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Hepatitis B virus-human immunodeficiency virus co-infection in France: a cross-sectional multicentre study

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SUMMARY

This prospective, multicentre study was conducted between September and October 2003 in 38 French departments of internal medicine, infectious disease and hepatogastroenterology and included 406 consecutive HBV-infected patients (positive HBsAg), half of whom were HIV-infected (53%). The aim was to outline the main characteristics of hepatitis B virus (HBV)-human immunodeficiency virus (HIV) co-infected patients in French hospitals. HBV-HIV co-infected patients (85% were receiving HAART; mean CD4 count $447 \pm 245/\mu$l, HIV RNA load <400 copies/ml, 67% of patients), compared to HIV-negative patients, were more often male, injecting drug users, HBeAg-positive and HCV-HIV co-infected ($P<10^{-4}$). They underwent liver biopsy less often (31% *vs.* 51%, $P<10^{-4}$), particularly those with severe immunodeficiency. They received anti-HBV treatment more often (75% *vs.* 45·7%, $P<10^{-4}$), mainly lamivudine and tenofovir. Significant improvements in the management of such patients are awaited mainly in the appraisal of liver disease by either liver biopsy or non-invasive alternatives to liver biopsy.

INTRODUCTION

Hepatitis B virus (HBV) infection is a worldwide disease that affects more than 350 million people. It is responsible for 1 200 000 deaths and more than 300 000 cases of liver cancer per year. It is predominant in Asia and Sub-Saharan Africa, where its prevalence reaches 10–20%, whereas in European countries and North America, the prevalence is 0·2–0·5% [1]. At the beginning of the 1990s, France was considered to be a country with a low prevalence (<0·5%), with ~100 000 HBV-infected patients [2]. The prevalence in blood donors dropped between 1986 and 2000 from 33·9/10 000 to 10·4/10 000 [3].

Human immunodeficiency virus (HIV)-infected patients are frequently co-infected with HBV due to common routes of viral transmission, mainly via sexual routes and injection drug use. The interaction between both diseases remains questionable, as studies have failed to elucidate univocal effects of HIV infection on HBV infection and vice versa. Earlier studies suggested that HBV infection may accelerate the clinical course of HIV-infected patients [4–6], whereas others have refuted this [7, 8]. On the other hand, HIV co-infection in HBV-infected patients is

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associated with a higher prevalence of persisting HBV DNA and HBeAg [9–14], and a higher risk of HBV-related cirrhosis [15], although this latter point is also debatable.

Epidemiological data available on HBV infection in France are scarce, including those on patients with HBV-HIV co-infection. We aimed, in this cross-sectional national French survey, to describe the main characteristics of HBV chronic infection in HIV-infected patients compared to those who are HIV negative.

PATIENTS AND METHODS

A data collection form was posted in September 2003 to the internal medicine, infectious disease and hepatogastroenterology departments of 89 French university and general hospital members of the GERMIVIC group (French Joint Study Group on Viral Hepatitis Infections). Participating centres were asked to provide complete information on each HBV-infected patient [defined by the presence of persisting hepatitis B surface antigen (HBsAg)] seen during the study period from 29 September to 27 October 2003. The questionnaire (available from the authors upon request) contained information regarding the date of diagnosis of HBV infection; patient demographics; geographic origin; presumed mode of contamination; alcohol consumption (<40, 40–80, >80 g/d); the presence of HBV-associated clinical manifestations, including asthenia, symptomatic acute hepatitis, clinical signs of cirrhosis [decompensated cirrhosis, hepatocellular insufficiency, imaging signs (portal hypertension, oesophageal varices)], liver cancer, symptomatic mixed cryoglobulinaemia and other autoimmune diseases; biochemical characteristics at the time of diagnosis; viral co-infection [hepatitis C virus (HCV), HIV, hepatitis delta virus (HDV)]; HBV virological and histological testing performed; and anti-HBV treatment.

