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SHORT COMMUNICATION

High rates of active hepatitis B and C co-infections in HIV-1 infected Cameroonian adults initiating antiretroviral therapy

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Objectives

To investigate the presence of hepatitis B virus (HBV) DNA and hepatitis C virus (HCV) RNA in HIV-infected patients initiating antiretroviral therapy in Cameroon.

Methods

Baseline blood samples from 169 patients were tested retrospectively for hepatitis B surface antigens (HBsAg), anti-hepatitis B core (anti-HBc), anti-HCV and – if HBsAg or anti-HCV result was positive or indeterminate – for HBV DNA or HCV RNA, respectively, using the Cobas Ampliprep/Cobas TaqMan quantitative assay (Roche Diagnostics GmbH, Mannheim, Germany).

Results

HBV DNA was detected in 14 of the 18 patients with positive or indeterminate HBsAg results [8.3% of the total study population, 95% confidence interval (CI) 4.6–13.5]. The median HBV viral load was 2.47×10^7 IU/mL [interquartile range (IQR) 3680–1.59×10^8; range 270 to $> 2.2 \times 10^8$]. Twenty-one patients (12.4%, 95% CI 7.9–18.4) were found with HCV RNA (all with positive HCV serology). The median HCV viral load was 928 000 IU/mL (IQR 178 400–2.06×10^6; range 640–5.5×10^6). No patient was co-infected with HBV and HCV. In multivariate analysis, HCV co-infection was associated with greater age [≥ 45 years *vs.* < 45 years, odds ratio (OR) 11.89, 95% CI 3.49–40.55, $P < 0.001$] and abnormal serum alanine aminotransferase level [$\geq 1.25 \times$ upper limit of normal (ULN) *vs.* $< 1.25 \times$ ULN, OR 7.81, 95% CI 1.54–39.66, $P = 0.01$]; HBV co-infection was associated with abnormal serum aspartate aminotransferase level (OR 4.33, 95% CI 1.32–14.17, $P = 0.02$).

Conclusions

These high rates of active HBV and HCV co-infections in HIV-positive Cameroonian patients requiring antiretroviral therapy underline the need to promote: (i) screening for HBV and HCV before treatment initiation; (ii) accessibility to tenofovir (especially in HBV-endemic African countries); and (iii) accessibility to treatment for HBV and HCV infections.

Keywords: Africa, antiretroviral therapy, HBV, HCV, HIV

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Introduction

While HIV-related morbidity and mortality are decreasing thanks to the scaling up of antiretroviral therapy in Africa, co-infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are catching the attention of medical doctors and other health professionals because of the consequent emerging impact of liver disease [1,2]. High seroprevalences of all three infections are found in Africa [1]. Unfortunately, the prevalence of active hepatitis B or C co-infections (i.e. positive HBV DNA or HCV RNA) in African patients requiring anti-HIV treatment has not been

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documented extensively. A recent South African study investigated HBV co-infection (but not HCV co-infection), while a Nigerian study investigated HCV co-infection (but not HBV co-infection) [3,4]. In contrast, we investigated the presence of both HBV DNA and HCV RNA in HIV-infected patients initiating antiretroviral therapy in Cameroon.

Patients and methods

Patients infected with HIV-1 initiated antiretroviral therapy in 2001–2003 in two major hospitals in Yaoundé in the context of two clinical research projects (109 and 60 patients, respectively) designed to assess antiretroviral treatment. Methods and patients have been described in detail elsewhere [5,6]. Briefly, the eligibility criteria were: age over 18 years; AIDS or a CD4 count below 350 cells/μL; a Karnofsky score over 50%; and no contraindications to antiretroviral treatment, including serum liver enzyme levels less than five times the upper limit of normal (ULN) value in the first project or less than three times the ULN value in the second project.

