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Therapeutic management and evolution of chronic hepatitis B: does HIV co-infection still matter?

The multicenter EPIB12 survey.

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BACKGROUND

- Chronic hepatitis B (CHB) is a major infection worldwide and is frequently associated with HIV infection in most countries, as reported by large surveys.
- HIV has been shown to have a negative impact on HBV evolution, with significant consequences on morbidity and mortality.
- Even though epidemiological characteristics still differ, some other differences between HIV-positive and HIV-negative patients are currently vanishing, since most of the first have improved immune status thanks to effective Highly Active AntiRetroviral Therapy (HAART), and since the latter are now treated with drugs with high anti-HBV efficacy.
- The longer time spent on anti-HBV drugs (and antiretroviral therapy) is also likely to reduce the differences between these patients.

OBJECTIVES

- to compare the management of chronic hepatitis B (CHB) in HIV-positive and HIV-negative patients,
- its evolution over time
- and the relationship with the current presentation of CHB (in particular cirrhosis and hepatocellular carcinoma).

PATIENTS AND METHODS

- 755 consecutive patients with past or present CHB were seen in October 2012 in 19 French participating centers.
- Out of these, 709 with known HIV status and with at least two HBV serological evaluations were analyzed.
- All of their data were retrospectively collected from the first visit onwards through a standardized questionnaire.
- The questionnaire contained information in particular regarding the date of diagnosis of HBV infection; patient demographics; geographic origin; presumed mode of contamination; alcohol consumption; the presence of HBV-associated clinical manifestations; viral co-infections: hepatitis C virus (HCV), HIV, hepatitis delta virus (HDV).
- All the data had to be noted in a time-dependent manner. The past history of each patient was divided into periods, each period being defined as an interval of time with the same anti-HBV treatment (i.e. standard interferon-alpha, pegylated-interferon-alpha, adefovir, lamivudine, emtricitabine, entecavir and tenofovir, alone or in combination), whatever the reason for this treatment has been initiated. Adding, withdrawing or modifying a drug with potential anti-HBV activity induced the end of a period and the beginning of a new one.
- Categorical variables were compared using Fisher's exact and chi-square tests, and continuous variables used the Mann Whitney U test or the Kruskall Wallis test. A forward step-by-step logistic regression was conducted for multivariate analysis of the factors associated with either undetectable HBV, cirrhosis or hepatocellular carcinoma (HCC).

RESULTS

Compared characteristics of HBV-HIV co-infected and HBV mono-infected patients

	HIV-positive patients (n = 299)	HIV-negative patients (n =410)	p*
Age, (mean ± SD, years)	42.9 +/- 10.6	40.9 +/- 14.5	0.04
Male gender, n (%)	209(69.9%)	243 (59.3%)	0.004
Geographic origin, n (%) **			<10^{-3}
France	137 (45.8%)	88 (21.5%)	
Europe	7 (2.5%)	55 (13.4%)	
Africa	134 (44.8%)	171 (41.7%)	
Asia	9 (3.0%)	85 (20.8%)	
Other/Unknown	12 (4.0%)	11 (2.7%)	
HDV seropositivity, n/N (%) **	21/216 (9.7%)	18/358 (5.0%)	0.03
Positive HDV RNA, n/N (%) **	7/19 (36.8%)	4/14 (28.5%)	0.62
HCV seropositivity, n/N (%) **	37/297 (12.5%)	14/405 (3.5%)	<10^{-3}
Positive HCV RNA, n/N (%) **	10/32 (31.3%)	3/14 (21.4%)	0.51
Daily alcohol intake >40gr, n/N (%) **	73/293 (24.9%)	54/387 (14.0%)	0.0003
Time from first HBV diagnosis (mean ± SD, years)	12.3 +/- 7.3	9.8 +/- 7.6	<10^{-3}
Time from first visit (mean ± SD, years)	11.3 +/- 8.8	8.6 +/- 6.9	<10^{-3}
HBV transmission route, n (%) **			<10^{-3}
Blood transfusion	10 (3.3%)	13 (3.2%)	
IVDU	27 (9.0%)	13 (3.2%)	
Sexual	142 (47.5%)	16 (3.9%)	
Mother to Child	22 (7.4%)	121 (29.5%)	
Other/Unknown	98 (32.8%)	247 (60.2%)	

SD = standard deviation; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus; IVDU = intravenous drug user (past or present)
* *p* value obtained with Fisher's exact or chi-square tests, and the Student's t test or Mann Whitney U test when appropriate, for comparisons between HIV-positive and HIV-negative patients
** when available