The presence of the following virological markers was noted for each patient: HBsAg, antibodies to the hepatitis B surface antigen (HBsAb), hepatitis Be antigen (HBeAg), antibodies to the hepatitis Be antigen (HBeAb), markers of HBV replication (detection of the HBV DNA in serum by PCR or branched-DNA probe assays), and markers of HDV co-infection (anti-HDV antibodies, serum HDV RNA). Among patients that had never received anti-HBV treatment, infection by a replicative precore mutant was defined by the association of a negative HBeAg, a positive HBeAb and a detectable serum HBV DNA (as proven by positive HBV PCR or branched-DNA probe assay).

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported as multiples of the upper limit of normal value ($\times$ ULN). Abnormal liver biochemistry was defined as at least one abnormal value of ALT and AST.

HIV infection was defined by the presence of anti-HIV antibodies on both ELISA and Western blot assays. The main features of HIV disease which were collected were: disease stage according to CDC classification, CD4 cell count, HIV viral load, and treatment with highly active anti-retroviral treatment (HAART). HCV infection was defined by the presence of anti-HCV antibodies (ELISA, 3rd generation) and a positive serum HCV RNA; HDV superinfection was defined by the presence of positive anti-HDV antibodies.

A liver biopsy was performed at the discretion of the physician. The pathologist of each participating centre used the METAVIR scoring system for classifying fibrosis stage and activity grade [16, 17]. Liver biopsies >10 mm in length were fixed, paraffin-embedded, and stained with either haematoxylin and eosin-safran and Masson's Trichrome or Picrosirius Red for collagen. For each liver biopsy, a fibrosis stage and an activity grade were established according to the following criteria. Fibrosis stages were on a scale from 0 to 4 (F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; F4, cirrhosis). Activity grading evaluating the intensity of necroinflammatory lesions was on a scale from 0 to 3 (A0, no histological activity; A1, mild activity; A2, moderate activity; A3, severe activity).

Questions regarding anti-HBV treatment focused on the absence of past or current treatment, and details of anti-HBV treatment, i.e. standard IFN-α, PEG-IFN-α, lamivudine, tenofovir, and adefovir.

Statistical analysis

Categorical variables were compared using Fisher's exact and χ^2 tests, and continuous variables used the Mann–Whitney U test. Stepwise multiple logistic regression analysis was used to assess independent associations. Variables included in the multivariate analyses were selected based on the results of univariate analyses ($P<0{\cdot}1$). All tests were two-sided and a P value of $<0{\cdot}05$ was considered statistically significant. All statistical analyses were performed using MedCalc® version 7.4.2.0 (Mariakerke, Belgium).

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RESULTS

Epidemiological and clinical features of the study population

Thirty-eight hospital departments participated in the study. A total of 406 patients with chronic HBV infection were included during the study period. Epidemiological, clinical and liver histological features are reported in Table 1.

HIV co-infection was present in 205/389 (52·7%) patients. The mean age was 41 ± 8·6 years and 87·5% of patients were male. According to CDC classification, 40·7% were in stage A, 23·6% in stage B and 35·7% in stage C. Eighty-five percent of these patients were receiving HAART. The mean CD4 cell count was 447 ± 245/μl, and the serum HIV RNA was <400 copies/ml in 67% of patients.

When compared to HIV-negative patients in univariate analysis (Table 2), HIV-infected patients were more often male (87·5% *vs.* 65·8%, $P<10^{-4}$), injecting drug users (IDU) (20·5% *vs.* 2·2%, $P<10^{-4}$), and more frequently infected through sexual transmission (66·8% *vs.* 13·04%, $P<10^{-4}$). HIV-infected patients had HBV-related clinical symptoms less often (65% *vs.* 75%, $P=0·007$), mainly asthenia (16·6% *vs.* 23·4%, $P=0·06$) and clinical signs of cirrhosis (8·3% *vs.* 16·8%, $P=0·01$). There was no significant difference in the distribution of viral or liver histological parameters when patients were stratified by ethnic origin (data not shown).