Hepatitis B and C markers were assessed retrospectively on baseline blood samples frozen at −80 °C. Enzyme immunoassays (EIA) were used to detect hepatitis B surface antigens (Monolisa Ag HBs Plus; Bio-Rad, Marnes la Coquette, France) and antibodies to hepatitis B core (Monolisa anti-HBc Plus; Bio-Rad). Plasma HBV DNA was tested in positive or indeterminate hepatitis B surface antigens (HBsAg) samples using the Cobas Ampliprep/Cobas TaqMan quantitative assay (Roche Diagnostics GmbH, Mannheim, Germany; quantification range of 12–2.2×10^8 IU/mL). Screening for antibodies to hepatitis C virus (anti-HCV) was performed using a third-generation EIA (Ortho HCV EIA 3.0; Ortho-clinical Diagnostics, Riratan, NJ, USA); positive or indeterminate samples were confirmed using a recombinant immunoblot assay (Chiron RIBA HCV 3.0 SIA; Chiron Corporation, Emeryville, CA, USA). HCV RNA was assessed using the Cobas Ampliprep/Cobas TaqMan quantitative assay (Roche Diagnostics GmbH; quantification range of 15–6.9×10^7 IU/mL) in samples that were positive or indeterminate for at least one screening test.

The Fisher's exact test was used to compare the distribution of qualitative variables between the infection groups (HBV or HCV co-infected patients *vs.* HIV mono-infected patients). For continuous variables, comparisons were based on the non-parametric Mann–Whitney two-sample test. Multivariate logistic regressions were used to identify factors associated with HBV or HCV co-infection. Analyses were performed using STATA 10.0 software (STATA Corporation, College Station, TX, USA).

Results

Between January 2001 and April 2003, 169 HIV-1 infected patients started antiretroviral therapy. Two-thirds of patients were women ($n = 113$). The median age was 35.0 years [interquartile range (IQR) 29.3–41.1]. Most patients were symptomatic for HIV (42% were at Centers for Disease Control and Prevention stage B and 44% were at stage C). The median CD4 count was 135 cells/μL (IQR 67–218) and median HIV-1 viral load was 5.3 $\log_{10}$-RNA copies/mL (IQR 4.7–5.6). Patients received either zidovudine, lamivudine and nevirapine ($n = 85$) or stavudine, lamivudine and nevirapine ($n = 84$).

Seventeen patients (10.1%) had positive HBsAg results; one other patient (0.6%) had an indeterminate result. In a sub-set of 109 patients, antibodies to hepatitis B core (anti-HBc) were found in 89 patients (81.7%) and three other patients (2.8%) had indeterminate results. HBV DNA was detected in 14 of the 18 patients with positive or indeterminate HBsAg results [8.3% of the total study population, 95% confidence interval (CI) 4.6–13.5]. The positive predictive value of HBsAg was 76.5% (13 of 17 patients). The median HBV viral load in the 14 patients was 2.47×10^7 IU/mL (IQR 3680–1.59×10^8; range 270 to $> 2.2 \times 10^8$). The only patient with an indeterminate HBsAg result was found to be positive for anti-HBc and had an HBV viral load of 3680 IU/mL.

Serology for HCV was positive in 28 patients (16.6%) and indeterminate in four other patients (2.4%). Twenty-one patients (12.4% of the total study population, 95% CI 7.9–18.4) were found with HCV RNA (all with positive HCV serology). Therefore, the positive predictive value of HCV serology was 75.0%. The median HCV viral load was 928 000 IU/mL (IQR 178 400–2.06×10^6; range 640–5.5×10^6). No patient was co-infected with HBV and HCV.

