-RNA. Of these, 63 (67.7%, 95%CI 57.2–77.1) had a detectable HDV-RNA with a median plasma HDV-RNA of 5.75 (3.67–7.15) log IU/mL. No differences were detected between HDV-RNA tested and not tested HDV Ab positive PLWH (Supplemental Table S1B). Genotype 1 was detected in 100% ($n=50$) of those tested.

HDV-RNA positive were more frequently Italians (97% vs. 73%), HCV Ab positive (79.4% vs. 47.3%), and with FIB-4 > 3.25 (34% vs. 10%), with an earlier year of enrolment (1997 vs. 2009) compared with HDV-RNA negative individuals (Table 1B). In the multivariable logistic regression model, only FIB-4 > 3.25, and earlier year of enrolment were confirmed to be independent factors associated with HDV-RNA positivity (Supplemental Table S2B).

3.2 | Clinical outcome according to HDV infection

Over a median follow-up of 5.1 (IQR 1.9–9.9) years, a total of 37 SLRE were diagnosed in 750 HBsAg positive PLWH; PLWH with SLRE at baseline ($n=5$) and without follow-up visit after baseline ($n=54$) were excluded. In detail, SLRE included 7 HCC and 30 end stage liver disease (47% ascites, 23.5% bleeding from oesophageal varices, 23.5% hepatic encephalopathy and 7% hepatorenal syndrome). A total of 60 HBV coinfected PLWH died for any causes without SLRE.

Breakdown of the number of events, prevalence and incidence of SLRE according to HDV status are reported in Table 2. The highest incidence rate (IR) was detected in the HDV Ab positive /HDV-RNA positive group: IR 23.7 per 1000 PYFU (95%CI: 12.2–41.4) and the lowest in the HDV Ab negative one (IR 3.6 per 1000 PYFU. 95%CI: 2.0–6.0).

The 5-year overall cumulative incidence function (CIF) of SLRE estimated by competing risk curves was 4.0% (95%CI 2.6–5.9). HDV-RNA positive PLWH had the highest CIF of reaching the SLRE endpoint (13.9%, 95%CI 6.0–24.4) and HDV Ab negative the lowest (1.9%, 95%CI: .9–3.5) (Figure 2).

Table 3 shows the sub-hazard ratio (SHR) and adjusted sub-hazard ratio (ASHR) of time to SLRE by HDV status: HDV Ab positive/HDV-RNA positive group had 6.6 (95%CI: 3.2–13.8) times higher risk of SLRE than HDV Ab negative ones. After controlling for time-fixed

TABLE 1 Baseline demographic and clinical characteristics of HBsAg positive participants by HDV Ab status at first screening (A) and by HDV-RNA status among HDV Ab positive (B).

