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ORIGINAL ARTICLE

Prevalence and virological profiles of hepatitis B infection in human immunodeficiency virus patients

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Abstract

AIM: To determine the prevalence of hepatitis B virus (HBV) in adult human immunodeficiency virus (HIV) patients with CD4+ T-cell count less than 500/mm^3 and without antiretroviral therapy; to describe different HBV-HIV coinfection virological profiles; and to search for factors associated with HBs antigen (HBsAg) presence in these HIV positive patients.

METHODS: During four months (June through September 2006), 491 patients were received in four HIV positive monitoring clinical centers in Abidjan. Inclusion criteria: HIV-1 or HIV-1 and 2 positive patients, age $\geqslant$ 18 years, CD4+ T-cell count < 500/mL and formal and signed consent of the patient. Realized blood tests included HIV serology, CD4+ T-cell count, quantitative HIV RNA load and HBV serological markers, such as HBsAg and HBc antibody (anti-HBcAb). We performed HBeAg, anti-HBe antibody (anti-HBeAb), anti-HBc IgM and quantitative HBV DNA load in HBsAg positive patients. Anti-HBsAb had been tested in HIV patients with HBsAg negative and anti-HBcAb-positive. HBV DNA was also tested in 188 anti-HBcAb positive patients with HBsAg negative status and without anti-HBsAb. Univariate analysis (Pearson χ^2 test or Fischer exact test) and multivariate analysis (backward step-wise selection logistic regression) were performed as statistical analysis.

RESULTS: Mean age of 491 patients was 36 ± 8.68 years and 73.3% were female. Type-1 HIV was found in 97% and dual-type HIV (type 1 plus type 2) in 3%. World Health Organization (WHO) clinical stage was 1, 2, 3 and 4 respectively in 61 (12.4%), 233 (47.5%), 172 (35%) and 25 patients (5.1%). Median CD4+ T-cell count was 341/mm^3 (interquartile range: 221-470). One hundred and twelve patients had less than 200 CD4+ T-cell/mm^3. Plasma HIV-1 RNA load was elevated ($\geqslant$ 5 log$_{10}$ copies/mL) in 221 patients (45%). HBsAg and anti-HBcAb prevalence was respectively 13.4% and 72.9%. Of the 66 HBsAg positive patients, 22 were inactive HBV carriers (33.3%), 21 had HBeAg positive hepatitis (31.8%) and 20 had HBeAg negative hepatitis (30.3%). HBeAg and anti-HBeAb were indeterminate in 3 of them. Occult B infection prevalence (HBsAg negative, anti-HBcAb positive, anti-HBsAb negative and detectable HBV DNA) was 21.3%. Three parameters were significantly associated with the presence of HBsAg: male [odds ratio (OR): 2.2; P = 0.005; 95% confidence interval (CI): 1.3-3.8]; WHO stage 4 (OR: 3.2; P = 0.01;

95% CI: 1.3-7.9); and aspartate aminotransferase (AST) level higher than the standard (OR: 1.9; P = 0.04; 95% CI: 1.02-3.8).

CONCLUSION: HBV infection prevalence is high in HIV-positive patients. HBeAg positive chronic hepatitis and occult HBV infection are more frequent in HIV-positive patients than in HIV negative ones. Parameters associated with HBsAg positivity were male gender, AIDS status and increased AST level.

Key words: Hepatitis B virus-human immunodeficiency virus coinfection; Prevalence; Virological profiles; Black Africa

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INTRODUCTION

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infections are real public health problems, particularly in high-prevalence areas such as sub-Saharan Africa. In the world, there are more than 30 million people living with HIV/AIDS (two thirds of which live in sub-Saharan Africa) and about 350 to 400 million chronic HBV carriers[1-3]. HBV infection was reported to increase mortality and morbidity in HIV patients. Indeed, HIV infection increases chronic HBV infection risk and promotes faster progression to cirrhosis and its complications, especially when HBV replication is important[4-9]. If HBV-HIV coinfection is very common in sub-Saharan Africa, there are few data on HBV infection virological aspects in HIV Black African patients[10-14]. This study's aims were to estimate HBV infection prevalence among an adult population, with HIV infection, less than 500 CD4+ T-cell/mm^3 and without antiretroviral therapy (ART), to describe the different profiles of virological B co-infected subjects and to search for HBs antigen (HBsAg) presence associated factors in these HIV patients.

