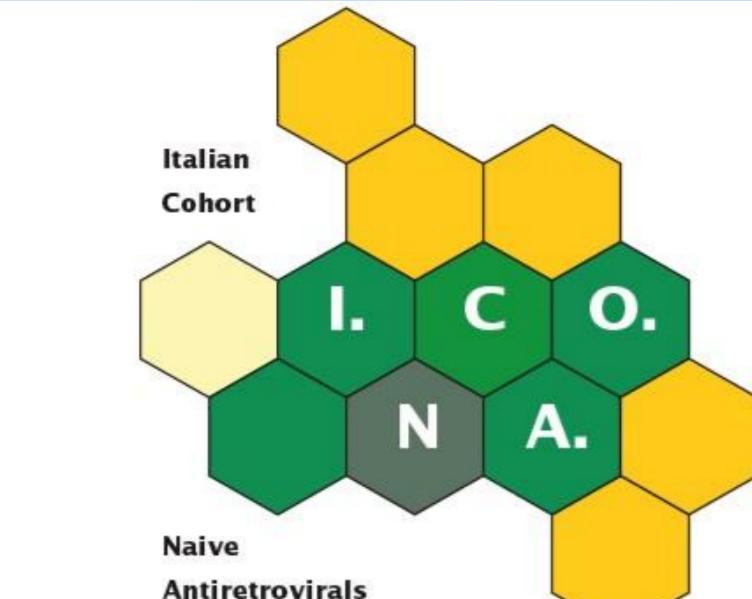


# Hepatitis Delta Virus (HDV) infection: frequency and outcome in Persons Living With HIV (PLWH). Data from the ICONA (Italian Cohort of Naïve for Antiretrovirals) cohort



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## Introduction

Overall, prevalence of HDV superinfection in Italy is estimated to be around 9% of HBV chronically infected [1]. The rate of HDV-Ab testing in HBsAg positive persons living with HIV (PLWH) is very low and even more the rate of HDV-RNA testing. HDV causes the most severe liver disease with also a faster progression among PLWH [2]; suppressive antiviral treatment was recently available for this infection, but the burden and natural history of hepatitis delta in the HIV population have not been well examined.

Moreover, a peculiar aspect for PLWH co-infected with HBV/HDV is that some of the antiretroviral drugs (boosted-protease inhibitors, efavirenz and etravirine) had an inhibitory effect on the Na+/ Taurocholate polypeptide cotransporter polypeptide (NTCP), a cellular receptor on hepatocytes serving for HBV and HDV virus entry [3].

## Aims

- to evaluate the prevalence of HDV among HBsAg pos PLWH of ICONA cohort, by assessment of both HDV-Ab and HDV-RNA
- to ascertain whether past and/or ongoing HDV infection results in higher risk of severe liver related events
- to evaluate the correlation between cumulative use of ARV drugs inhibiting NTCP on the level of HDV viremia

## Methods

### Study population

- . PLWH enrolled in the ICONA cohort with available data on HBV and HDV serology or stored plasma samples for testing;
- . For the analysis on risk of liver events PLWH with at least one FU visit after baseline have been included.

### Viral markers detection

- . HDV-Ab titre determination using the Liaison XL Murex Anti-HDV assay (Diasorin), lower limit of detection of 1 AU/ml;
- . HDV-RNA quantification by the Robogene v.2 assay, a lower limit of quantification of 6 IU/ml.

### Endpoints

- . Prevalence of HDV-Ab pos among HBsAg pos carriers
- . Prevalence of HDV-RNA pos among HDV-Ab pos PLWH
- . Time to Liver Related Hard Outcomes (LRHO, first event between decompensated cirrhosis, hepatocellular carcinoma and liver-related death)

### Statistical analyses

- . Demographic and clinical data between following groups have been compared:
  1. HBsAg pos / HDV-Ab neg vs. HBsAg pos / HDV-Ab pos
  2. HBsAg pos / HDV-Ab pos / HDV-RNA neg vs. HBsAg pos / HDV-Ab pos / HDV-RNA pos
- . Correlation between levels of HDV-RNA and total months of exposure with ARV drugs inhibiting NTCP using Pearson's coefficient and linear regression models.
- . Risk of liver disease progression (LRHO) according to HDV status has been evaluated using standard survival analysis (Kaplan-Meier curves and log-rank test) and Cox-regression models crude and adjusted for time fixed covariates at baseline (age, alcohol use, CD4 nadir) and HCV-Ab/HCV-RNA status as time-dependent covariate. Participants' follow-up accrued from first HDV-serology available up to the time of developing the LRHO or to last clinical visit.