Evolution of hepatitis B infection according to HIV status

	HIV-positive patients (n = 299)	HIV-negative patients (n = 410)	p*
Wild type virus, n/N (%) **	100/212 (47.6%)	107/346 (30.9%)	0.006
First HBV DNA (mean ± SD, $\log_{10}$ IU/ml)	3.10 +/- 2.89	3.53 +/- 2.50	0.05
First ALT (mean ± SD, x normal value)	1.7 +/- 5.3	1.7 +/- 3.8	0.95
First METAVIR Fibrosis score *** (mean ± SD)	1.4 +/- 1.1	1.6 +/- 1.1	0.38
HBV treatment received during the entire medical history, (n, %)	**285 (95.3%)**	**233 (56.8%)**	**<10^{-3}**
Mean time spent on anti-HBV therapy (mean ± SD, months) (n)****	**101.6 +/- 62.9**	**45.3 +/- 61.0**	**<10^{-3}**
On lamivudine monotherapy	36.9 +/- 46.2 (169)	10.2 +/- 30.1 (70)	<10^{-3}
On lamivudine/emtricitabine	88.7 +/- 61.0 (275)	22.6 +/- 46.7 (107)	<10^{-3}
On adefovir	1.6+/-10.2 (14)	12.4+/-29.4 (84)	<10^{-3}
On tenofovir	54.7 +/- 42.0 (242)	9.9 +/- 19.3 (121)	<10^{-3}
On entecavir	2.0 +/- 10.2 (18)	7.8 +/- 18.4 (88)	<10^{-3}

LOQ = limit of quantification; SD = standard deviation; ALT = alanine transferase; Ag = antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; IVDU = intravenous drug user (past or present)
* *p* value obtained with Fisher's exact or chi-square tests, and Student's t test or Mann Whitney U test when appropriate, for comparisons between HIV-positive and HIV-negative patients
** when assessable/available
*** assessed either via liver biopsy and/or biological test and/or liver elastometry, when available
**** for all the patients, with n indicating the number of patients who were treated with this drug
***** in patients who had at least once positive HBe antigenemia

	HIV-positive patients (n = 299)	HIV-negative patients (n = 410)	p*
YMDD mutations **	10/16 (62.5%)	24/79 (30.4%)	0.01
Last HBV DNA (mean ± SD, $\log_{10}$ IU/ml) **	0.68 +/- 1.66	1.53 +/- 2.06	<10^{-3}
Last HBV DNA < 2,000 IU/ml (n/N, %) **	239/260 (91.9%)	322/390 (82.6%)	<10^{-3}
Last HBV DNA below LOQ (n/N, %) **	**208/260 (80.0%)**	**215/390 (55.1%)**	**<10^{-3}**
HBe Ag loss (n/N, %) *****	24/81(29.6%)	32/94 (34.0%)	0.53
HBe seroconversion (n/N, %) *****	10/81 (12.3%)	22/91 (24.2%)	0.05
HBs Ag loss (n/N, %) **	39/257 (15.2%)	34/351 (9.7%)	0.04
HBs seroconversion (n/N, %) **	20/201 (10.0%)	22/293 (7.5%)	0.34
Last METAVIR Fibrosis score (mean ± SD) ***	1.7 +/- 1.3	1.6 +/- 1.2	0.18
Last clinical presentation **			
Cirrhosis, n/N (%)	32/297 (10.8%)	55/402 (13.7%)	0.25
Hepatocellular carcinoma, n/N (%)	**2/297 (0.7%)**	**19/402 (4.7%)**	**0.002**

Main factors associated with undetectable levels of serum HBV DNA (univariate and multivariate analysis)