Liver histological features

HIV-infected patients had had liver biopsies less often than those who were HIV-negative (31·3% *vs.* 51·4% respectively, $P=0·0002$). The rate of liver biopsy was also lower in symptomatic HIV-infected patients (CDC stages B and C) compared to asymptomatic patients (CDC stage A) [21·9% (23/105) *vs.* 35·6% (26/73), $P=0·04$]. HIV-infected patients with CD4 cell counts of <350/μl had undergone liver biopsy less frequently than those with counts ⩾350/μl [19·21% (14/73) *vs.* 37·71% (46/122) respectively, $P=0·01$]. There was no significant difference in the rate of liver biopsies between HIV-positive patients with CD4 counts >350/μl and HIV-negative patients (41·4% *vs.* 51·4%, $P=0·2$). Compared to HIV-negative patients, HIV-infected patients did not present with more severe liver histological damage in terms of mean fibrosis scores (2·1 ± 1·3 *vs.* 1·96 ± 1·4) and activity scores (1·5 ± 0·65 *vs.* 1·4 ± 0·9), or in terms of severe liver fibrosis (METAVIR F3–F4: 34·9% *vs.* 35·0%). HIV-HBV co-infected patients who received anti-HBV treatment had higher mean liver histological fibrosis scores (2·1 ± 1·2 *vs.* 1·0 ± 0·8, $P=0·003$). There was no significant difference when stratification

Table 1. *Main features of the 406 HBV-infected patients*

Number of patients	406
Age (mean ± S.D., yr)	40·8 ± 11·9
Sex (% male)	76
Geographic origin, *n* (%)	360 (89)
Europe	176 (49)
Sub-Saharan Africa	111 (31)
Asia	43 (12)
Other	30 (8)
Routes of infection when known, *n* (%)	263 (65)
Sexual transmission	170/263 (65)
Vertical transmission	50 (19)
Injecting drug use	47 (18)
Blood transfusion	16 (6)
Clinical manifestations, *n* (%)	
Asymptomatic	286 (70)
Asthenia	82 (20)
Clinical signs of cirrhosis	48 (12)
Acute hepatitis	7 (2)
Hepatocarcinoma	1 (0·2)
Autoimmune diseases	8 (2)
AST WNL*, *n* (%)	245/359 (68)
ALT WNL, *n* (%)	265/394 (67)
Alcohol comsuption (>40 g/day), *n* (%)	22/354 (9)
Liver biopsy, *n* (%)	169 (42)
METAVIR Activity score	1·5 ± 0·8
METAVIR Fibrosis score	2·1 ± 1·3
METAVIR F3–F4, *n* (%)	64 (38)
METAVIR F4, *n* (%)	37 (22)
Co-infection, *n* (%)	
HIV	205/389 (53)
HCV	46/385 (12)
HDV	23/235 (10)
Virological markers, *n* (%)	
HBe Ag-positive	135/340 (40)
HBe Ab-positive	196/332 (59)
Detectable serum HBV DNA†	214/366 (59)
Infection by a precore mutant‡	37/115 (32)

HIV, Human immunodeficiency virus; HCV, hepatitis C virus; HDV, hepatitis delta virus.

* WNL, Within normal limit.

† By PCR or DNA branched assay.

‡ The serological profile of an infection by a precore mutant, analysed only in untreated anti-HBV patients ($n=115$), was defined by the association of (1) negative HBeAg, (2) positive HBe antibodies (Ab) and (3) persistence of a viral replication as proven by a positive HBV PCR or DNA-branched probe assay.

