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

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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 of 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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RESULTS

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

Characteristics	All neg	HCVAb+	HBcAb+	HCVAb+/HBcAb+	HBsAg+	p	Total
	N= 5264	N= 490	N= 1840	N= 620	N= 367		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)

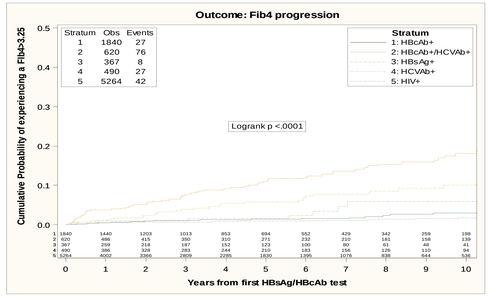
8581 HIV-positive patients were selected, subdivided as follows: HBsAg- / HBcAb- / HCVAb- 5264 patients; 490 HCVAb+; 1840 HBsAg - / HBcAb+; 620 HBsAg- / HBcAb+ / HCVAb+; 367 HBsAg+ / HCVAb-. The majority were male (72%), with a median age of 39 years (IQR 32-46) and 82.2% of patients infected by sexual mode of transmission. Regarding the viroimmunological data at enrollment: 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	3.93 (2,23-6.92)	<.001
Only HBcAb+	1.74 (1.07, 2.82)	0.025	1.45 (0.88-2.38)	0.144
HBcAb+/HCVAb+	**12.34 (8.45, 18.03)**	**<.001**	**6.85 (4.05-11.60)**	**<.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 as 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