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## References

[1] Brancaccio G et al. Int J Infect Dis. 2023 [2] Fernandez-Montero JV et al. Clin Infect Dis. 2014; [3] Yan H et al. Antiviral Res. 2015

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## 1. Prevalence of HDV markers among HBsAg positive PLWH in ICONA

- . 1,028 out of 18,285 PLWH (5.6%) displayed at least 1 HBsAg-pos test (5.8% of ever tested). Of these, 809 (78.7%) have been screened for HDV Ab.
- . **152/809 HBsAg pos PLWH (18.8%) showed anti HDV reactivity**
- . Table 1 shows comparisons on clinical and demographic data in HDV Ab pos and neg

	HDV-Ab negative N=657 (81.2%)	HDV-Ab positive N=152 (18.8%)	p-value
Age, median (IQR)	39 (33-47)	37 (33-43)	0.025
Female, n (%)	119 (18.1)	12 (7.9)	0.002
Italian, n (%)	500 (76.9)	137 (90.1)	<0.001
HIV transmission group, n (%)			<0.001
MSM	244 (37.1)	20 (13.2)	
IDU	104 (15.8)	102 (67.1)	
Heterosexual	262 (39.1)	21 (13.8)	
Other/missing	42 (6.4)	9 (5.9)	
Geo Origin, n (%)			0.028
Africa	71 (10.8)	6 (3.9)	
Asia	8 (1.2)	2 (1.3)	
Europe	536 (81.6)	141 (92.8)	
Latin America	33 (5.0)	2 (1.3)	
North Africa and the Middle East	7 (1.0)	1 (0.7)	
Oceania/North America	2(0.3)	0 (0.0)	
Alcohol use, n (%)			0.944
Yes	144 (21.9)	23 (38.9)	
No	230 (35.0)	36 (23.7)	
Unknown	283 (43.1)	93 (61.2)	
Months between HDV-Ab measurement and last available FU, months median (IQR)	51.8 (16.5-107.0)	63.2 (19.2-140.6)	0.100
Last available follow up in 2021-2022	275 (41.9)	35 (23.0)	<0.001
ART started, n (%)	597 (90.9)	121 (79.6)	<0.001
AIDS at enrolment in the cohort	103 (15.7)	18 (11.8)	0.232
Baseline* CD4 count, cells/ $\mu$ l, median (IQR)	322 (145-497)	307(148-565)	0.650
Baseline* HIV-RNA, log10, cps/ml, median (IQR)	4.73 (4.05-5.25)	4.46 (3.50-5.01)	0.017
FIB-4 > 3.25 at HDV-Ab measurement, n (%)	69 (11.0)	36 (25.2)	<0.001
FIB-4 > 3.25 at the last available FU, n (%)	60 (9.2)	39 (26.2)	<0.001
Liver decompensation at enrolment in the cohort n (%)	1 (0.1)	1 (0.7)	0.258
Liver decompensation at the last available FU, n (%)	9 (1.4)	10 (6.6)	<0.001
HCC at enrolment in the cohort, n (%)	0 (0.0)	3 (2.0)	<0.001
HCC at the last follow up, n (%)	2 (0.3)	8 (5.3)	<0.001
Death for any cause, n (%)	59 (8.9)	30 (19.7)	<0.001
Liver related death, n (%)	11 (1.67)	16 (10.5)	<0.001
HCV Ab at HDV Ab measurement, n (%)	104 (15.8)	100 (65.8)	<0.001
HCV-RNA at HDV-Ab Measurement among HCVAb pos n (%)	16 (15.4)	11 (11.0)	0.001
*lowest CD4 count / highest HIVRNA measurement before HDV test			

Table 1: Demographic and clinical characteristics of HBsAg positive PLWH by HDV Ab status

## 2. NTCP inhibitors and HDV viremia

- . No significant correlation between the total months of ART drugs inhibiting NTCP, and HDV-RNA plasma levels at baseline (log10 scale), Pearson rho= -0.258, p=0.091.
- . Also in the linear regression model adjusted for CD4 count at ART start, HCV status and age, previous cumulative exposure with NTCPs inhibitors ARV was not associated with lower plasma HDV-RNA at baseline (per 1 month more, beta=-0.011 log10 HDV-RNA IU/ml, p=0.256) (Figure1).

