POSTER: P250
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HBcAb positivity is an independent risk factor for appearance of HIV viral blips in HIV-HBV coinfected patients on antiretroviral therapy

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Introduction

Due to the introduction of Antiretroviral Therapy (ART), and in particular with the introduction rnof drugs active against Hepatitis B virus (HBV), such as Lamivudine (LAM), Tenofovir (TDF) and other nucleoside/nucleotide analogues (NA), HBV infection control has strongly increased in HIV coinfected patients. However, it is known that HIV/HBV coinfected patients, compared to HIV mono-infected patients, reach immune-virologic control with more difficulty and show a higher rate of acquired immunodeficiency syndrome (AIDS) events and end-stage liver disease (ESLD) condition, despite the introduction of ART. In HBsAg-positive ART-treated patients, an impaired CD4 recovery and an accelerated evolution towards AIDS was demonstrated, combined with an increased HBV replication, liver disease progression, hepatocellular carcinoma (HCC) prevalence and liver-related mortality.

No suggestion has been provided regarding the management of HIV-positive patients with HBV-resolved infections (i.e., HBcAb or HBcAb/HBsAb positivity). The resolution of HBV infections is known to be associated with HBV reactivation in immunocompromised patients subsequent to transplantation or chemotherapy for solid or haematological neoplasia. As part of the resolution of HBV infections, occult Hepatitis B (OBI), defined as the absence of HBs antigen (HBsAg) in the presence of intrahepatic or plasma HBV replication, is also known as a risk factor for the evolution of HBV infection in cases of cirrhosis, ESLD and HCC in immunocompromised patients. There are very few data on the influence that resolved HBV infection and OBI may have on HIV infection control, especially in people with low HBV infection prevalence.

Methods and Patients

An observational retrospective study on 671 HIV-positive patients that took place since January 2007 at the Infectious Diseases Unit of the Policlinico Tor Vergata in Rome, Italy, was conducted. Specifically, for this study, a database was built, including all baseline complete haematochemical data, HBV and HCV serology, HIV-RNA viral load, CD4+ cells count, time of HIV infection diagnosis and start of ART treatment for all of the patients. Data on flares of the transaminases (defined as an increase of AST or ALT >50 UI/L), HIV viral blips (defined as a single detection of HIV-RNA >50 cp/mL), virological failure (defined as repeated HIV-RNA values ≥50–1000 copies/mL) and time to achieve viral undetectability (defined as stable HIV-RNA < 50 cp/mL) were collected during follow-up examination. Moreover, data regarding the antiviral treatment for chronic hepatitis B (CHB) (LAM, TDF, TAF or etravirine) were also gathered. When available, HBV-DNA viral load was collected.

Inclusion and exclusion Criteria

671 patients were screened for inclusion. Four hundred and one patients were excluded due to the lack of virological or immunological data at baseline, and 16 patients were excluded because ofr the loss of HBV serology data. Twenty-three patients were excluded due to the presence of transaminase flares due to hepatic drug toxicity (2 patients) and acute Hepatitis A Virus (HAV) infection (21 patients). Two hundred and thirty-one patients were ultimately studied.

Tab. 1: Comparison between HBcAb/ HBsAb+/- positive vs HBV negative patients.
Tab 2: Univariate and Multivariate analysis of variable associated with an increased Risk of HIV viral blips occurrence

Objectives

The primary endpoint of this study was to investigate the impact of the HBV antigen/antibody profile (i.e., HBsAg, HBcAb and/or HBcAb/HbsAb positivity) on overall mortality. Furthermore, we investigated the role of the HBcAb/HBsAb positivity status on the clinical and virological evolution of HIV infections evaluating the impact on the appearance of AIDS-related events and non-AIDS related eventsT. The following non-AIDS events were considered: hypertension, diabetes, bone disorders (osteopenia/osteoporosis), renal impairment, cardiovascular disorders and cancer.The influence of the HBcAb/HBsAb+/- positivity status on the onset of virological failure or viral blips during ART was also investigated.

