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


1 University of Milano Bicocca, School of Medicine, Milan, Italy; 2 ASST GOM Niguarda, Infectious Diseases, Milan, Italy; 3 University of Rome Tor Vergata, Department of Experimental Medicine, Italy; 4 Icosa Foundation, Milan, Italy; 5 INMI, Unit of Microbiology and Biodi, Rome, Italy; 6 University of Rome Tor Vergata, Department of Medicine of Systems, Clinical Infectious Diseases, Rome, Italy; 7 RMI, Clinical and Research Infectious Diseases Department , Rome, Italy; 8 University of Padua, Department of Molecular Medicine, Padua, Italy; 9 University S. Apollo, Infectious Diseases Unit, Naples, Italy; 10 ASST Santi Piacentini Carlo, Clinic of Infectious Diseases, Milano, Italy; 11 University of Milano, Department of Health Sciences, Milano, Italy; 12 Alma Mater Studiorum University, University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; 13 IRCSS Azienda Ospedaliero Universitaria S. Orsola Malpighi, Infectious Diseases Unit, Bologna, Italy; 14 Bambino Gesù Pediatric Hospital, Rome, Italy.

Introduction

Overall, prevalence of HDV infection in Italy is estimated to be around 9% of HBV chronically infected [1]. The rate of HDV 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 in 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 separate aspect for PLWH co-infected with HBV/HDV is that some of antiretroviral drugs (boosted protease inhibitors, efavirenz and etravirine) had an inhibitory effect on the Na+ /HCO3- cotransporter responsible for acidification of endosomal compartments (NTCP), a cellular receptor on hepatocytes serving for HBV and HDV virus entry [3].

Aims

- to evaluate the prevalence of HDV among HBsAg positive persons living with ICONA cohort, by assessment of both HDV-Ag 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 ART 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-Ag titre determination using the Liaison XL Murex Anti-HDV assay (DiaSorin), lower limit of detection of 1 AU/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:
  - HDVAg pos / HDV Ab neg vs. HBsAg pos / HDV Ab pos
  - 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 ART 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 HBsAg/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.

Funding

The study is supported by GlaxoSkiolda and a grant for HDV screening. Funder had no role in data analysis and interpretation.

References


Results

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 test (5.8% of ever tested). Of these, 809 (78.7%) have been screened for HDV Ab.
- 152/609 HBsAg pos PLWH (18.8%) showed anti HDV reactivity

Table 1 shows comparisons on clinical and demographic data in HDV Ab pos and neg
- A total of 95 out of 152 (62.5%) had stored plasma available to test HDV-RNA.
- Of these, 63 (87.7%) were HDV-RNA pos.
- HDV-RNA were more frequently observed in patients with HDV infection (97% vs 72%) and more frequently with a FIB-4 >3.25 (34 vs 9.7%) compared with HDV-RNA neg (Table 2).

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=0.189.
- Also in the linear regression model adjusted for CD4 at start ART, HDV status and age, previous cumulative use of NTCPs inhibitors ARV was not associated with lower plasma HDV-RNA at baseline (per 1 month more, beta=-0.101 log10 HDV-RNA IU/mL, p=0.256) (Figure 1).

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 ESDL).
- By Kim curves (Figure 2), the 5-year cumulative probability of LRHO was 4.2% (95%CI 2.8-6.3%).
- 2.0% (1.3-3.9) for HDVAb neg
- 17.0% (4.1-27.6) for HDVAb pos / HDV-RNA missing
- 12.0% (4.9-32.8) for HDVAb pos / HDV-RNA were
- 14.8% (7.3-26.7) for HDV Ab pos / HDV-RNA pos (log-rank p<0.01)

Table 3: Demographic and clinical characteristics of HDVAb positive participants by HDV-RNA status

- After controlling for baseline factors at time-fixed (age, alcohol consumption, nadir CD4 count) and time-dependent (HCV Ab status) covariates in a Cox regression model PLWH HBsAb pos/HDV-RNA pos has a 4.8-fold higher risk of LRHO compared to HDV Ab neg (Table 3)

Conclusions

Of PLWH tested, one out of five HBV/HIV coinfected individuals had been infected with HDV.
- HDV were frequently male IDU with HBV Ab pos/HCV RNA neg. Globally, 12% showed coinfection with 4 viruses (HBV, HIV, HCV).
- We did not find a possible role of ARVs drugs that inhibit NTCP of HDV viremia at first screening, possibly due to the small sample size.
- After adjustment for confounders – including HCV co-infection- HDV infection is related to a higher incidence of LRHO in PLWH.
- Pharmacological suppression of HDV replication may improve the prognosis in PLWH with active HDV replication.