MATERIALS AND METHODS

This is a multicenter cross-sectional study conducted in Abidjan, Cote D'Ivoire and approved by the Ivorian Ministry of Health ethics committee. We included all adult patients who had a consultation in one of the four sites identified for the study over the period of June 1 to September 31, 2006 and who met the following inclusion criteria: HIV-1 or HIV dual (1 and 2) infection, no history of ART, last available CD4+ T-cell count less than 500/mm^3, unknown previous HBV status and informed consent to participate in the study. These four recruitment centers (Integrated Center of Bioclinical Research of Abidjan, General Medicine Department of Yopougon Teaching Hospital, Department of Infectious and Tropical Diseases of Treichville Teaching Hospital, Integrated Center for Bio-Clinical Research in Treichville, Abidjan) were regular monitoring and support centers for HIV-infected people. Socio-demographic data, clinical history and physical examination data (including clinical manifestations of liver disease) were collected on a standardized basis. Blood samples were obtained from all patients after they signed a written agreement. The following tests were routinely performed: blood count (MaxM® Coulter Beckman Coulter, Fullerton, CA, United States), a measurement of serum transaminase assays (Cobas Integra 400 plus® Roche Diagnostics, Mannheim, Germany), a CD4+ T-cell count by flow cytometry (FACSCalibur®Becton Dickinson, San Jose, CA, United States), plasma HIV-1 RNA levels quantification (Generic HIV, viral load assay threshold detectability of 300 copies/mL, Biocentric, Bandol, France) and a search for HBsAg and anti-HBc antibody (anti-HBcAb) (Mini Vidas®, Biomerieux, Marcy l'Etoile, France). All HBsAg positive patients were tested for HBeAg, anti-HBe antibody (anti-HBeAb) and IgM anti-HBc. We searched for anti-HBs Ab in all HBsAg negative and anti-HBcAb positive patients. We also conducted a plasma HBV DNA quantitative determination test in all HBsAg positive patients and in the first 188 patients with HBsAg negative, anti-HBcAb positive and anti-HBs Ab negative (Cobas® Amplicor HBV Monitor assay threshold detectability of 35 copies/mL or 6 IU/mL, Roche Diagnostics). We detected HBV infection in different virological profiles in these patients, according to laboratory tests results. HBeAg positive patients were considered infected with wild-type virus (HBeAg positive hepatitis); HBeAg negative patients with normal transaminases and viremia under 2000 IU/mL were considered inactive HBV carriers; HBeAg negative patients with elevated transaminases and viremia higher than 2000 IU/mL were considered infected with precore mutant virus (HBeAg negative hepatitis); occult HBV infection was diagnosed when HBV DNA was detectable in patients with HBsAg negative, anti-HBcAb positive and anti-HBsAb negative status.

Statistical analysis

In univariate analysis, we compared the differences between HBsAg positive and HBsAg negative patients using the Pearson χ^2 test or the Fisher exact test. A multivariate analysis (backward stepwise logistic regression) was performed to identify factors likely to be associated with the

presence of HBsAg positivity in HIV patients. Variables included in the univariate analysis were: age, gender, body mass index (BMI), World Health Organization (WHO) stage, CD4+ T-cell count, liver enzymes and HIV viral load. All variables with "*P*" value under 0.25 in univariate analysis were included in the multivariate analysis initial model. Statistical analysis was performed using WSTATA version 9.0 software.

RESULTS

Of 608 HIV patients contacted during the study period, 506 (83.2%) met inclusion criteria. Finally, 491 of them (97%) were included in the study. Figure 1 represents the flow chart of the study population distribution according to HBV serological markers. Mean age was 36.1 ± 8.68 years (range 18-66 years) and 73.3% were women. Overall, 98 (20%) were illiterate, 171 (34.8%) had primary school education and 222 (45.2%) had at least secondary school level of education. Thirty-three patients (6.7%) had reportedly received an HBV vaccine, 17 patients (3.5%) had an accidental blood exposure history and 39 patients (7.9%) a blood transfusion history. The distribution, by WHO clinical stage, was 61 patients (12.4%), 233 patients (47.5%), 172 patients (35%) and 25 patients (5.1%), respectively, in stage 1, 2, 3 and 4. Jaundice and hepatomegaly were found respectively in 6 (1.2%) and 18 (3.7%) patients. Table 1 shows clinical and laboratory features of 491 patients. HBV DNA was present in 59 out of 66 HBsAg positive patients (89.4%). Among HBsAg positive 66 patients, 21 (31.8%) had HBeAg positive hepatitis, 20 (30.3%) had HBeAg negative hepatitis and 22 (33.3%) had a profile of HBV inactive carrier. For 3 patients with HBsAg positive (4.6%), HBeAg and anti-HBeAb were negative. Biochemical and virological profile of these three patients was comparable to the 22 HBV inactive carriers (normal transaminases and viral DNA B less than 2000 IU/mL). Anti-HBc IgM was present in 2 of 66 HBsAg positive patients (3%). In both patients, transaminases were normal, HBeAg positive, anti-HBeAb negative and very high viral load (6 090 000 IU/mL and 110 000 000 IU/mL). Occult B infection was found in 40 of 188 patients (21.3%). Table 2 summarizes HBV DNA quantitative values according to HVB infection type. Thirty-three previously vaccinated patients were all positive for anti-HBcAb. Six of them were HBsAg positive and of the 27 remaining patients negative for HBsAg, 13 had anti-HBsAb. The relationship between HBsAg presence and baseline patient characteristics are summarized in Table 3. In multivariate analysis, male gender, WHO stage 4 and elevated aspartate aminotransferase (AST) level were found to be significantly associated with HBsAg positivity.