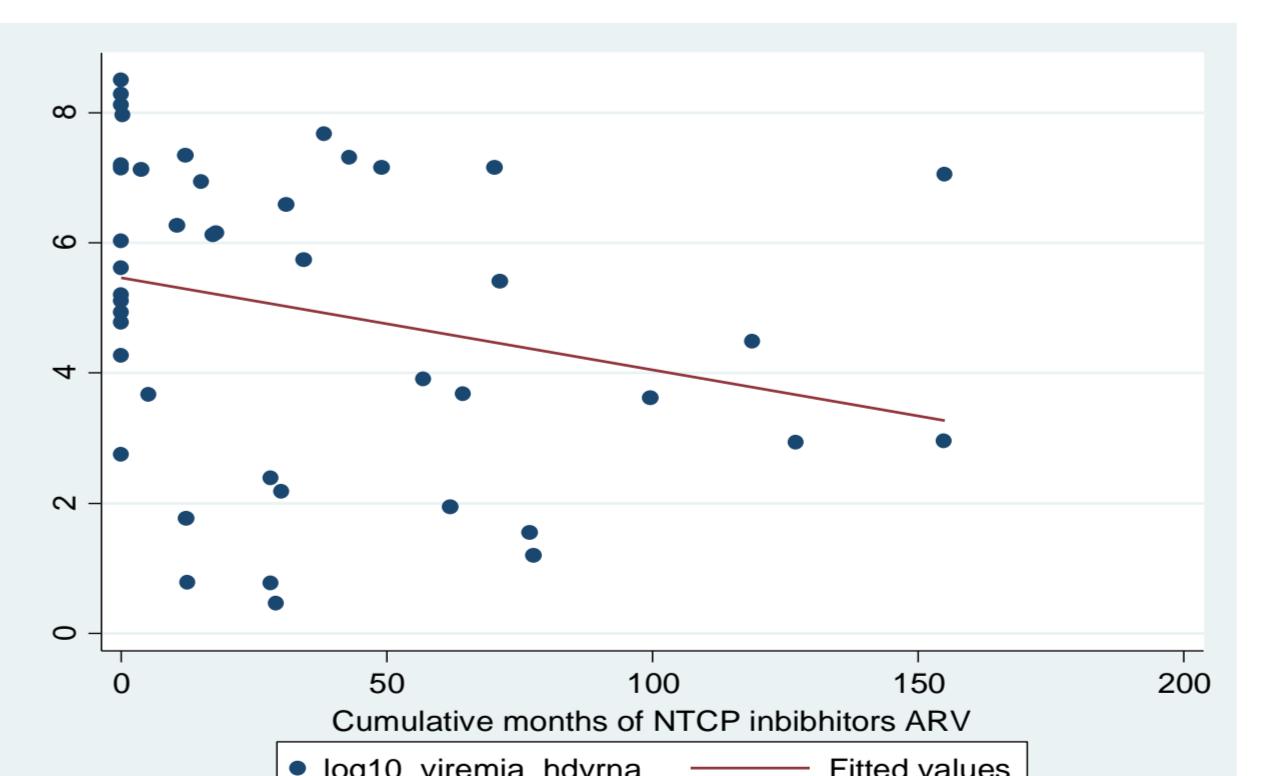


Figure 1. scatter plot of plasma HDV-RNA (log10 trasformation) at baseline and previous cumulative months on NTCP inhibitors, with linear fitting

## Results

### 3. Liver outcomes according to HDV infection

- . Over a median follow-up of 5.1 (2.0-9.9) years, a total of 37 LRHO occurred in 736 HBsAg pos PLWH (13 liver-related death, 7 HCC and 17 ESLD).

