Coinfection with Hepatitis B Virus and/or Hepatitis C Virus is a risk factor for HIV virological rebound after achieving virological suppression on first ART: results from ICONA Study Italian cohort

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BACKGROUND

A growing body of evidence suggests that co-infections (e.g., malaria, tuberculosis, herpes simplex virus type 2, cytomegalovirus) may promote HIV replication and that HIV replication and coinfections may contribute to the pathogenesis of immune activation and to the maintenance of the HIV DNA reservoir also during ART and this mechanism probably underlies the major risk of chronic liver damage and progression of HIV infection showed in coinfected subjects. Direct Active Antivirals (DAA) have changed the clinical scenario of HIV / HCV coinfected patients. Regarding HIV / HBV coinfection, more than 7.4% of a of PLWH was HBsAg-positive. In addition, a proportion of PLWH HBsAg-negative have antibodies against the HBV core antigen (HBcAb), as a sign of previous infection. HBsAg going negative does not mean clearance of HBV DNA and many of these PLWHs may have an occult HBV infection (OBI). According to the update of the Taormina declaration, the detection of HBcAb in the blood can be used as a surrogate marker to identify OBI in subjects with an immunosuppressive condition. In the PLWH population, prevalence rates of OBI ranging from 10% to 45% have been reported. OBI in PLWH has been associated with worse evolution of both HBV liver disease and HIV infection. Detection of HBcAb in PLWH at diagnosis of HIV infection has been associated cryptic HBV replication, a delay in achieving undetectable HIV viremia after ART initiation and a significantly greater presence of viral rebound during cART.

STUDY DESIGN AND METHODS

Study population

This analysis includes prospectively collected data of PLWH enrolled in the ICONA Foundation Study cohort. ICONA is an observational cohort of PLWH who were antiretroviral naïve at the time of enrolment..

Endpoint and inclusion criteria

Participants of the ICONA Foundation Study Cohort with evidence of HIV Virological Success (VS, defined as two consecutive HIV-RNA ≤50 cp/ mL achieved upon initiation of their first line ART) were enrolled in the study. The date of the second HIV-RNA≤50 copies/mL on first ART was defined as the baseline [BL] for the analysis. Participants were prospectively evaluated to investigate the influence of viral hepatitis co-infection on the risk of occurrence of HIV Virological Rebound (VR, defined as two consecutive HIV-RNA values ≥ 50 cp/ml) after baseline. Participants who were never tested for viral hepatitis or never achieved confirmed suppression after starting first line ART were excluded.

Statistical Analysis

Time to experience VR was analysed by means of standard survival analysis techniques such as KM curves and Cox regression models with time- fixed covariates measured at BL. The following factors were identified as possible confounders of the association of interest and were included in the multivariable models: AIDS event, Duration of HIV viral load (VL) suppression, mode of HIV transmission, VL at start of cART, CD4 cells nadir, Previous ART failure, nationality, anchor drug in baseline ART .

AIM

The aim of this study has been to evaluate whether the presence of hepatitis viruses, HCV and HBV (HBsAg positivity and/or HBcAb positivity), could influence the control of HIV replication during effective ART. The risk of viral rebound (2 detections of HIV-RNA> 50 copies / ml), after achieving viral suppression in course of effective therapy, was evaluated in HCV, HBcAb and HBsAg co-infected patients compared with HIV-monoinfected subjects.