DISCUSSION

Our study results confirm the high prevalence of HBV infection among HIV patients in Côte d'Ivoire, and more generally in sub-Saharan Africa, as evidenced by most studies on the subject[10,13,15-22]. Indeed, the prevalence of HBsAg and that of anti-HBcAb were respectively 13.4% and 72.9% in our patients. In African studies comparing HBV infection prevalence in HIV-positive and HIV-negative patients, rates of HBsAg and anti-HBcAb did not differ significantly by HIV status[10,11,15,16]. In areas with high HBV endemicity, such as sub-Saharan Africa, two main contamination modes are perinatal or vertical transmission and horizontal transmission within the family in early childhood[23-28]. In these areas, contamination

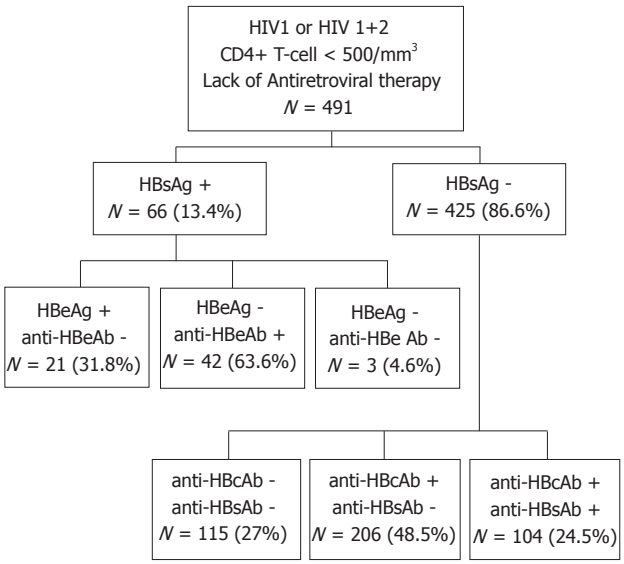

Figure 1 Study population distribution flow chart through hepatitis B virus serological markers. HBsAg: HBs antigen; anti-HBcAb: anti-HBc antibody; anti-HBeAb: anti-HBe antibody.

Table 1 Study population baseline characteristics (491 patients)

Patients baseline characteristics	
Female gender, *n* (%)	360/491 (73.3)
Median age, yr (IQR)	35 (30-41)
BMI (kg/m^2), *n* (%)	
< 18.5	115 (23.4)
18.5-25	281 (57.2)
> 25	95 (19.4)
WHO clinical stage, *n* (%)	
1 or 2	294/491 (60)
3 or 4	197/491 (40)
HIV serology, *n* (%)	
HIV-1	476 (97)
HIV-1 and HIV-2	15 (3)
Median CD4+ T-cell count (/mm^3) (IQR)	341 (221-470)
CD4+ T-cell < 200/mm3, *n* (%)	112/491 (22.8)
Median plasma HIV RNA (Log$_{10}$ copies/mL) (IQR)	4.87 (4.15-5.45)
Plasma HIV-1 RNA > 5 log$_{10}$ copies/mL, *n* (%)	221/491 (45)
Serum transaminase level, *n* (%)	
AST > UNV	81/491 (16.5)
ALT > UNV	41/491 (8.4)

IQR: Interquartile range; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; UNV: Upper normal value (50 UI/mL); WHO: World Health Organization; HIV: Human immunodeficiency viruses.