(A)	HDV Ab negative 657 (81.2%)	HDV Ab positive 152 (18.8%)	*p*-value
Age, median (IQR)	39 (33–47)	37 (33–43)	.025
Sex, Female, *n* (%)	119 (18.1)	12 (7.9)	.002
HIV transmission group, *n* (%) MSM PWID Heterosexual Other/missing	244 (37.1) 104 (15.8) 262 (39.9) 42 (6.4)	20 (13.2) 102 (67.1) 21 (13.8) 9 (5.9)	<0.001
Italian, *n* (%)	500 (76.1)	137 (90.1)	<.001
Geographical origin, *n* (%) Africa Asia Europe Latin America North Africa and the Middle East Oceania/North America	71 (10.8) 8 (1.2) 536 (81.6) 33 (5.0) 7 (1.0) 2(.3)	6 (3.9) 2 (1.3) 141 (92.8) 2 (1.3) 1 (0.7) 0 (.0)	.028
Year enrolment, median (IQR)	2009 (1998–2014)	1998 (1997–2002)	<.001
Alcohol use, *n* (%) Yes No Unknown	144 (21.9) 230 (35.0) 283 (43.1)	23 (38.9) 36 (23.7) 93 (61.2)	.944
ART started (ever), *n* (%)	597 (90.9)	121 (79.6)	<.001
Nadir CD4 (ever), *n* (%)	247 (99–396)	214 (106–327)	.076
HIV-RNA in log10 copies/mL, median (IQR)	4.73 (4.05–5.25)	4.46 (3.50–5.01)	.017
AIDS, *n* (%)	103 (15.7)	18 (11.8)	.232
CD4 count, cells/μL, median (IQR)	322 (145–497)	307 (148–565)	.650
ALT, U/L, median (IQR)	33 (22–63)	61 (35–104)	<.001
Metabolic syndrome, *n* (%)	160 (24.3%)	18 (11.8%)	.001
FIB-4 > 3.25 at HDV Ab measurement, *n* (%)	69 (11.0)	36 (25.2)	<.001
Liver decompensation at baseline, *n* (%)	1 (.1)	1 (.7)	.258
HCC at baseline, *n* (%)	0 (.0)	3 (2.0)	<.001
HCV Ab positive at baseline, *n* (%)	108 (16.4)	100 (65.8)	<.001
(B)	**HDV-RNA negative 30 (32.3%)**	**HDV-RNA positive 63 (67.7%)**	***p*-value**
Age, median (IQR)	46(37–48)	43 (37–49)	.957
Sex, Female, *n* (%)	3(10.0)	4 (6.3)	.533
HIV transmission group, *n* (%) MSM PWID Heterosexual Other/missing	3 (10–0) 18 (60.0) 7 (23.3) 2 (6.7)	7 (11.1) 44 (69.8) 6 (9.5) 6 (9.5)	.350
Italian (%)	22 (73.3)	61 (96.8)	<.001
Year enrolment, median (IQR)	2000 (1997–2012)	1997 (1997–2000)	.054
Alcohol use, *n* (%) Yes No Unknown	8 (26.7) 12 (40.0) 10 (33.3)	20 (31.7) 19 (30.2) 24 (38.1)	.641
CD4 count, cells/μL, median (IQR)	300 (76–503)	256 (156–497)	.699
HIV-RNA in log10 copies/mL, median (IQR)	4.56 (3.99–5.15)	4.39 (3.42–4.89)	.181
Nadir CD4 count, cells/μL, median (IQR)	61 (13–76)	211 (60–302)	.025
Metabolic syndrome, *n* (%)	3 (10.0)	8 (12.7)	.706

(Continues)

TABLE 1 (Continued)

(B)	HDV-RNA negative 30 (32.3%)	HDV-RNA positive 63 (67.7%)	*p*-value
FIB-4 > 3.25, *n* (%)	3 (10.3)	21 (34.4)	.054
HDV-RNA, log10 IU/mL, median (IQR)		5.75 (3.67–7.15)	
HDV-RNA < 1000 IU/mL, *n* (%)		14 (22.2)	
HCV Ab positive at baseline, *n* (%)	26 (47.3)	50 (79.4)	<.001

TABLE 2 Proportion, incidence rate (IR) and cumulative incidence function (CIF) at 5-years of SLRE by HDV status.

	N PLWH	SLRE	Prevalence (95%CI)	IR x1000PYFU (95%CI)	CIF 5-years
HDV Ab neg	612	15	2.4% (1.4–4.0)	3.6 (2.0–6.0)	1.9% (.9–3.5)
HDV Ab pos/HDVRNA missing	50	6	12.0% (4.5–24.3)	17.2 (6.3–37.5)	10.2% (3.1–22.2)
HDV Ab pos/HDV-RNA neg	29	4	13.8% (3.9–31.7)	13.7 (3.8–35.1)	12.0% (3.0–27.7)
HDV Ab pos/HDV-RNA pos	59	12	20.3% (11.0–32.8)	23.7 (12.2–41.4)	13.6% (6.0–24.4)
HDV-RNA > 1.000 IU/mL	43	8	18.6% (8.4–33.4)	23.7 (10.2–46.7)	13.8% (5.0–27.0)
HDV-RNA ≤ 1.000 IU/mL	14	3	21.4% (4.6–50.8)	21.4 (4.4–62.8)	15.4% (2.5–38.8)