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Table 2. *Main characteristics of HBV-infected patients according to HIV co-infection*

	HIV-positive patients ($n=205$)	HIV-negative patients ($n=184$)	P*
Age (mean ± S.D., yr)	41 ± 8·6	40 ± 14	0·09
Male, *n* (%)	175/200 (88)	121/184 (66)	$<10^{-5}$
Injecting drug use, *n* (%)	42/205 (21)	4/184 (2)	$<10^{-4}$
Sexual transmission, *n* (%)	137/205 (67)	24/184 (13)	$<10^{-4}$
Vertical transmission, *n* (%)	0/205 (0)	42/184 (23)	$<10^{-5}$
Europe, n (%)	107/168 (64)	61/176 (35)	$<10^{-5}$
Sub-Saharan Africa, n (%)	50/168 (30)	60/176 (34)	0·4
Asia, n (%)	0/168 (0)	39/176 (22)	$<10^{-5}$
Asthenia, *n* (%)	34/205 (17)	43/184 (23)	0·06
Clinical cirrhosis, *n* (%)	17/205 (8)	31/184 (17)	0·01
HBeAg+, *n* (%)	87/163 (53)	45/163 (28)	$<10^{-4}$
Detectable HBV DNA, *n* (%)	110/184 (60)	99/168 (59)	0·9
Precore mutant, *n* (%)†	7/39 (18)	28/71 (39)	0·02
HDV infection, *n* (%)	13/85 (15)	8/141 (6)	0·02
HCV infection, *n* (%)	39/198 (20)	6/184 (3)	$<10^{-4}$
Liver biopsy, *n* (%)	63/201 (31)	94/183 (51)	$<10^{-4}$
METAVIR Activity score (mean ± S.D.)	1·5 ± 0·65	1·4 ± 0·9	0·5
METAVIR Fibrosis score (mean ± S.D.)	2·1 ± 1·3	1·96 ± 1·4	0·4
F3–F4, *n* (%)	22/63 (35)	33/94 (35)	0·9
F4, *n* (%)	14/63 (22)	20/94 (21)	0·1
ALT (xULN) (mean ± S.D.)	1·46 ± 1·1	1·8 ± 3·8	0·07
ALT WNL, *n* (%)	127/200 (64)	126/178 (71)	0·2
AST (xULN) (mean ± S.D.)	1·35 ± 1	1·67 ± 3·7	0·04
AST WNL, *n* (%)	130/200 (65)	106/144 (74)	0·1
Anti-HBV treatment, *n* (%)	154/205 (75)	84/184 (46)	$<10^{-4}$
Standard IFN-α	29/205 (14)	37/184 (20)	0·1
PEG-IFN-α	3/205 (2)	13/184 (7)	0·005
Lamivudine	148/205 (72)	63/184 (34)	$<10^{-4}$
Adefovir	17/205 (8)	37/184 (20)	0·001
Tenofovir	57/205 (28)	2/184 (1)	$<10^{-4}$

ULN, Upper limit of normal; WNL, within normal limit.

* P value obtained with Fisher's exact and χ^2 tests, or the Mann–Whitney U test when appropriate.

† The serological profile of an infection by a precore mutant, analysed only in untreated anti-HBV patients ($n=115$), was defined by the association of (1) negative HBeAg, (2) positive HBe antibodies (Ab) and (3) persistence of a viral replication as proven by a positive HBV PCR or DNA-branched probe assay.

was done on CD4 cell counts (mean fibrosis score 2·12 ± 1·3 when CD4 count is $>200/\mu$l, compared to 2·5 ± 2·12 when CD4 count is $\leqslant 200/\mu$l, $P=0·78$).

Virological features

Compared to HIV-negative patients, those with HBV-HIV co-infection were HBeAg-positive more often (53·4% *vs.* 27·6%, $P<10^{-4}$), and inversely, had HBeAb less often (43·8% *vs.* 73·4%, $P<10^{-4}$). There was no significant difference for serum HBV DNA detection (59·8% *vs.* 58·9%). The presence of a serological profile for precore mutants in patients who had never been treated for their HBV infection was less frequent in HIV-positive patients than in those who were HIV negative (17·9% *vs.* 39·4%, $P=0·02$). Regarding other viral co-infections, HIV-infected patients had HCV co-infection more frequently (19·7% *vs.* 3·3%, $P<10^{-4}$) and HDV co-infection (15·3% *vs.* 5·7%, $P=0·02$) (Table 2). It was of note that HIV-positive patients were less frequently tested for HDV infection (41·5% *vs.* 76·6%, $P<10^{-4}$).