Table 2 Hepatitis B virus DNA quantitative values by hepatitis B virus infection type

Type of viral B infection	Viral infection B DNA (UI/mL)		
	Median	Interquartile range	Range
HBeAg positive hepatitis	2.1×10^7	1.1×10^7-1.1×10^8	27200-1.1×10^8
HBeAg negative hepatitis	139 000	8760-1.1×10^8	3030-1.1×10^8
Viral B inactive chronic carriers	331	62-641	8-1540
Occult B infection	46	16-149	7-258

by HIV occurs generally late in adolescents and adults because of sexual transmission predominance. By contrast, in areas of low HBV endemicity, such as western countries, most infections occur in adolescents and young adults. Vertical and horizontal transmissions within the family in early childhood are marginal. HBV infection transmission is mainly parenteral and sexual[9,29]. Contamination of both viruses generally occurs in the same period in young adults and sexually active adolescents. Thus, in these areas, HBV infection among HIV-positive patients is ten times more common than among HIV-negative ones[9,29].

In our study, 33 patients reported having received a complete HBV vaccine (Genhevac B or Euvax B recombinant vaccine). HBV vaccine was not systematic in HIV patients. Besides, vaccines were administered to these adults without preliminary assessment to eliminate previous viral B infection. Indeed, the assessment of these patients showed that 6 of them had active viral B infection (HBsAg positive and anti-HBcAb positive), 13 patients had past HBV infection with immunization status (HBsAg negative, anti-HBcAb and anti-HBs Ab positive) and 14 of them had past B virus infection with anti-HBs Ab clearance (HBsAg negative, anti-HBcAb positive without anti-HBs Ab). Several studies showed that HBV vaccination efficiency depends on the immunity status of HIV-positive patients[30-33]. Therefore, there is a good correlation between CD4+ T-cell count and vaccinal response[30-33]. This aspect has never been studied in our context.

Among HBsAg positive patients, the proportion of inactive carriers of HBV and that of patients with HBeAg positive hepatitis or HBeAg negative hepatitis were similar (about 30% for each of the three groups). The prevalence of patients with HBeAg positive hepatitis seemed higher in our study compared with HIV-negative data, confirming the results of previous African studies[10,25,26,28,34,35]. Moreover, our study reported a 21.3% prevalence for occult B infection. In a South African study[11], the authors compared occult B virus infection rates among HIV-positive and HIV-negative patients. Occult B infection prevalence was significantly higher among HIV-positive subjects (22.1% against 2.4% in HIV-negative subjects, $P < 0.001$). In contrast, B viremia of our patients with occult infection was not higher than values found in HIV-negative cases[11,13,36-39]. Most Western studies show that HIV infection reduces the likelihood of spontaneous recovery from HBV infection, promotes progression to chronicity, cirrhosis and its complications, HBV seroreversion, HBV reactivation and occult B infection[4-9]. WHO recommends that in countries with limited resources, if routine HBV DNA testing is not feasible, ART must start earlier in HIV patients carrying HBsAg, irrespective of CD4+ T-cell count or WHO clinical stage[40]. This treatment shall include a nucleosidic analogue (lamivudine or emtricitabine) and a nucleotidic analogue (tenofovir). In this context, the role of HBV DNA must be specified in HBV-HIV coinfected patients, especially for occult B infection diagnosis and treatment.

Three parameters were associated with the presence of HBsAg in our patients: male gender (OR: 2.2; $P = 0.005$; 95% CI: 1.3-3.8); WHO stage 4 (OR: 3.2; $P = 0.01$; 95% CI: 1.3-7.9); and increased level of AST (OR: 1.9; $P = 0.04$; 95% CI: 1.02-3.6). Male gender predominance has been reported in several HBV-HIV coinfection studies[12,19,41]. Moreover, it is now well admitted that in HIV patients with AIDS status and HBV coinfection, HBV infection is more likely to evolve to chronic disease compared to HIV-HBV co-infected patients with much higher level of CD4+ T-cell count or to HBV mono-infected patients[4-9]. Because of immunosuppressant, seroreversion and HBV reactivation are more likely to occur in them[4-9]. The most frequent elevation of AST in our HBsAg positive patients is more difficult to interpret as non-specific and probably of multifactorial origin (weight loss with muscle wasting, liver opportunistic disease localization, active hepatitis B disease, hepatitis due to another virus). Taking hepatotoxic drugs for opportunistic infections treatment and alcohol abuse were excluded by systematic search for these factors for the inclusion of our patients. Literature data show that, besides drug-induced liver toxicity (ART, anti-tuberculosis therapy or other treatments), promoted itself by the existence of a chronic viral liver disease, transaminases elevation is fairly well correlated with HBsAg presence in HIV patients[41,42].

