

SHORT COMMUNICATION

# Occult hepatitis B virus coinfection in HIV-positive African migrants to the UK: a point prevalence study

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## Objectives

Occult (surface antigen-negative/DNA-positive) hepatitis B virus (HBV) infection is common in areas of the world where HBV is endemic. The main objectives of this study were to determine the prevalence of occult HBV infection in HIV-infected African migrants to the UK and to determine factors associated with occult coinfection.

## Methods

This anonymized point-prevalence study identified Africans attending three HIV clinics, focussing on patients naïve to antiretroviral therapy (ART). Stored blood samples were tested for HBV DNA. Prevalence was calculated in the entire cohort, as well as in subpopulations. Risk factors for occult HBV coinfection were identified using logistic regression analysis.

## Results

Among 335 HIV-positive African migrants, the prevalence of occult HBV coinfection was 4.5% [95% confidence interval (CI) 2.8–7.4%] overall, and 6.5% (95% CI 3.9–10.6%) and 0.8% (95% CI 0.2–4.6%) in ART-naïve and ART-experienced patients, respectively. Among ART-naïve anti-HBV core (anti-HBc)-positive patients, the prevalence was 16.4% (95% CI 8.3–25.6%). The strongest predictor of occult coinfection was anti-HBc positivity [odds ratio (OR) 7.4; 95% CI 2.0–27.6]. Median HBV DNA and ALT levels were 54 IU/mL [interquartile range (IQR) 33–513 IU/mL] and 22 U/L (IQR 13–27 U/L), respectively.

## Conclusions

Occult HBV coinfection remains under-diagnosed in African HIV-infected patients in the UK. Given the range of HBV DNA levels observed, further studies are warranted to determine its clinical significance and to guide screening strategies and ART selection in these patients.

**Keywords:** African, HIV, occult hepatitis B, prevalence

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## Introduction

Between 2 and 20% of HIV-positive individuals in sub-Saharan Africa are also infected with hepatitis B virus (HBV) [1,2]. Progression of liver disease is more rapid in HIV/HBV coinfection [3], and there is also an increased risk of hepatotoxicity of antiretroviral drugs [4]. It is unclear whether HBV infection affects progression of HIV infection, or response to antiretroviral therapy (ART). As HBV

transmission in sub-Saharan Africa usually occurs in early childhood, many years before HIV is acquired [1], it is likely that African adults with HIV/HBV coinfection are at higher risk of developing cirrhosis or hepatocellular carcinoma (HCC) than those who acquire HBV infection as adults. Occult HBV infection is characterized by negative HBV surface antigen (HBsAg) serology with positive HBV DNA detection, and is usually seen in patients with antibodies against HBV core (anti-HBc) and/or surface antigen (anti-HBs). Occult HBV coinfection appears common in Africa [2,5–7] and some areas of Europe [8–10], but less so in the USA [11]. Its prevalence in potentially high-risk subpopulations in the UK such as migrants from Africa and

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Asia is unknown, and routine screening for occult HBV coinfection is not recommended in national guidelines. It is not clear whether such patients are at increased risk of hepatotoxicity secondary to ART, whether their long-term risk of developing liver disease is increased, or whether their response to ART is optimal; however, it appears that occult HBV and hepatitis C virus (HCV) coinfection is associated with faster progression of fibrosis and poorer response of HCV to interferon- $\alpha$  [12]. Furthermore, while HBV DNA levels are usually low, a previous study based in Ghana described a subset of HBsAg-/HBV DNA+ HIV-positive patients with high rates of HBV replication and therefore presumably at high risk of liver disease progression [2]. In the light of these previous observations, the aim of this study was to determine the prevalence of occult HBV coinfection in HIV-positive patients of African origin attending three HIV clinics in England, while also exploring factors associated with occult coinfection.

## Methods

Adults ( $\geq 18$  years old) attending HIV clinics in London (Royal Free Hospital), Newcastle (Royal Victoria Infirmary) and Middlesbrough (James Cook University Hospital) were screened for study eligibility, with only those of African origin, having an available stored serum or plasma sample and having negative HBsAg tests within 2 years of the date of the sample collected for inclusion. Anonymized data were collected from case notes and electronic records on patients' demographics, antiretroviral therapy, clinical characteristics and laboratory results, specifically liver function tests, CD4

cell counts, HIV viral loads and HBV serology. Stored samples were tested for HBV DNA using a quantitative real-time polymerase chain reaction (PCR) assay (lower limit of detection 14 IU/mL) at the Royal Free Virology Department, as previously described [2]. The prevalence of occult HBV coinfection was calculated with 95% confidence intervals (CIs) in the entire population, as well as in ART-naïve patients and those taking ART. The prevalence of occult coinfection was also calculated in the anti-HBc-positive ART-naïve population. Data were then analysed using logistic regression to determine the association of occult coinfection with patient covariates. The study was approved by the Durham and Tees Valley Research Ethics Committee.