Anti-HBV therapy

HBV-HIV co-infected patients received anti-HBV treatment more frequently than HIV-negative patients (75% *vs.* 46%, $P<10^{-4}$), i.e. lamivudine (72% *vs.* 34%, $P<10^{-4}$) and tenofovir (27·8% *vs.* 1·1%, $P<10^{-4}$). Inversely, they received adefovir and PEG-IFN-α less frequently (8% *vs.* 20%, $P=0·0008$; and 1·5% *vs.* 7%, $P=0·005$ respectively).

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Table 3. *Main factors associated with cirrhosis in HIV-HBV co-infected patients*

	HIV-HBV co-infected patients		Univariate analysis *P**	Multivariate analysis	
	Cirrhotic	Non-cirrhotic		OR (95% CI)	*P*†
Age (mean ± S.D., yr)	43·6 ± 8·8	40·6 ± 8·5	0·1	1·06 (1·02–1·2)	0·006
Male sex, *n* (%)	19/23 (83)	156/177 (88)	0·3	—	—
HCV+, *n* (%)	8/22 (36)	31/176 (18)	0·04	3 (0·97–9·6)	0·056
HDV+, *n* (%)	3/13 (23)	10/72 (14)	0·3	—	—
HBe Ag+, *n* (%)	12/20 (60)	75/143 (52)	0·5	—	—
HBV DNA+, *n* (%)	15/21 (71)	95/163 (58)	0·25	—	—
Precore mutant, *n* (%)‡	3/19 (15·8)	18/138 (13)	0·5	—	—
Anti-HBV therapy, *n* (%)	22/23 (96)	132/182 (73)	0·015	13·6 (1·5–122)	0·02

* *P* values were obtained with Fisher's exact test or the Mann–Whitney *U* test when appropriate.
† *P* values were obtained after a stepwise logistic regression.
‡ The serological profile of an infection by a precore mutant, analysed only in untreated anti-HBV patients ($n = 115$), was defined by the association of (1) negative HBeAg, (2) positive HBe antibodies (Ab) and (3) persistence of a viral replication as proven by a positive HBV PCR or DNA-branched probe assay.

Among HIV-positive patients, those with cirrhosis (22 patients) received anti-HBV therapy more frequently than those without cirrhosis (95·7% *vs.* 72·5% respectively, $P = 0{\cdot}015$). Among patients receiving anti-HBV treatment at the time of the study ($n = 198$), serum HBV DNA remained positive in 61% (76/124) of HIV-infected patients compared to 54% (40/74) of HIV-negative patients ($P = 0{\cdot}4$).

HBV-HIV co-infection and cirrhosis

Among HIV-positive patients, 23 patients (11·2%) had clinical or histological signs of cirrhosis. Compared to those without cirrhosis (Table 3), patients with cirrhosis tended to be older (43·6 ± 8·8 *vs.* 40·6 ± 8·5 years, $P = 0{\cdot}1$), were HCV-positive more frequently (36·4% *vs.* 17·6%, $P = 0{\cdot}04$) and were receiving anti-HBV therapy (95·7% *vs.* 72·5%, $P = 0{\cdot}015$). There was not a significant difference in either group in regards to the prevalence of HBeAg, serum HBV DNA detection, or precore mutants, nor in the HIV viral load, CD4 count, or mode of acquisition. In multivariate analysis (Table 3), the factors associated with cirrhosis in HIV-infected patients included advanced age (OR 1·05, 95% CI 1·02–1·08, $P < 10^{-3}$), HCV infection (OR 3, 95% CI 0·97–9·6, $P = 0{\cdot}056$), and use of anti-HBV therapy (OR 13·6, 95% CI 1·5–122, $P = 0{\cdot}02$).

