IMPACT OF HBCAB+ ON ADVANCED LIVER FIBROSIS DEVELOPMENT IN HIV-HBV INFECTED PATIENTS

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V. Malagnino*[1] , A. Cozzi-Lepri[2] , L. Sarmati[1] , A. Cingolani[3] , C. Cerva[1] ,F. Ceccherini Silberstein[1] , A. Vergori[4] , G. Cuomo[1] , C.Federico Perno[6] ,M. Puoti[6] , M. Andreoni[1] , A. D'Arminio Monforte[6] , for the ICONA Foundation Study Group

1 University of Rome Tor Vergata, Rome, Italy ~ *2* University College London, London, UK ~ *3* Catholic University of the Sacred Heart, Rome, Italy ~ *4* IRCCS Lazzaro Spallanzani, Rome, Italy ~ *5* University of Modena and ReggioEmilia, Modena, Italy ~ *6* University of Milan, Milan, Italy

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BACKGROUND

Due to the introduction of combined Antiretroviral Therapy (cART), including active anti-HBV agents, HBV infection control has strongly increased in HIV coinfected patients. Conversely, no suggestion has been provided regarding the management of HIV-positive patients with HBV-resolved infections (i.e., HBcAb or HBcAb/HBsAb positivity).

STUDY DESIGN AND METHODS

The aim of the study was to investigate the impact previous HBV infection (intended as HBsAg-/AntiHBc+ serology) on general mortality and the evolution of liver fibrosis. HIV+ patients (pts) enrolled from the ICONA Foundation Study Cohort were prospectively evaluated to investigate the influence of resolved HBV infection (HBcAb+) on the risk of occurrence of advanced liver fibrosis (defined as Fibrosis-4 score[FIB-4]>3.25). We included patients free from liver fibrosis (FIB-4 <3.25) at the date of their first available serology test (baseline). We distinguished 5 HIV+ patients subgroups according to HBV/HCV serology at baseline: a) HCV-/HBsAg-/HBcAb-, b) HCVAb+, c) HBsAb+, d) HBsAg-/HBcAb+/HCVAb+, e) HBsAg+. The different characteristics of the different populations have been described and compared with Kruskal-Wallis or Chi2 according to appropriateness (Tab.1). Standard survival analysis by means of Kaplan-Meier curves and Cox regression models with time-fixed covariates measured at baseline was performed (Tab2 and Fig.1).

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Contact Information: malagninovincenzo@gmail.com

RESULTS

Tab.1: Subgroups analysis based on HBV/HCV serology

Characteristics	All neg N= 5264	HCVAb+ N= 490	HBcAb+ N= 1840	HCVAb+/HBcAb+ N= 620	HBsAg+ N= 367	p	Total N= 8581
Age, years	37 (30, 44)	39 (33, 45)	42 (36, 50)	42 (37, 47)	39 (33, 46)	<.001	39 (32, 46)
Gender, female, n(%)	1242 (23.6%)	188 (38.4%)	332 (18.0%)	139 (22.4%)	76 (20.7%)	<.001	1977 (23.0%)
Mode of HIV Transmission:						<.001	
IDU	109 (2.1%)	281 (57.5%)	42 (2.3%)	448 (72.5%)	13 (3.6%)		893 (10.5%)
Homosexual contacts	2434 (46.5%)	80 (16.4%)	908 (49.8%)	61 (9.9%)	156 (43.0%)		3639 (42.7%)
Heterosexual contacts	2340 (44.5%)	110 (22.4%)	763 (41.5%)	90 (14.5%)	174 (47.4%)		3477 (40.5%)
Other/Unknown	354 (6.8%)	18 (3.7%)	109 (6.0%)	19 (3.1%)	20 (5.5%)		520 (6.1%)
Not italian, n(%)	955 (18.1%)	40 (8.2%)	536 (29.1%)	65 (10.5%)	112 (30.5%)	<.001	1708 (19.9%)
AIDS diagnosis, n(%)	455 (8.6%)	55 (11.2%)	218 (11.8%)	77 (12.4%)	54 (14.7%)	<.001	859 (10.0%)
Calendar year of baseline**	2012 (2009, 2015)	2009 (2003, 2013)	2012 (2008, 2015)	2006 (2003, 2012)	2012 (2008, 2016)	<.001	2012 (2008, 2015)
CD4 count, cells/mmc	432 (263, 618)	446 (295, 636)	409 (225, 621)	440 (278, 649)	423 (223, 642)	0.011	428 (257, 623)
CD4 count nadir, cells/mmc	368 (207, 544)	347 (170, 500)	330 (164, 517)	330 (188, 506)	323 (144, 510)	<.001	352 (188, 532)
CD8 count, cells/mmc	877 (618, 1230)	825 (641, 1206)	880 (619, 1242)	903 (653, 1271)	830 (626, 1188)	0.438	875 (624, 1232)
HIV-1-RNA, log10 copies/mL	4.38 (0.00, 8.00)	3.90 (0.00, 7.04)	4.34 (0.00, 7.81)	3.74 (0.00, 6.88)	4.36 (0.00, 7.00)	<.001	4.31 (0.00, 8.00)
CD4 <=200/mmc, n(%)	861 (18.6%)	69 (15.3%)	364 (22.3%)	92 (15.7%)	75 (23.6%)	<.001	1461 (19.2%)
Follow-up time, months	40 (13, 75)	48 (16, 100)	43 (15, 80)	48 (15, 110)	36 (9, 75)	<.001	41 (13, 79)