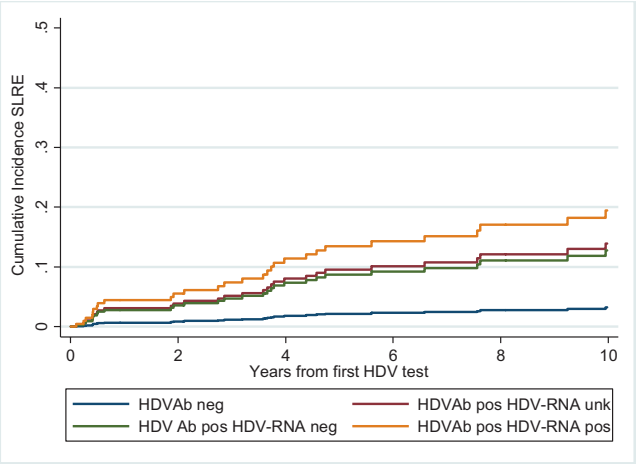

FIGURE 2 Cumulative incidence function of severe liver-related events (SLRE) by competing risk analysis according to hepatitis D virus (HDV) status at first HDV screening in HBsAg pos people living with HIV (PLWH).

confounders, the association was attenuated but the effect size was still remarkable with an ASHR of 4.6 (95%CI: 2.0–10.5).

We stratified HDV-RNA positive PLWH according to the level of viremia at baseline. Compared to HDV Ab negative the ASHR of SLRE was similar in the two groups of low and high HDV viremia: 4.8 (95% CI 1.4–16.9) in subjects with HDV-RNA ≤1000 IU/mL and 4.4 (95% CI 1.7–11.4) for those with baseline HDV-RNA >1000 IU/mL.

3.3 | Clinical outcome according to HBV/HDV/HCV infection

We then evaluated the role of triple HBV/HDV/HCV infection on the progression to SLRE. HBsAg positive /HDV Ab positive/HCV Ab positive individuals showed the highest incidence of SLRE: 23.6 ×1000 PYFU (95%CI: 14.4–36.6) (Table 4).

By competing risk curves, the 5-year CIF of SLRE was highest in the hepatitis triple infected group (14.8%, 95%CI: 8.3–23.1) and lowest in the HCV negative/HDV negative one (1.3%, 95%CI .5–3.0) (Figure 3).

The triple hepatitis infected group was confirmed to be a strong independent factor associated with SLRE (vs. HCV negative/HDV negative group ASHR: 11.9, 95%CI: 4.6–30.9) (Table 5).

We then evaluated the impact of HCV-RNA negativisation on the clinical outcome of HDV Ab positive individuals: even if not statistically significant due to the low number of events, the individuals with persistent HCV-RNA positivity showed a not significant double risk of SLRE as compared to those eradicating HCV (ASHR: 2.0, 95%CI .54–7.4).

3.4 | Role of nadir CD4 on progression to SLRE in HDV positive PLWH

We then analysed 114 HDV Ab positive PLWH who started ART, and considered the date of ART initiation as baseline.

HDV Ab positive PLWH with nadir CD4 ≤200/mmc showed a significantly higher independent risk of SLRE 3.9 times higher (95%CI: 1.0–14.5) as compared to patients with CD4 > 200/mmc at nadir.

3.5 | SLRE or death as clinical outcome

Using SLRE and death for any reason as end-point, HDV-RNA positive PLWH had 2.3 times (95%CI: 1.3–4.0) independent higher risk of the event compared to HDV Ab negative ones. In these analyses the HDV-RNA cut-off of 1000 copies/mL was associated with a different outcome: PLWH with HDV-RNA ≤1000 copies/mL did not show a statistically significant higher risk of SLRE or death (AHR 1.5,

TABLE 3 Sub-hazard ratio (SHR) and adjusted SHR (ASHR) of SLRE according to HDV status from fitting unadjusted and adjusted fine-grey regression model (using death as competing event).