- . By KM curves (Figure2), the 5-years cumulative probability of LRHO was 4.2% (95%CI 2.8-6.3):
  - 2.0% (1.0-3.9) for HDVAb neg
  - 11.0% (4.1-27.6) for HDVAb pos / HDV-RNA missing
  - 12.0% (4.0-32.8) for HDVAb pos / HDV-RNA neg
  - 14.8% (7.3-28.7) for HDVAb pos / HDV-RNA pos (log-rank p<0.01)

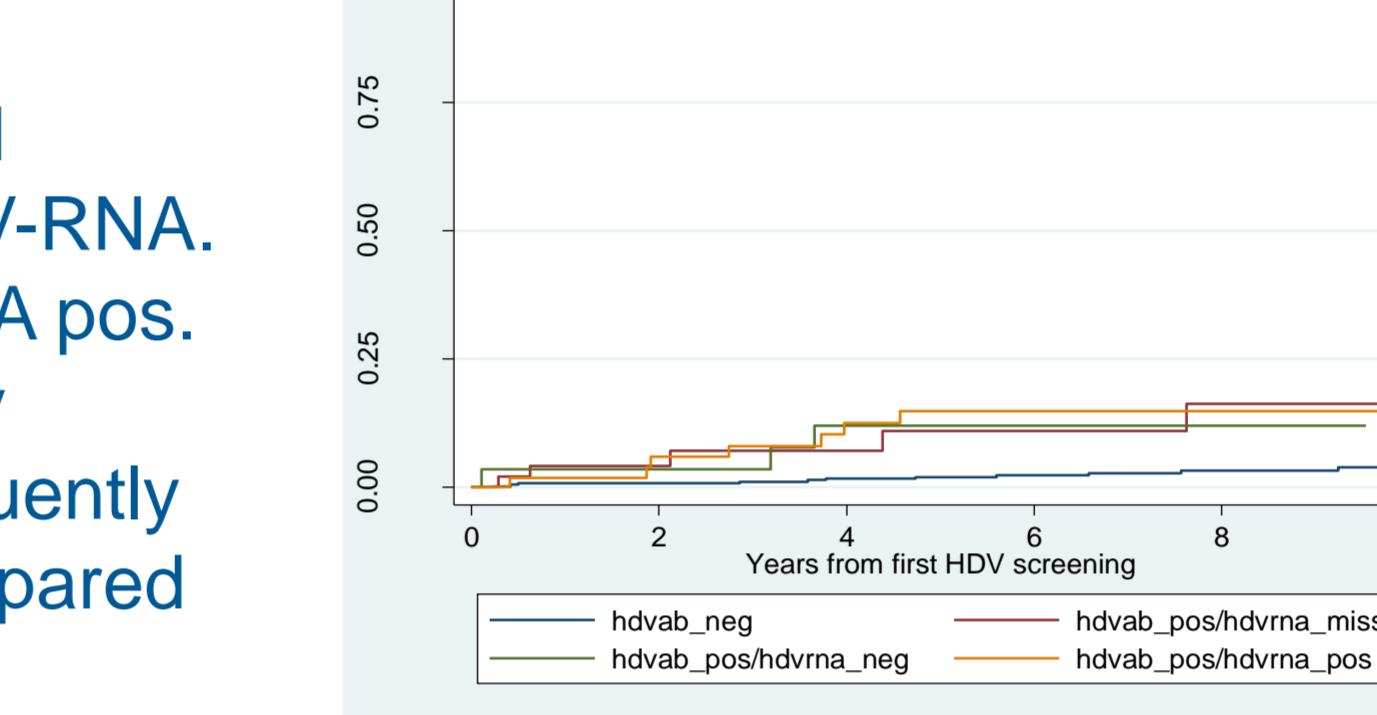


Figure 2. Kaplan-Meier curves of LRHO from first HDV screening according to HDV status among HBsAg positive PLWH

HDV status	HR	95%CI	p	AHR	95%CI	p
HDVAb neg	1			1		
HDVAb pos / HDV-RNA missing	4.99	1.93	0.001	3.34	1.20	0.25
HDVAb pos / HDV-RNA negative	3.87	1.28	0.017	2.19	0.69	0.180
HDVAb pos / HDV-RNA positive	6.60	3.07	<0.001	4.82	2.05	0.132

Adjusted for baseline Alcohol use (Yes/No), CD4 cell nadir, age and time-dependent HCV Status (HCVAb neg, HCV-RNA pos, HCV-Ab pos HCV-RNA neg, HCV-Ab pos HCVRNA missing) from fitting a Cox Regression model

Table 3- Hazard Ratio (HR) and Adjusted HR (AHR) of developing LRHO after first HDV screening from fitting a Cox Regression model

After controlling for baseline factors at time-fixed (age,