DISCUSSION

This cross-sectional study evaluates the main characteristics of chronic HBV-HIV co-infection in France with a focus on cirrhosis and associated factors. Our study population shared classical epidemiological characteristics such as young age (before the 4th decade), male predominance and viral transmission via the sexual route [18–20]. Only 12% of patients had clinical signs of cirrhosis, whereas histological cirrhosis was found in more than one fifth of patients, a prevalence close to those reported in previous studies (from 17% to 28·5%) [18–20]. The presence of cirrhosis was associated with HCV co-infection and advanced age. From a virological point of view, 40% of patients had positive HBeAg, and more than one half had detectable serum HBV DNA. Of note, a significant proportion of HIV-positive patients did not have a routine investigation done for HDV infection.

HBV-HIV co-infection was present in more than half of the patients included in this study. This high prevalence of HIV infection among our HBV-infected patients does not necessarily reflect the prevalence of HIV infection in HBV-infected patients followed in France. One explanation may be the high proportion (18/38) of participating departments of infectious diseases or internal medicine with a greater activity of infectious diseases, mainly HIV infection. Another argument may be the common routes of transmission in both diseases.

Regarding liver disease, HBV-HIV co-infected patients had less frequent clinical signs of cirrhosis and had lower AST and ALT serum levels. These results contribute to the debate concerning the effects of HIV infection on the course of chronic HBV infection. No differences in liver histology were seen

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between HIV-positive and HIV-negative patients in terms of liver activity and fibrosis scores or in the rate of extensive fibrosis (F3–F4) and cirrhosis (F4). Our results are in accordance with previous reports that did not document more severe lesions and sometimes found less liver histological damage in HBV-HIV co-infected patients [21, 22]. Other studies, however, have suggested an increased risk of progression to cirrhosis in HIV-positive patients [14, 15] or in some subgroups with HDV super-infection [13–15]. These results may be due to a shorter duration of HBV infection in HIV-infected patients, who were mainly infected through intravenous drug use and sexual routes; in HIV negative patients, however, the major mode of contamination was through vertical transmission (Table 2).

Our data should be interpreted while taking into account the more frequent use of anti-HBV therapy and lower rate of liver biopsy in HIV-positive patients. The great majority of HIV-positive patients were receiving anti-HBV treatment, mainly that of lamivudine and/or tenofovir, whereas less than half of HIV-negative patients were receiving anti-HBV treatment. The anti-HBV treatment was given more frequently in HIV-positive patients with clinical or histological cirrhosis. The more frequent use of anti-HBV drugs in HIV-positive patients is undoubtedly due to a high prescription rate of HAART, including lamivudine or tenofovir, drugs that are active in both HBV and HIV infections. HIV-positive patients receiving anti-HBV treatment may benefit from liver histological improvement or stabilization, leading to a lower rate of cirrhosis, as was reported in HBV mono-infected patients [23, 24].

The second fact that may be considered in the discussion of the low rate of cirrhosis in HIV-positive patients is the lower proportion of liver biopsy. Indeed, HIV-positive patients had liver biopsy less often than HIV-negative patients, with the resultant risk of the rate of cirrhosis being underestimated. This was particularly true for HIV-positive patients with CD4 counts $<350/\mu$l, in whom only 19% had had a liver biopsy. HIV-positive patients with CD4 counts $>350/\mu$l and HIV-negative patients both had similar rates of liver biopsy. The increase of validated non-invasive diagnostic tests of liver activity and fibrosis should simplify screening for the severity of viral liver diseases in a larger number of HIV-positive patients [25, 26].