RESULTS

Table1 – Subgroups analysis based on HBV/HCV serology

Characteristics	HIV+ Group A	HCV+/HBsAg-/HBcAb- Group B	HCV-/HBsAg-/HBcAb+ Group C	HCV+/HBsAg-/HBcAb+ Group D	HCV/HBsAg+/HBcAb+ Group E	P*
	N=4108	N=290	N=1362	N=390	N=230	
Female, n (%)	872 (21.2%)	104 (35.9%)	229 (16.8%)	83 (21.3%)	45 (19.6%)	<0.001
Age, years, median (IQR)	38 (31-46)	45 (38-53)	45 (38-53)	46 (41-51)	42 (35-51)	<0.001
Nationality, Not Italian, n (%)	730 (17.8%)	30 (10.3%)	402 (29.5%)	50 (12.8%)	77 (33.5%)	<0.001
Calendar year of BL, median (IQR)	2015 (2012-2017)	2013 (2007-2016)	2014 (2011-2016)	2011 (2006-2015)	2014 (2011-2016)	<0.001
Mode of HIV transmission, n (%)						<0.001
IDU	87 (2.1%)	152 (52.6%)	26 (1.9%)	265 (68.5%)	9 (3.9%)	
Homosexual contacts	1997 (49%)	54 (18.7%)	670 (49.9%)	46 (11.9%)	98 (42.8%)	
Heterosexual contacts	1769 (43.1%)	77 (26.6%)	582 (42.7%)	68 (50.4%)	116 (50.4%)	
Other/Unknokwn	226 (5.5%)	6 (2.1%)	66 (4.9%)	8 (2.1%)	6 (2.6%)	
CD4+ cell nadir, median (IQR)	307 (174-441)	254 (141-379)	277 (132-406)	237 (122-348)	276 (124-416)	<0.001
AIDS event at diagnosis, n (%)	**464 (11.3%)**	**37 (12.8%)**	**198 (14.5%)**	**50 (12.8%)**	**34 (14.8%)**	**0.011**
HIV viral load, cp/ml, median (IQR)	**1.52 (1.27-1.60)**	**1.57 (1.30-1.70)**	**1.57 (1.28-1.62)**	**1.60 (1.30-1.70)**	**1.57 (1.28-1.69)**	**0.003**
First line cART						<0.001
2NRTI+INI	1071 (26.1%)	49 (16.9%)	330 (24.2%)	49 (12.6%)	50 (21.2%)	
2NRTI+NNRTI	1259 (30.7%)	92 (31.7%)	403 (29.6%)	121 (31%)	73 (31.7%)	
2NRTI+PI	1214 (29.5%)	111 (38.3%)	481 (35.3%)	170 (43.6%)	81 (35.2%)	
Other	564 (13.7%)	38 (13.1%)	148 (10.9%)	50 (12.8%)	26 (11.3%)	
FU time, months, median (IQR)	46 (24-78)	46 (18-78)	48 (24-84)	52 (21-89)	51 (20-85)	0.209

Abbreviations: NRTI: Nucleoside Reverse-Trascriptase Inhibitors; INI: Integrase Inhibitors; PI: Protease Inhibitors; NNRTI: Non Nucleosides Reverse Transcriptase Inhibitors; HBcAb: anti-HBc; HBsAg: HBs antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; IQR, interquartile ratio. *Chi-square or Kruskal-Wallis test.