	Last HBV DNA below LOQ (n = 423)	Last HBV DNA above LOQ (n = 227)	p*	Multivariate analysis **	p
Age at last visit (mean ± SD, years)	**44.6 +/- 12.7**	**35.9 +/- 12.0**	**<10^{-3}**	**1.03 [1.01-1.05]**	**<10^{-3}**
Male gender (n/N, %)	287/423 (67.8%)	121/227 (53.3%)	<10^{-3}		
Black skin/ethnicity (n/N, %)	149/423 (35.2%)	105/227 (46.3%)	0.006		
Alcohol (n/N, %)	82/423 (19.4%)	35/227 (15.4%)	0.22		
IVDU (n/N, %)	35/423 (8.3%)	12/227 (5.4%)	0.19		
HDV positive (n/N, %)	24/334 (7.2%)	11/ 202 (5.4%)	0.42		
HCV positive (n/N, %)	87/423 (20.6%)	18/227 (7.9%)	<10^{-3}		
Detectable HCV RNA (n/N, %)	8/415 (1.9%)	1/225 (0.4%)	0.06		
HIV positive (n/N, %)	208/423 (49.2%)	51/227 (22.9%)	<10^{-3}		NS
Increase in CD4 (mean ± SD, /mm^3) ***	159 +/- 233	49 +/- 127	<10^{-3}		
Wild type HBV (n/N, %)	127/302 (42.1%)	65/214 (30.4%)	0.98		
Time elapsed since first positive HBsAg (mean ± SD, years)	12.6 +/- 7.6	7.7 +/- 6.3	<10^{-3}		
First HBV DNA level (mean ± SD, $\log_{10}$ IU/ml)	**3.17 +/- 2.73**	**3.78 +/- 2.42**	**0.008**	**0.87 [0.80 -0.95]**	**0.001**
First ALT (mean ± SD, x normal value)	2.0 +/- 5.5	1.3 +/- 2.6	0.09		
First METAVIR fibrosis score (mean ± SD)	1.8 +/- 1.1	1.2 +/- 0.9	<10^{-3}		
Has been on lamivudine monotherapy (n/N, %)	**160/423 (37.9%)**	**28/227 (12.3%)**	**<10^{-3}**	**0.31 [0.15-0.66]**	**0.002**
YMDD mutations (n/N, %)	27/61 (44.2%)	6/31 (19.4%)	0.02		
Has been on adefovir (n/N, %)	73/423 (17.3%)	9/227 (4.0%)	<10^{-3}		
Time spent on HBV therapy (mean ± SD, months)	**91.9 +/- 63.8**	**25.2 +/- 50.3**	**<10^{-3}**	**1.03 [1.02-1.03]**	**<10^{-3}**

HBV = hepatitis B virus; LOQ = limit of quantification; SD = standard deviation; IVDU = intravenous drug user (past or present); HDV = hepatitis delta virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ALT = alanine transferase; HBsAg = HBs antigen
* *p* value obtained with Fisher's exact or chi-square tests, and Student's t test or Mann Whitney U test when appropriate, for comparisons between patients with last HBV DNA below the LOQ and those with last HBV DNA above the LOQ
** Odds ratio for a one unit increase (i.e. one year older, one log10 IU/ml higher, or one additional month on HBV therapy)
*** a value of 0 was attributed to HIV-negative patients.
**** alone or in combination

Main factors associated with cirrhosis (multivariate analysis)

	OR	p
Age (+ 1 year)	**1.06 [1.04-1.09]**	**<10^{-3}**
Male gender	1.78 [0.93-3.41]	0.08
Alcohol (daily intake>40 g)	1.78 [1.14-2.78]	0.01
HCV positive	2.64 [1.11-6.26]	0.03
HDV positive	2.61 [1.07-6.36]	0.03

Main factors associated with hepatocellular carcinoma (HCC) (multivariate analysis)

	OR	p
Age (+ 1 year)	**1.05 [1.01-1.09]**	**<0.01**
Male gender	10.00 [1.27-78.60]	0.03
Cirrhosis	10.11 [3.43-29.82]	**<10^{-3}**
HIV positive	0.15 [0.03-0.67]	0.01

CONCLUSIONS

- By comparison with the previous EPIB studies,
  - HIV-coinfected patients are still more often infected with "wild type" HBV, more often coinfected with HCV and HDV, and followed for a longer period of time than their HBV-monoinfected counterparts in France.
  - By contrast, the negative impact of HIV infection on chronic hepatitis B in the HAART era is likely to further decrease, if not disappear (by contrast with HCV and HDV).
- Although HCC is more frequently associated with cirrhosis, the unexpected lower prevalence observed in HIV-positive patients may suggest that a higher rate of viral suppression associated with antiviral therapies for a longer duration could reduce the risk, as recently reported.
- These findings:
  - support the recommendations to start HAART whatever the CD4 count in HIV/HBV- coinfected patients, including drugs with anti-HBV efficacy;
  - highlight that these recommendations should (re-) emphasize the need not only for a preliminary full assessment of the impact of CHB on the liver, but also for regular re-evaluations during follow up;
  - discourage from using lamivudine as anti-HBV monotherapy as part of HAART in HIV-HBV co-infected patients, to prevent difficulties in future HBV therapy in these patients;
  - suggest that:
    - increasing and improving the assessment of HBV infection in HIV-positive patients, and
    - widening the indication for HBV therapy in HIV negative ones,
    - could result in the management of CHB in HBV mono-infected patients becoming even closer to that in HIV-HBV co-infected patients in the near future.

GERMIVIC STUDY GROUP

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