Patients co-infected with HBV or HCV were comparable in most characteristics to those infected with HIV alone (Table 1). However, HCV co-infected patients were more likely to be older and to have serum liver enzyme elevations. HBV co-infected patients had significant serum aspartate aminotransferase (AST) elevations only. In multivariate analysis, HCV co-infection remained associated with greater age [≥ 45 years *vs.* < 45 years, odds ratio (OR) 11.89, 95% CI 3.49–40.55, $P < 0.001$] and abnormal serum alanine aminotransferase (ALT) level ($\geq 1.25 \times$ ULN *vs.* $< 1.25 \times$ ULN, OR 7.81, 95% CI 1.54–39.66, $P = 0.01$) but not with abnormal serum AST level ($\geq 1.25 \times$ ULN *vs.* $< 1.25 \times$ ULN, OR 2.65, 95% CI 0.72–9.78, $P = 0.14$). After adjustment for gender and serum ALT level, HBV co-infection was associated with abnormal serum AST level only (OR 4.33, 95% CI 1.32–14.17, $P = 0.02$).

Table 1 Patient characteristics by infection group

	HIV mono-infected patients ($n = 134$)	HBV co-infected patients ($n = 14$)	*P*-value*	HCV co-infected patients ($n = 21$)	*P*-value†
Women (*n*)	91 (68%)	7 (50%)	0.2	15 (71%)	0.8
Age (years)					
Median (IQR)	34.4 (28.4–39.7)	35.2 (32.2–41.1)	0.4	45.2 (37.6–52.5)	<0.001
Classes (*n*)			0.8		<0.001
<35	73 (54%)	7 (50%)		5 (24%)	
35–44	49 (37%)	5 (36%)		5 (24%)	
45–54	12 (9%)	2 (14%)		8 (38%)	
≥55	0	0		3 (14%)	
Body mass index (kg/m^2) [median (IQR)]‡	23.2 (21.6–24.7)	22.9 (21.3–24.2)	0.5	22.1 (20.1–25.7)	0.3
Karnofsky score (*n*)			0.4		0.4
<90%	20 (15%)	0		4 (19%)	
90%	52 (39%)	6 (43%)		5 (24%)	
100%	62 (46%)	8 (57%)		12 (57%)	
CDC clinical stage (*n*)			0.9		0.7
A	19 (14%)	1 (7%)		3 (14%)	
B	58 (43%)	6 (43%)		7 (33%)	
C	57 (43%)	7 (50%)		11 (52%)	
CD4 count (cells/μL)					
Median (IQR)	138 (67–222)	113 (45–151)	0.4	150 (84–218)	0.9
Classes (*n*)			0.6		0.9
<50	23 (17%)	4 (29%)		3 (14%)	
50–99	31 (23%)	2 (14%)		4 (19%)	
100–199	39 (29%)	5 (36%)		7 (33%)	
≥200	41 (31%)	3 (21%)		7 (33%)	
HIV-1 viral load ($\log_{10}$ copies/mL)§					
Median (IQR)	5.3 (4.7–5.5)	5.1 (4.8–5.9)	0.5	5.3 (4.7–5.6)	0.8
Classes (*n*)			0.6		0.8
<4.0	14 (11%)	0		1 (5%)	
4.0–4.9	38 (29%)	5 (36%)		6 (29%)	
≥5.0	81 (61%)	9 (64%)		14 (67%)	
ALT level (×ULN)					
Median (IQR)	0.6 (0.4–0.7)	0.7 (0.5–0.9)	0.2	0.9 (0.6–1.3)	<0.001
≥1.25 (*n*)	8 (6%)	1 (7%)	0.9	7 (33%)	0.001
AST level (×ULN)¶					
Median (IQR)	0.8 (0.6–1.1)	1.1 (0.9–1.6)	0.03	1.4 (1.0–1.8)	<0.001
≥1.25 (*n*)	21 (17%)	6 (46%)	0.02	11 (55%)	<0.001

*HBV co-infected patients *vs.* HIV mono-infected patients.
†HCV co-infected patients *vs.* HIV mono-infected patients.
‡Three missing values.
§One missing value.
¶Nine missing values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control; IQR, interquartile range; ULN, upper limit of normal.

Discussion

In this study, we found high rates of active HBV and HCV co-infection in HIV-positive patients initiating antiretroviral therapy in Cameroon (8.3 and 12.4%, respectively). Most of these patients had high HBV or HCV viral load and moderate serum liver enzyme elevations.