	SHR	95%CI	*p*	ASHR[a]	95%CI	*p*
HDV Ab neg	1			1		
HDV Ab pos/HDVRNA missing	4.58	1.77–11.85	.002	3.25	1.22–8.65	.018
HDV Ab pos/HDVRNA neg	4.16	1.36–12.67	.012	3.14	1.00–9.91	.050
HDV Ab pos/HDVRNA pos	6.61	3.17–13.79	<.001	4.61	2.02–10.5	<.001

[a]Adjusted for baseline CD4, age, alcohol use, metabolic syndrome and HCV status.

TABLE 4 Proportion, incidence rate (IR) and cumulative incidence function (CIF) at 5-years of SLRE by HDV and HBV status.

	N PLWH	SLRE	Prevalence (95%CI)	IR x1000PYFU (95%CI)	CIF 5-years
HDVAb+HCVAb+	101	20	19.8% (12.5–28.9)	23.6 (14.4–36.4)	14.8% (8.3–23.1)
HDVAb+HCVAb−	37	2	5.4% (.6–18.2)	6.7 (.8–24.3)	3.9% (.3–16.6)
HDVAb- HCVAb+	133	9	6.7% (31.5–12.4)	8.6 (3.9–16.3)	3.7% (1.2–8.5)
HDVAb− HCVAb−	455	6	13.2% (4.8–28.5)	2.1 (.7–4.4)	1.3% (.5–3.0)

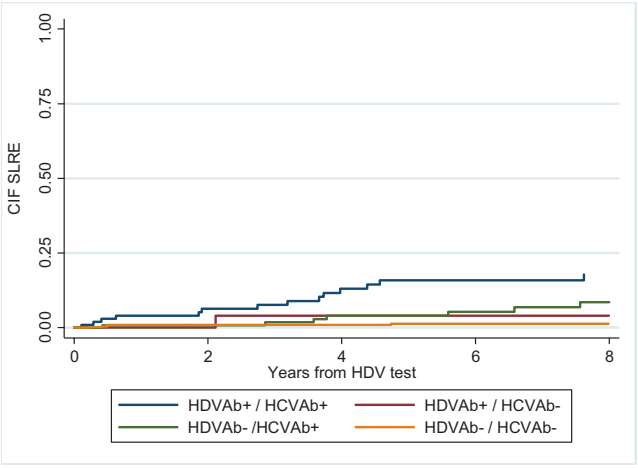

FIGURE 3 Cumulative incidence function of severe liver-related events (SLRE) by competing risk analysis according to HDV-RNA status in HBsAg pos/HDV Ab pos people living with HIV (PLWH).

95% CI .4–4.8) whereas those with baseline HDV-RNA >1000 IU/mL showed a 2.5-fold (95% CI 1.3–4.6) higher risk of SLRE or death as compared to HDV Ab negative (Supplementary Table S3).

Individuals with persistent HCV-RNA positivity showed a not significant double risk of SLRE or death as compared to those eradicating HCV (AHR: 2.4, 95%CI .50–12.2).

3.6 | HDV sequencing and assessment of HDV genotype

For PLWH with active HDV replication and with a sufficient amount of plasma sample ($N = 50$), the nucleotide sequence, covering the portion of HDV genome (from nucleotide 889 to 1289) encompassing the 3′ end of the delta protein-coding gene, was obtained by Sanger sequencing based on La Gal et al.[16] Details are reported in Supplemental Material. HDV sequences were analysed using SeqScape-v.2.6 software (Applied-Biosystems). The HDV genotypes were attributed by phylogenetic tree constructed by Neighbor-Joining method on MEGA6 software, using the reference sequences retrieved from Karimzadeh et al.[17]

3.7 | Statistical analyses

For the prevalence of HDV Ab and HDV-RNA, the baseline for comparisons was the date of the first HDV serology test. Only participants with an HBsAg positive test were included and grouped according to the exposure of interest (HDV Ab positive vs. HDV Ab negative and HDV-RNA positive vs. HDV-RNA negative). Characteristics of the groups at baseline were compared in a cross-sectional analysis. Wilcoxon Rank Sum and Chi-square tests have been used for comparing continuous and categorical data as appropriate, by HDV serological/virological groups. Data of PLWH excluded from the analysis because of missing HDV Ab or HDV-RNA test were compared to the tested ones. We then performed two unadjusted and adjusted logistic regression analyses to identify factors associated with being HDV Ab positive or HDV-RNA positive among those HDV Ab positive. Factors associated with $p < .05$ in the unadjusted models were retained for the adjusted ones.