Aside from these controversies and hypotheses, there seems to be consensual agreement that chronic HCV infection induces a more aggressive liver disease in HIV-positive patients, as supported by our results and others' [27–30], including a higher risk of cirrhosis. This was also demonstrated in HCV-HBV co-infected patients [18, 31, 32]. These data underline the importance of the appraisal of HCV infection in HIV-HBV co-infected patients with a more cautious follow-up, including liver fibrosis assessment and the introduction of specific antiviral therapies, as proposed by the recent European Consensus Conference [27–30]. The slight but significant association between cirrhosis and advanced age might only reflect the longer duration of HBV infection.

HDV infection is also a known risk factor for cirrhosis [33]. This does not clearly appear in our study, but 23% of cirrhotic HIV-positive patients were HDV positive compared to 14% of non-cirrhotic HIV-positive patients. It is of note that HIV-positive patients were less frequently tested for HDV infection compared to HIV-negative patients.

A serological profile of HBV infection by a replicative precore variant (HBeAg-negative, HBeAb-positive, and positive serum HBV DNA) was reported in 32% of the global population included in this study. We excluded patients who had been or were still receiving anti-HBV treatment in order to reduce the risk of confounding the HBeAg/HBeAb seroconversion during therapy and the occurrence of precore mutants. The prevalence of replicative precore variants is slightly higher than that reported in a previous French multicentre study in HBV mono-infected patients (22%) [34]. The comparison with other studies becomes difficult because of the great geographic diversity and the lack of genotyping proofs. Compared to HIV-negative patients, HBV-HIV co-infected patients had a lower prevalence of precore mutants, and inversely, were HBeAg-positive more often. As precore mutants are thought to be secondary to immunological selection [35], one can speculate that the HIV-related immunocompromised status may have favoured the persistence of the wild-type virus with persisting HBeAg.

Serum HBV DNA was positive in the same proportions for both HIV-positive and HIV-negative patients. However, viral load quantification was not available. Previous studies clearly demonstrated a higher frequency of persistent viral replication in HIV-positive patients with higher serum HBV DNA levels, a greater incidence of positive HBeAg and reduced rates of HBeAg seroconversion [9–14].

In conclusion, HBV-HIV co-infected patients in France are more often male, injecting drug users, and

HBeAg positive. One-third of them presented with severe liver fibrosis at the time of biopsy, although they underwent liver biopsy less often than HBV mono-infected patients. Cirrhosis was associated with advanced age and HCV co-infection. The exact role of anti-HBV therapy in such a population requires further prospective studies, as most patients in this series received such therapy as anti-HIV treatment.

APPENDIX. Members of the GERMIVIC Study Group

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Lai CL, *et al.*** Viral hepatitis B. *Lancet* 2003; **362**: 2089–2094.
2. **Goudeau A, Dubois F.** Incidence and prevalence of hepatitis B in France. *Vaccine* 1995; **13** (Suppl. 1): S22–25.