The true prevalence of co-infections could even be higher because seronegative blood samples were not tested for HBV DNA or HCV RNA. Higher rates of negative HBsAg or anti-HCV EIA results in viraemic samples have been observed in immunocompromised HIV-infected patients [2,7]. In addition, the exclusion of patients presenting with serum liver enzyme levels higher than three or five times the ULN values (depending on the initial study) could have led to an underestimation of the prevalence. The comparison of our HBV and HCV estimates to those reported by the few other African studies in patients initiating antiretroviral therapy should be viewed as indicative only because of the methodological differences. In South Africa, HBV DNA was detected in 40.6% of 192 patients (100% of 44 HBsAg-positive patients and 23.0% of 148 HBsAg-negative patients) [3]. In Cameroon's neighbour Nigeria, 8.2% of 146 patients were found with HCV RNA (all patients were tested for HCV viraemia) [4]. The prevalence of co-infections in other HIV-infected populations are much lower. For instance, HBV DNA was detected in 2.4% of pregnant women in both Côte d'Ivoire and South Africa [8,9]. The prevalence of HCV RNA was 0% in blood donors in Tanzania and 1.0% in pregnant women in Côte d'Ivoire [8,10].

Frequent co-infections are also found in Europe and the USA, where the prevalence of HIV, HBV and HCV in the general population is lower than in Africa. However, the predominant modes of transmission of all three infections are similar in Western countries (intravenous drug use and sexual contact) [11,12] whereas they appear very dissimilar in Africa (for HIV, the heterosexual route; for HBV, close contact within households during early childhood and, to a lesser extent, vertical transmission; and for HCV, unclear routes of transmission) [1,2].

Undetected HBV or HCV co-infections had clinical implications for antiretroviral therapy in our patients. All HBV co-infected patients received anti-HBV lamivudine monotherapy, which has been shown to lead to frequent emergence of drug resistance [13] and, consequently, to possible acute hepatitis, fulminant hepatic failure and death [2]. The World Health Organization now recommends the use of tenofovir plus either lamivudine or emtricitabine as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of antiretroviral therapy in HBV co-infected patients whenever possible (tenofovir has been available in Cameroon since 2007) [14]. Also, 46 and 55% of HBV and HCV co-infected patients, respectively, received nevirapine despite moderate liver enzyme elevations. In these patients, efavirenz or a third NRTI is preferred [14].

Two strategies should be considered for the management of HIV-infected patients needing treatment in Africa. Where possible, testing for HBsAg and anti-HCV should be performed systematically in addition to serum liver enzymes before initiating antiretroviral therapy in order to avoid nevirapine and anti-HBV lamivudine monotherapy when necessary. Moreover, where possible (infrequent at present in most African settings), HBV DNA and HCV RNA should also be tested when hepatic infection is suspected in order to identify patients with occult hepatitis B (negative HBsAg and positive HBV DNA) or false negative anti-HCV EIA results. Testing for HBV DNA would also limit the inessential use of the costly tenofovir (23.5% of our HBsAg-positive patients were not viraemic). If quantitative assay can be performed, HBV DNA level (or HCV RNA level if anti-HCV treatment is available) would serve to manage antiviral therapy (initiation and response). Alternatively, if testing of HBV and HCV is not feasible, first-line antiretroviral regimen in HBV-endemic African countries should include tenofovir plus either lamivudine or emtricitabine systematically. The combination of tenofovir, emtricitabine and efavirenz, once a day, appears a very good option. If nevirapine is prescribed, serum liver enzymes should be monitored closely.

In conclusion, active HBV and HCV co-infections were frequent in HIV-positive Cameroonian patients requiring antiretroviral therapy. This finding underlines the need to promote: (i) screening for HBV and HCV before treatment initiation; (ii) accessibility to tenofovir (especially in HBV-endemic African countries); and (iii) accessibility to treatment for HBV and HCV infections (in addition to NRTIs).

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