Prevalence of HDV infection (HDV Ab positive) and active HDV infection (HDV-RNA positive) were given with a 95% confidence interval (CI).

Incidences of SLRE, according to groups, were calculated as number of SLRE divided by person-year follow-up (PYFU) after the first HDV screening.

Among PLWH free from SLRE at baseline, competing risk curves have been used to plot the cumulative incidence function (CIF) of developing SLRE stratified from baseline by HDV status; the 5-year

TABLE 5 Sub-hazard ratio (SHR) and adjusted SHR (ASHR) of SLRE according to HCV Ab / HDV Ab at baseline from fitting unadjusted and adjusted fine-grey regression model (using death as competing event).

	SHR	95%CI	*p*	AHSR[a]	95%CI	*p*
HDVAb− HCVAb−	1			1		
HDVAb+ HCVAb+	11.72	4.74–28.96	<.001	11.93	4.60–30.93	<.001
HDVAb+ HCVAb−	3.65	.76–17.62	.107	3.76	0.73–19.27	.113
HDVAb− HCVAb+	4.23	1.52–11.82	.006	4.07	1.45–11.45	.008

[a]Adjusted for baseline CD4, age, metabolic syndrome alcohol use.

estimated cumulative incidence of SLRE has been also calculated according to HDV status. Risk of SLRE in HBsAg positive PLWH according to HDV Ab and HDV-RNA has been estimated using competing risk Fine-Grey regression models, using death as competing event. Potential confounding identified were age, CD4 at baseline, alcohol use and HCV status at baseline. Although presence of metabolic syndrome at baseline is not a confounding factor, is considered a strong predictor of the outcome and therefore was further included as covariate to improve the efficiency of the model. The analysis was repeated after stratification of HDV-RNA positive patients using 1000 IU/mL cut-off of HDV viral load, to evaluate the risk of SLRE for low and high viremia compared to HDV Ab negative group. We also evaluated the role of triple hepatitis infection (HBV/HCV/HDV) on SLRE considering HCV Ab and HDV Ab status at baseline as exposure of interest.

Standard survival analysis (Kaplan–Meier curves) and unadjusted and adjusted Cox regression models were used to estimate the role of HDV status on the risk of SLRE or death. Cox regression models were adjusted for sex, age, CD4, AIDS, alcohol use, HCV status and metabolic syndrome.

A sensitivity analysis including only HDV Ab positive, HCV-RNA positive individuals, was performed to evaluate the impact of HCV-RNA negativisation on the progression to SLRE and to SLRE or death.

We evaluated also the risk of SLRE according to nadir CD4 cell counts higher or lower than 200 cells/mmc at ART start (baseline) among HDV Ab positive PLWH who started ART. The Fine-Grey regression models were adjusted for age, alcohol use, HDV-RNA and HCV status, and metabolic syndrome.

4 | DISCUSSION

In our study we demonstrate a high prevalence of hepatitis Delta infection among the HBsAg positive individuals enrolled in the ICONA cohort, including around 20000 PLWH living in Italy. In detail, the prevalence of HBsAg in the ICONA cohort was of 5.6%, HDV Ab was detected in 18.8% of them and HDV-RNA in 67.7% of the HDV Ab positive ones. To underline, the prevalence among non-PLWH across the ICONA enrolment period ranged 8.3%–9.0% of HBsAg positive individuals in care.[18]

In our study, HDV prevalence is slightly higher than the Swiss HIV and the EuroSida cohorts,[6,19] both including PLWH with a similar percentage of untested individuals. The higher prevalence of HDV in our cohort is not explained by PWID prevalence, which is similar in the two studies, but is well known that HDV is more frequent in the general population from the southern part of Europe.[6,9]

In this study, it was observed that among HBsAg positive PLWH, HDV-RNA active replication, even if at a single point of observation, is associated with more advanced liver fibrosis, as demonstrated by FIB-4. However, it should be taken into account that viral RNA may be intermittently detected in blood in patients with anti-HDV reactivity, so our data could misestimate the relationship between HDV replication and liver damage.[20]