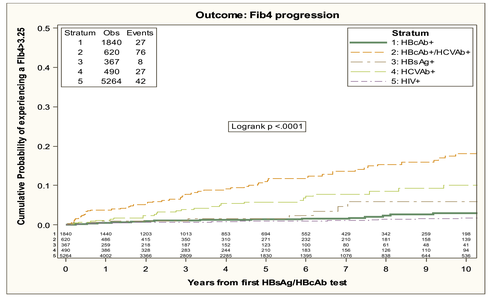
8581 HIV-positive patients were selected, subdivided as follows: HBsAg- / HBcAb- / HCVAb- 5264 patients; 490 HCVAb+; 1840 HBsAg - / HBcAb+; 620 HBsAg- / HBcAb+ / HCVAb+; 367 HBsAg+ / HCVAb-. The majority were male (72%), with a median age of 39 years (IQR 32-46) and 82.2% of patients infected by sexual mode of transmission. Regarding the viroimmunological data at enrolment: our population showed a CD4 count at baseline 428 cells/mmc (IQR 257-623) and a nadir value of CD4 352 cells/mmc (IQR 188-532), compared to a viral load 4,31 log10 copies/mL (IQR 2,57-5). By evaluating the different subpopulations, we highlight how HBsAg- / HBcAb + / HCVab and HBcAb-isolated patients tended to be older [42 (IQR 36-50) and 42 (IQR 37-47), respetctevely] and HCVAb+ with serostatus of previous HBV infection had more frequently a risk factor of acquisition through intravenous drug addiction (IDU) [448 (72,5%)]. Interestingly, patients with a previous HBV infection with or without HCVAb+ or HBsAg-positive patients had a lower Nadir CD4+ cells count: 330 (IQR 188-506), 330 (IQR 164-517) and 323 (IQR 144-510) respectively.

The Kaplan-Meier estimates showed an increased probability of fibrosis elevation in the three years estimates in HBcAb-isolated patients [1,2 (0,6-1,8)] and even more in HCV+/HBcAb+ patients [8,0 (CI 95% 5,6-10,5)]. HBcAb+ serology was confirmed as an important factor in the progression of fibrosis in ten-year estimates: HBcAb-isolated patients showed a 3% 10-years risk of fibrosis progression, while HCV+/HBcAb+ patients 18,7% of risk of fibrosis progression, incrementing the calculated estimates of HCV+patients without HBcAb+.

Cox regression model (Tab. 2), with adjustement for age, mode of trasmission and nation of birth, showed a significant increased relative hazard of experiencing a progression in liver fibrosis evaluated by FIB-4>3,25 during the follow up in patients with HCVAb positive serology [HR 5,75 (CI 95% 3,54-9,35)], HBcAb+/HCVAb+ patients [HR 11,08 (CI 95% 7,58-16,19)], while HR adjusted in multivariate analysis for HBcAb-isolated patients doesn't confirm the increased risk in univariate analysis [u-HR 1,74 [CI 95% 1,07-2,82)].

Figure 1: Kaplan-Meier estimates of probability of Fib4 elevation>3.25

	No. events by 3 year	3-year percent (95% CI)	No. events by 10 years	10-year percent (95% CI)
All-negative	29	0.7 (0.4, 1.0)	42	1.8 (1.1, 2.5)
HCVAb+	15	4.2 (2.1, 6.4)	27	11.1 (6.6, 15.5)
HBcAb+	17	1.2 (0.6, 1.8)	24	3.0 (1.5, 4.5)
HBcAb+/HCVAb+	**39**	**8.0 (5.6, 10.5)**	**66**	**18.7 (14.2, 23.2)**
HBsAg+	4	1.5 (-0.0, 3.0)	8	5.8 (1.4, 10.2)



Tab. 2: Unadjusted and adjusted relative hazards of Fib4>3.25

	Unadjusted RH (95% CI)	p	Adjusted* RH (95% CI)	p
Exposure group				
All neg	1.00		1.00	
Only HCVAb+	5.74 (3.54, 9.32)	<.001	5.75 (3.54, 9.35)	<.001
Only HBcAb+	1.74 (1.07, 2.82)	0.025	1.40 (0.86, 2.29)	0.177
HBcAb+/HCVAb+	**12.34 (8.45, 18.03)**	**<.001**	**11.08 (7.58, 16.19)**	**<.001**
HBsAg+	2,78 (1,30-5,91)	0.008	2.44 (1.14- 5.22)	0.021

*adjusted for age, mode of transmission and nation of birth

CONCLUSIONS

In a large cohort of ART-naive HIV patients, we found that the risk of progression to liver fibrosis (defined as a confirmed FIB-4 >3.25)was elevated in HBcAb+ compared to HIV-mono-infected participants, and especially high in people also infected with HCV, after controlling for confounders such a age, mode of HIV transmission and nationality. Further studies are needed to evaluate the residual risk of fibrosis in HBcAb+ individuals after eradication of HCV by DAA