HBV infection prevalence is elevated among our HIV patients. This prevalence seems similar to that observed in HIV-negative subjects. Among HBV serological profiles observed in our study, HBeAg positive chronic hepatitis and occult HBV infection are more frequent in HIV-positive patients than in HIV negative ones. Parameters associated with HBsAg positivity were male gender, AIDS status and increased AST levels. In HIV patients, HBV serological markers (especially HBsAg) must be part of the initial check-up. When HBV-HIV coinfection is diagnosed, ART must include molecules likely to be active on both viruses. Determination of HBV DNA load should be performed in HIV-infected patients with HBsAg negative, anti-HBcAb positive and anti-HBsAb negative in order to detect occult HBV infection cases that can also benefit from the same ART as HBsAg positive HIV patients.

Table 3 Relationship between HBs antigen positivity and baseline characteristics

Baseline characteristics	Univariate analysis			Multivariate analysis	
	HBsAg (+)[1] *n* = 66 (%)	HBsAg (-)[1] *n* = 425 (%)	*P* value	OR (95% CI) *n* = 491	*P* value
Age > 35 yr[2]	57.6	48	0.15	-	-
Gender, male	43.9	24	0.001	2.2 (1.3-3.8)	0.005
BMI < 18.5 kg/m^2	34.9	21.7	0.06	-	-
WHO stage 4[3]	13.6	3.8	0.003	3.2 (1.3-7.9)	0.01
AST > UNV	30.3	14.4	0.001	1.9 (1.02-3.6)	0.04
ALT > UNV	16.7	7.1	0.009	-	-
CD4+ T-cell < 200/mm3	34.9	20.9	0.01	-	-
HIV RNA ≥ 5 Log	59.1	42.8	0.02	1.5 (0.9-2.7)	0.12

[1]HBsAg positive and HBsAg negative. [2]median age. [3]Stage four of World Health Organization (WHO) clinical classification or AIDS. BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; UNV: Upper normal value (50 UI/mL); HBsAg: HBs antigen.

COMMENTS

Background

Hepatitis B virus (HBV) is the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in African and Asian areas where HBV prevalence is high. Most of the countries affected by hepatitis B are also affected by a high human immunodeficiency viruses (HIV) burden, leading to frequent HIV-HBV co-infection. However, few data are available on HIV-HBV co-infection from regions with high chronic hepatitis B prevalence.

Research frontiers

Describe virological profiles of HBV-HIV co-infection in sub-Saharan Africa area and their particularity regarding worldwide data.

Innovations and breakthroughs

Our study results confirm the high prevalence of HBV infection among HIV patients in sub-Saharan Africa, as evidenced by most studies on the subject. Besides, among HBV serological profiles observed in our study, HBeAg positive chronic hepatitis and occult HBV infection are more frequent in HIV-positive patients than in HIV negative ones. These observations may be due to late consultation of our patients and an advanced stage of HIV disease (40.1% were at World Health Organization (WHO) stage 3 or 4 and 22.8% with less than 200 CD4+ T-cell/mm^3). At this stage, occult infections, HBV seroreversions and reactivations are more frequent.

Applications

In countries with limited resources, if routine HBV DNA testing is not feasible, antiretroviral therapy (ART) must start earlier in HIV patients carrying HBsAg, irrespective of CD4+ T-cell count or WHO clinical stage. This treatment should include a nucleosidic analogue (Lamivudine or Emtricitabine) and a nucleotidic analogue (Tenofovir). DNA VHB measurement should be a part of the initial checkup tests of the HIV positive patient carrier of Ag HBs as well as the patients who have a past HBV infection without immunization (HBsAg negative and anti-HBc positive without anti-HBs) in order to facilitate occult HBV infections diagnosis and management.

Terminology

HBeAg positive hepatitis (patients infected with wild-type virus): HBeAg positive patients with elevated transaminases and HBV DNA higher than 2000 IU/mL; HBeAg negative hepatitis (patients infected with precore mutant virus): HBeAg negative patients with elevated transaminases and HBV DNA higher than 2000 IU/mL; Inactive HBV carriers: HBeAg negative patients with normal transaminases and HBV DNA under 2000 IU/mL; Occult HBV infection: HBV DNA detectable in patients with HBsAg negative, anti-HBcAb positive and anti-HBs Ab negative status.

Peer review

In this descriptive and analytical study, the authors describe different HBV-HIV co-infection virological profiles and analyze the relationship between the patient's baseline characteristics and HBsAg positivity. The results are interesting and suggest that HBV infection diagnosis and ART start-up (Tenofovir with Lamivudine or Emtricitabine) should be earlier to improve HBV-HIV co-infection prognosis.

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