In a median of 5 years follow-up, HDV-RNA positive PLWH were those with the highest prevalence of severe liver events: 20.0% versus 2.4% in HDV negative individuals. In our cohort, the risk of evolution to severe liver events is 4.6 times higher in PLWH with replicating HDV infection than those negative for HDV. Our results are in keeping with a previous study by the Swiss HIV Cohort Study showing that the cumulative probability for overall death, liver-related death and HCC were significantly higher in HDV-RNA positive than HDV-RNA negative patients.[19]

The overall risk of liver disease progression in our study could be also explained by three characteristics of our cohort.

First, HDV-RNA positive PLWH were infected with HDV genotype 1, characterised by higher levels of serum HDV-RNA and ALT, more prone to progress to chronic hepatitis evolving to an unfavourable long-term clinical outcome as compared to HDV genotype II.[21,22]

Second point, we have also to consider the role of HCV in the evolution to severe liver disease, as HCV coinfection was present in 65% of HDV Ab positive and in 71% of HDV-RNA positive PLWH. In the setting of HBsAg positive individuals, the 5-year probability of SLRE is 14.8% in triple coinfected versus 1.3% in HBV monoinfected PLWH; the adjusted risk of new SLRE is 12 times higher in triple coinfected versus HBV monoinfected PLWH. The role of HCV on progression of liver disease is well known[23]; here we demonstrated a role of HCV among HIV/HBV coinfected individuals with HDV coinfection.

We could also speculate, even if not able to demonstrate due to the lack of power, that eradicating HCV might reduce the risk of liver disease progression also in presence of HDV infection. As a consequence, as already suggested by other Authors,[24] treatment of the three hepatitis viruses, HBV, HDV and HCV is mandatory in PLWH

to limit the progression to decompensated liver disease. Moreover, as a consquence of viral interference, among triple infected individuals, HDV plays a major role on liver disease progression,[25] and as delta treatment is now available, it could be advisable to treat HDV positive individuals as soon as possible.

Third point, HIV-related immunodepression plays its role both in HBV and in HBV-HDV individuals: among PLWH with nadir CD4 less than 200 cells/mmc, the risk of severe liver events is four times higher than in individuals with CD4 counts above 200 cells/mmc, independently from any hepatitis virus infection. The role of immunodepression in shortening the time to SLRE is well known; here we demonstrate that this is true also for individuals with HDV infection.[26]

Further, looking at HDV, among HIV-uninfected individuals it has been demonstrated a correlation between HDV viral load, with a cut-off of 1000 IU/mL and outcome.[10,11,27] Our data suggest that among PLWH, even in the presence of low levels of HDV replication, a substantial risk of evolution towards decompensated liver disease or HCC does persist. This could be related to the additional effects of immune suppression and to the HCV coinfection. As a consequence, it could be hypothesised that in PLWH a partial suppression of HDV replication is not necessarily associated with a better prognosis, as in HIV-uninfected persons,[11,27] and that treatment-induced 2 log decrease of HDV-RNA levels could be a less solid end-point for effective treatment of HDV in PLWH.

We have not evaluated how many HDV positive individuals had been treated in the past with alfa-interferon, known to have some effect on disease progression, but presumably, the rate of HDV cure is very low[28]; we are sure that bulevirtide, the new antiviral showing to slow down disease progression by antiviral action[29–31] was not used in out populatiom, as it is available in Italy only from few months.

Our study has several limitations: first, the data on HDV prevalence might be overestimated, due to a possible selection bias in HDV screening; moreover, it does not completely reflect the population on care at present; we could not acquire more detailed data on liver disease and on other clinical parameters (such as stiffness or liver biopsy) due to the retrospective analyses, and moreover, data on alcohol intake are frequently missing and not collected with standardised procedures. As refers to liver fibrosis, we acknowledge that the FIB-4 index used, might not be a reliable score, like all non-invasive markers, due to the presence of active inflammation and necrosis in chronic HDV hepatitis.[32] Further, we have limited data on HDV genotype, that could result in a different prognosis,[21,22] but all the tested PLWH harboured genotype 1, predominant in Italians,[33] concordantly with the demographic data of our cohort. Finally, HCV coinfection has not been in-depth disentangled into active and eradicated one's.