Results

TAB.1

Study population	HBcAb/HBsAb+/- positive (n=85)	HBV negative (n=136)	P-value
Age, years, median (IQR)	48 (39-55)	39 (29-48)	**0,0001**
Risk factors, n. (%)			
sexual	68 (34%)	125 (62,5%)	**0,01**
IDUs	17 (54,8%)	11 (35,5%)	**0,01**
Follow-up, months, median (IQR)	61,9 (34,8-92,3)	56,3 (36,2-84,3)	0,56
Flaire of transaminases, median (IQR)	56 (65,9%)	49 (36%)	**<0,0001**
FIB-4 at baseline, median (IQR)	1,12 (0,68-1,81)	0,76 (0,48-1,2)	**0,001**
Anti-HCV+, n.(%)	7 (8,2%)	5 (3,6%)	0,23
CD4+ at baseline, cell/mmc, median (IQR)	188 (78-334)	293 (127-443)	**0,02**
Nadir CD4+ cell/mmc, median (IQR)	176 (52-284)	239 (97-390)	**0,01**
Baseline HIV viremia, cp/mL median (IQR)	109,8 (45,6-330,7)	63 (22,4-241,1)	0,14
Undetectability at 6th month, median (IQR)	50 (59,5%)	115 (84,6%)	**<0,0001**
AIDS-related events, Y/N, n. (%)	35 (41,1%)	26 (19,1%)	**0,002**
non-AIDS related events,Y/N, n. (%)	48 (56,5%)	39 (28,7%)	**<0,0001**
Antiretroviral drugs, n (%):			
-Lamivudine	14 (16,4%)	22 (16,1%)	0,95
-Tenofovir/TAF	62 (72,9%)	106 (77,9%)	0,66
-No anti-HBV agent	9 (10,6%)	8 (5,9%)	0,28
HIV virological failure, median (IQR)	18 (21,7%)	14 (10,3%)	0,06
HIV viral blips, median (IQR)	62 (74,7%)	30 (22,1%)	**<0,0001**
Deaths, n.(%)	6 (7,1%)	2 (1,5%)	**0,006**

TAB 2.

	Univariate		Multivariate*	
	aOR (95% CI)	p	aOR (95%)	p
Age > 40 years	1,67 (0,98-2,85)	0,057	0,84 (0,43-1,65)	0,62
IDU	1,91 (0,89-4,13)	0,09	1,37 (0,52-3,58)	0,51
HIV-RNA >10^6 cp/mL	2,48 (1,45-4,25)	**0,001**	1,52 (0,76-3,05)	0,23
CD4+ at baseline >350/mmc	0,35 (0,19-0,64)	**0,001**	1,85 (0,65-5,24)	0,24
CD4+ Nadir >350/mmc	0,17 (0,08-0,37)	**<0,0001**	0,17 (0,05-0,57)	**0,005**
Undetectability at 6th month	0,17 (0,08-0,33)	**<0,0001**	0,26 (0,12-0,56)	**0,001**
HBcAb/HbsAb+/- positivity	8,1 (4,3-14,9)	**<0,0001**	6,01 (3,04-11,9)	**<0,0001**

Eighty-five (36,8%) patients were HBcAb-positive; among them, 36 (15,6%) were HbsAb negative, and 49 (21,2%) were HBsAb positive. With respect to HBV negative subjects, HBcAb/HBsAb+/- positive patients had significantly more episodes of transaminase flares with respect to HBV-negative subjects (p<0,0001), had significantly lower CD4+ cell counts at baseline (p=0,02) and significantly lower nadir of CD4+ cell counts (p=0,02) than HBV-negative subjects. A significantly higher number of AIDS-related (35 [41,5%]) and non-AIDS-related events (48 [56,5%]) were detected in HBcAb/HBsAb+/- positive subjects with respect to HBV-negative patients (26 [19,1%] and 39 [28,7%],p 0.002 and p<0,0001, respectively). At the end of the follow-up period, 62 (74,7%) HBcAb/HBsAb+/- positive patients versus 30 (22,1%) of the HBV-negative subjects developed HIV viral blips (p<0,0001).

A multivariate analysis showed that HBcAb/HBsAb +/- positivity was strongly associated with the occurrence of HIV viral blips during ART (P<0,0001). Conversely, a baseline nadir of CD4+ cell count, na nadir >350/mmc and achieving HIV viral undetectability within 6 months from ART initiation hhad a protective role against the appearance of HIV viral blips appearance during effective ART (p=0,005 and p=0,001).

Conclusions

Presence of HBcAb/HBsAb+/- positivity is a strong risk factor for the appearance of HIV viral blips during ART with an adjusted odds ratio of 6.01, whereas a CD4+ nadir > 350 mmc and the achievement of HIV viremia undetectability within 6 months of ART are protective factors against the appearance of HIV viral blips during the course of therapy. This finding showed that a "previous HBV" serologic status must be considered during follow up, despite antiretroviral strategy. In particular, HBcAb+ status must be highlighted before a HAART simplification, introducing a NUC-Sparing or PI-Lamivudine strategy, without a first-line drug against HBV.