## Results

A total of 335 patients were identified who fulfilled the eligibility criteria, with both sufficient data and a stored sample, from the three clinics: 216 were ART-naïve and 114 'on-ART' at sampling. The prevalence of occult coinfection, defined as HBsAg-negative/HBV DNA-positive, was 4.5% (95% CI 2.8–7.4%) in the entire population, 6.5% (95% CI 3.9–10.6%) in the ART-naïve subgroup and 0.8% (95% CI 0.2–4.6%) in the ART-treated subgroup. Within the ART-naïve subgroup, the prevalence of occult coinfection among anti-HBc-positive patients was 16.4% (95% CI 8.3–25.6%). The characteristics of the population are shown in Table 1. Patients with occult HBV coinfection were more likely to be male, to be naïve to ART, to originate from East Africa and to have positive anti-HBs or anti-HBc. In samples testing positive for HBV DNA, the median HBV

**Table 1** Characteristics of the population studied

	HBV DNA positive ( <i>n</i> = 15)	HBV DNA negative ( <i>n</i> = 320)
Age (years) [median (IQR)]	40 (36–40)	36 (32–42)
Female [ <i>n</i> (%)]	8 (53)	226 (71)
CD4 count (cells/ $\mu$ L) [median (IQR)]	281 (144–301)	330 (190–530)
Nadir CD4 count (cells/ $\mu$ L) [median (IQR)]	278 (163–295)	275 (88–389)
HBV DNA load (IU/mL) [median (IQR)]	54 (33–513)	
HIV viral load ( $\log_{10}$ copies/mL) [median (IQR)]	4.42 (4.24–4.8)	4.58 (3.85–4.9)
Anti-HBc-positive [ <i>n</i> (%)]	12 (80)	106 (33)*
Anti-HBs-positive [ <i>n</i> (%)]	10 (66)	179 (56)
HCV IgG-positive [ <i>n</i> (%)]	0 (0)	6 (2)
ALT elevated [ <i>n</i> (%)]	2 (13)	37 (11)
ALT (u/L) [median (IQR)]	22 (13–27)	19 (15–26)
ART-naïve [ <i>n</i> (%)]	14 (93)	202 (63)*
African region of origin [ <i>n</i> (%)]		
South	7 (47)	177 (55)
Central	1 (7)	8 (3)
East	5 (33)	58 (18)
West	2 (13)	76 (24)

HBV, hepatitis B virus; IgG, immunoglobulin G; IQR, interquartile range; anti-HBc, hepatitis B virus core antibody; anti-HBs, hepatitis B virus surface antibody; HCV, hepatitis C virus; ART, antiretroviral therapy; ALT, alanine aminotransferase.

\* $P < 0.05$  by  $\chi^2$  or Fisher's exact test.

**Table 2** Univariate analysis of factors associated with occult hepatitis B virus (HBV) infection

	OR (95% CI)	P
Age (per 10 years older)	0.97 (0.4–2.2)	0.42
Sex (female)	0.41 (0.3–1.5)	0.14
CD4 (per 100 cells/ $\mu$ L increase)	0.99 (0.3–2.7)	0.45
HIV viral load (per 1000 copies/mL increase)	1.04 (0.9–1.2)	0.22
Anti-HBc-positive	7.41 (4.1–11.6)	0.003
Anti-HBs-positive	2.66 (0.8–5.2)	0.11

anti-HBc, hepatitis B virus core antibody; anti-HBs, hepatitis B virus surface antibody; CI, confidence interval; OR, odds ratio.

DNA level was low, at 54 IU/mL [interquartile range (IQR) 33–513 IU/mL; absolute range 16–5279 IU/mL], and there was no evidence of higher alanine aminotransferase (ALT) levels in this group (Table 1), nor any correlation between ALT level and HBV DNA. Given that most patients with occult coinfection were in the ART-naïve subgroup, logistic regression analysis was carried out on this subgroup. Univariate analysis (Table 2) identified only positive anti-HBc as significantly associated with occult coinfection [odds ratio (OR) 7.41; 95% CI 2.0–27.6;  $P = 0.003$ ]. While male gender (OR 2.4;  $P = 0.14$ ) and positive anti-HBs (OR 2.7;  $P = 0.11$ ) were also moderately associated with occult coinfection, neither of these associations (nor those for other covariates studied) reached a pre-specified definition of significance of  $P < 0.1$ , and hence multivariate analysis was not performed.

## Discussion

This study has shown that occult HBV coinfection is not uncommon among HIV-positive African migrants to the UK, particularly (at 16%) in anti-HBc-positive patients when tested prior to commencement of ART. The true rate in this population may be higher, as this was a point-prevalence study and some patients demonstrate intermittently positive HBV DNA [10]. Furthermore, it is likely that the observed rate was lower in the ART-treated subgroup because drugs such as lamivudine or tenofovir, which often suppress HBV DNA to undetectable levels, were commonly used. The reason for HBsAg tests being negative in these patients is not clear: it is likely that in most cases the assays commonly used lacked sensitivity; however, some patients may have developed diagnostic escape mutants secondary to lamivudine or emtricitabine use, as was found in a previous study in Africa [2]. Whether routine HBV DNA screening of patients at higher risk of occult HBV coinfection (such as those originating from high-prevalence regions or with anti-HBc-positive serology) can be justified or is cost-effective is dependent on the true

clinical significance of occult HBV infection in this patient group. There is very little direct data to inform this question. One study in Africa failed to find any adverse impact of occult coinfection on response to ART [13]. As the risk of progression of liver disease is greater in patients with HBV DNA levels  $> 2000$  IU/mL [14], and our study and most other published studies [5–11,15] have shown median HBV DNA levels well below this threshold, it would seem unlikely that many patients with occult HBV coinfection are at high risk of developing cirrhosis or HCC. However, it is possible that patients with higher HBV DNA levels who have been infected since childhood are at higher risk and would therefore benefit from ART containing drugs active against HBV given sooner than under current guidelines. Other potential benefits of identifying occult HBV coinfection in this population are preventing HBV transmission (mother to child or to close contacts), by immunization of contacts, and avoiding lamivudine monotherapy (for HBV) in ART combinations with the associated risk of HBV lamivudine resistance [2]. Further research is needed to quantify the risks of developing liver disease, hepatotoxicity of ART and development of drug resistance in occult HIV/HBV coinfection to inform this question, as well as the reasons for low sensitivity of HBsAg assays.

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