3. **Pillonel J, *et al.*** Prevalence of HBV, HCV, HIV and HTLV in autologous blood donors in France between 1993 and 2000 [in French]. *Transfusion Clinique et Biologique* 2002; **9**: 289–296.
4. **Hadler SC, *et al.*** Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *Journal of Infectious Diseases* 1991; **163**: 454–459.
5. **Eskild A, *et al.*** Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. *AIDS* 1992; **6**: 571–574.
6. **Ockenga J, *et al.*** Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *Journal of Hepatology* 1997; **27**: 18–24.
7. **Solomon RE, *et al.*** Human immunodeficiency virus and hepatitis delta virus in homosexual men. A study of four cohorts. *Annals of Internal Medicine* 1988; **108**: 51–54.
8. **Gilson RJ, *et al.*** Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS* 1997; **11**: 597–606.
9. **Kellerman SE, *et al.*** Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *Journal of Infectious Diseases* 2003; **188**: 571–577.
10. **Bodsworth N, Donovan B, Nightingale BN.** The effect of concurrent human immunodeficiency virus infection on chronic hepatitis B: a study of 150 homosexual men. *Journal of Infectious Diseases* 1989; **160**: 577–582.
11. **Koblin BA, *et al.*** Effect of duration of hepatitis B virus infection on the association between human immunodeficiency virus type-1 and hepatitis B viral replication. *Hepatology* 1992; **15**: 590–592.
12. **Mai AL, *et al.*** The interaction of human immunodeficiency virus infection and hepatitis B virus infection in infected homosexual men. *Journal of Clinical Gastroenterology* 1996; **22**: 299–304.
13. **Housset C, *et al.*** Interactions between human immunodeficiency virus-1, hepatitis delta virus and hepatitis B virus infections in 260 chronic carriers of hepatitis B virus. *Hepatology* 1992; **15**: 578–583.
14. **Colin JF, *et al.*** Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999; **29**: 1306–1310.
15. **Thio CL, *et al.*** HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002; **360**: 1921–1926.
16. **Cable E.** Intraobserver and interobserver variations in liver biopsy further improvements than those reported here could be interpretation in patients with chronic hepatitis C. *Hepatology* 1994; **20**: 15–20.
17. **Bedossa P, Poynard T.** An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; **24**: 289–293.
18. **Di Marco V, *et al.*** The long-term course of chronic hepatitis B. *Hepatology* 1999; **30**: 257–264.
19. **Janssen HL, *et al.*** Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1999; **30**: 238–243.
20. **van Zonneveld M, *et al.*** Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004; **39**: 804–810.
21. **Perrillo RP, Regenstein FG, Roodman ST.** Chronic hepatitis B in asymptomatic homosexual men with antibody to the human immunodeficiency virus. *Annals of Internal Medicine* 1986; **105**: 382–383.
22. **Goldin RD, *et al.*** Histological and immunohistochemical study of hepatitis B virus in human immunodeficiency virus infection. *Journal of Clinical Pathology* 1990; **43**: 203–205.
23. **Marcellin P, *et al.*** Adefovir dipivoxil for the treatment of hepatitis Be antigen-positive chronic hepatitis B. *New England Journal of Medicine* 2003; **348**: 808–816.
24. **Hadziyannis SJ, *et al.*** Adefovir dipivoxil for the treatment of hepatitis Be antigen-negative chronic hepatitis B. *New England Journal of Medicine* 2003; **348**: 800–807.
25. **Myers RP, *et al.*** Serum biochemical markers accurately predict liver fibrosis in HIV and hepatitis C virus co-infected patients. *AIDS* 2003; **17**: 721–725.
26. **Myers RP, *et al.*** Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. *Journal of Hepatology* 2003; **39**: 222–230.
27. **Poynard T, *et al.*** A comparison of fibrosis progression in chronic liver diseases. *Journal of Hepatology* 2003; **38**: 257–265.
28. **Soto B, *et al.*** Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *Journal of Hepatology* 1997; **26**: 1–5.
29. **Martin-Carbonero L, *et al.*** Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clinical and Infectious Diseases* 2004; **38**: 128–133.
30. **Romeo R, *et al.*** Hepatitis C is more severe in drug users with human immunodeficiency virus infection. *Journal of Viral Hepatology* 2000; **7**: 297–301.
31. **Gaeta GB, *et al.*** Epidemiological and clinical burden of chronic hepatitis B virus/hepatitis C virus infection. A multicenter Italian study. *Journal of Hepatology* 2003; **39**: 1036–1041.
32. **Donato F, Boffetta P, Puoti M.** A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *International Journal of Cancer* 1998; **75**: 347–354.
33. **Hadziyannis SJ.** Review: hepatitis delta. *Journal of Gastroenterology and Hepatology* 1997; **12**: 289–298.
34. **Zarski JP, *et al.*** Comparison of anti-HBe-positive and HBe-antigen-positive chronic hepatitis B in France. French Multicentre Group. *Journal of Hepatology* 1994; **20**: 636–640.
35. **Hadziyannis SJ, Vassilopoulos D.** Hepatitis Be antigen-negative chronic hepatitis B. *Hepatology* 2001; **34**: 617–624.