Figure: Kaplan Meier estimates of probability of VR

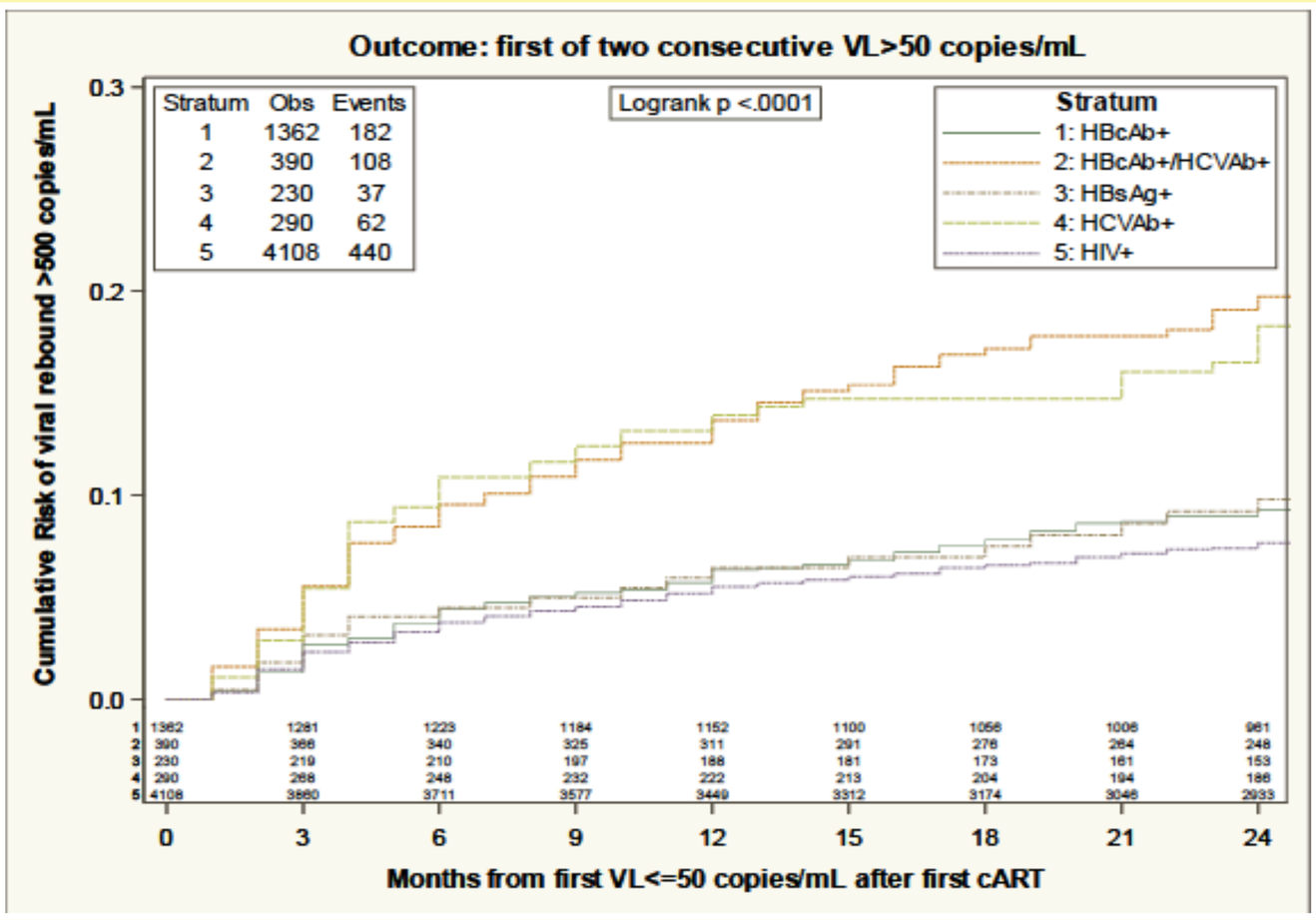

Table 2: Unadjusted and adjusted relative hazards of viral rebound >50 copies/mL

	Unadjusted RH (95% CI)	p	Adjusted[1] RH (95% CI)	p	Adjusted[2] RH (95% CI)	p	Adjusted[3] RH (95% CI)	p
Exposure group								
HIV+	1		1		1		1	
Only HCVAb+	2.10 (1.61, 2.74)	<.001	1.99 (1.40, 2.83)	<.001	1.69 (1.18, 2.40)	0.004	2.00 (1.40, 2.85)	<.001
Only HBcAb+	1.24 (1.04, 1.47)	0.015	1.26 (1.01, 1.57)	0.037	1.17 (0.94, 1.45)	0.170	1.25 (1.01, 1.56)	0.042
HBcAb+/HCVAb+	2.60 (2.11, 3.21)	<.001	1.84 (1.30, 2.59)	<.001	1.49 (1.05, 2.12)	0.026	1.76 (1.25, 2.48)	0.001
HBsAg+	1.49 (1.07, 2.09)	0.019	1.58 (1.04, 2.40)	0.033	1.45 (0.95, 2.20)	0.085	1.54 (1.01, 2.34)	0.042

[1]AIDS, Duration of VL suppression, Mode of HIV transmission, VL at cART; [2]CD4 cell nadir, Mode of HIV transmission, Previous ART failure, VL at cART, nationality;
[3]Duration of VL suppression, Mode of HIV transmission, VL at cART, anchor drug in baseline ART

CONCLUSIONS

The results showed that co-infection with HCV and/or HBV is associated with an increased risk of VR compared to HIV mono-infection, after controlling for key confounders. Co-infected participants HBcAb+/HCV+ and HCV+ had, respectively, a 1.76-fold and 2-fold greater risk of VR than HIV monoinfected group. Also, a significant difference was found in the risk of VR in the HBsAg+ and HBcAb+ co-infected groups, which showed respectively a 1.54- and 1.25-fold higher risk of VR > 50 cp/ml, supporting the theory that persistent HCV and HBV replication could contribute to the poor control of HIV suppression during ART.

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