On the other side, the strengths of our study are the number of PLWH in follow-up in the ICONA cohort, letting us to draw conclusions based on solid data and the long follow-up, with a median of 5 years together with the data on HDV-RNA and on HCV coinfection, missing in other cohort analyses.[6,18]

In conclusion, we demonstrated that HBV coinfected PLWH carry infection with HDV in around one-fifth of cases, in more than two out of three cases the virus is replicating and in 60% HCV infection does coexist. These individuals rapidly progress to a life-threatening situation as severe liver disease. Then treatment of HCV coinfection and maintenance of high CD4 counts may play a key role in improving the prognosis of these patients, but suppression of HDV replication without HDV-RNA negativisation could not be the key factor in improving their prognosis. We need urgently drugs active on HDV replication, to be available and free of charge for these patients aimed to obtain HDV-RNA negativisation.

AUTHOR CONTRIBUTIONS

Study conception: Antonella d'Arminio Monforte, Romina Salpini, Alessandro Tavelli, Valentina Svicher, Massimo Puoti, Francesca Ceccherini Silberstein. Study Design: Antonella d'Arminio Monforte, Romina Salpini, Alessandro Tavelli, Valentina Svicher, Massimo Puoti. Data collection: Romina Salpini, Lorenzo Piermatteo, Alessandro Tavelli, Stefano D'Anna, Vincenzo Malagnino, Valentina Mazzotta, Roberto Rossotti, Elena Rosselli del Turco; Experiments and Procedures: Romina Salpini, Lorenzo Piermatteo, Stefano D'Anna, Stefania Carrara, Valentina Svicher, Francesca Ceccherini Silberstein. Statistical analysis: Alessandro Tavelli. Interpretation of results: Antonella d'Arminio Monforte, Alessandro Tavelli, Valentina Svicher, Massimo Puoti, Giuseppina Brancaccio, Roberto Rossotti, Francesca Ceccherini Silberstein, Giovanni Battista Gaeta, Andrea Antinori, Cristina Mussini, Giulia Carla Marchetti, Sergio Lo Caputo. Writing original draft: Antonella d'Arminio Monforte, Alessandro Tavelli. Writing review & editing: All authors.

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CONFLICT OF INTEREST STATEMENT

ADM served as consultant or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, Janssen-Cilag, GSK, Merck Sharp & Dohme and received research grants from Gilead Sciences and ViiV Healthcare. VMazzotta served as a paid consultant to GSK and received research institutional funding from Gilead Sciences. GM received speakers' honoraria and travels' grant by Gilead Sciences, ViiV Healthcare and Janssen-Cilag. CM received speakers' honoraria or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme and Janssen-Cilag and received research grants from Gilead Sciences. AA has served as a paid consultant to Astra Zeneca, Gilead Sciences, GSK, Janssen-Cilag, Merck, Moderna, Pfizer, Viatris and ViiV Healthcare and received research institutional funding from Astra Zeneca, Gilead Sciences and ViiV Healthcare. SLC received speakers' honoraria from Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme, Astra Zeneca, GSK and Janssen-Cilag, received support for travel meetings from Gilead Sciences, Janssen-Cilag and ViiV Healthcare and grant for research from Gilead Sciences. VS received speakers' honoraria and research grants from Roche, Fujirebio, Diasorin and Gilead Sciences. MP received honoraria for speaking and consulting from AbbVie, GSK, Gilead Sciences, Merck, Angelini and Novartis and received research grants from Gilead Sciences and AbbVie. RS, AT, LP, SDA, SC, VMalagnino, GB, GBG, ERDT, RR and FCS had nothing to disclose.

ETHICAL STATEMENTS

The ICONA Foundation study was approved by the Ethics Committee (institutional review board) of each participating institution. All of the individuals enrolled provided a written informed consent at the time of the enrolment. All procedures of the study were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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SUPPORTING INFORMATION

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

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