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Occult hepatitis B/HIV co-infection in African migrants to the UK: a point prevalence study

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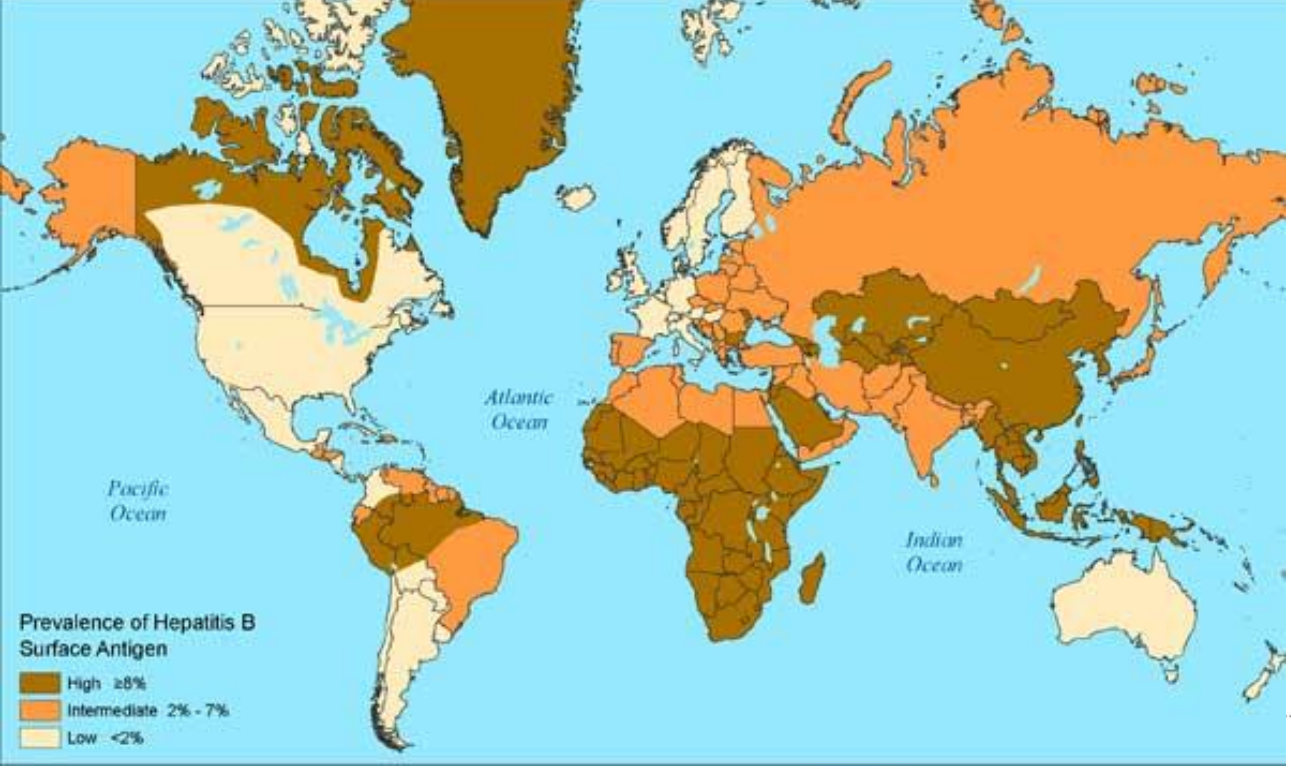
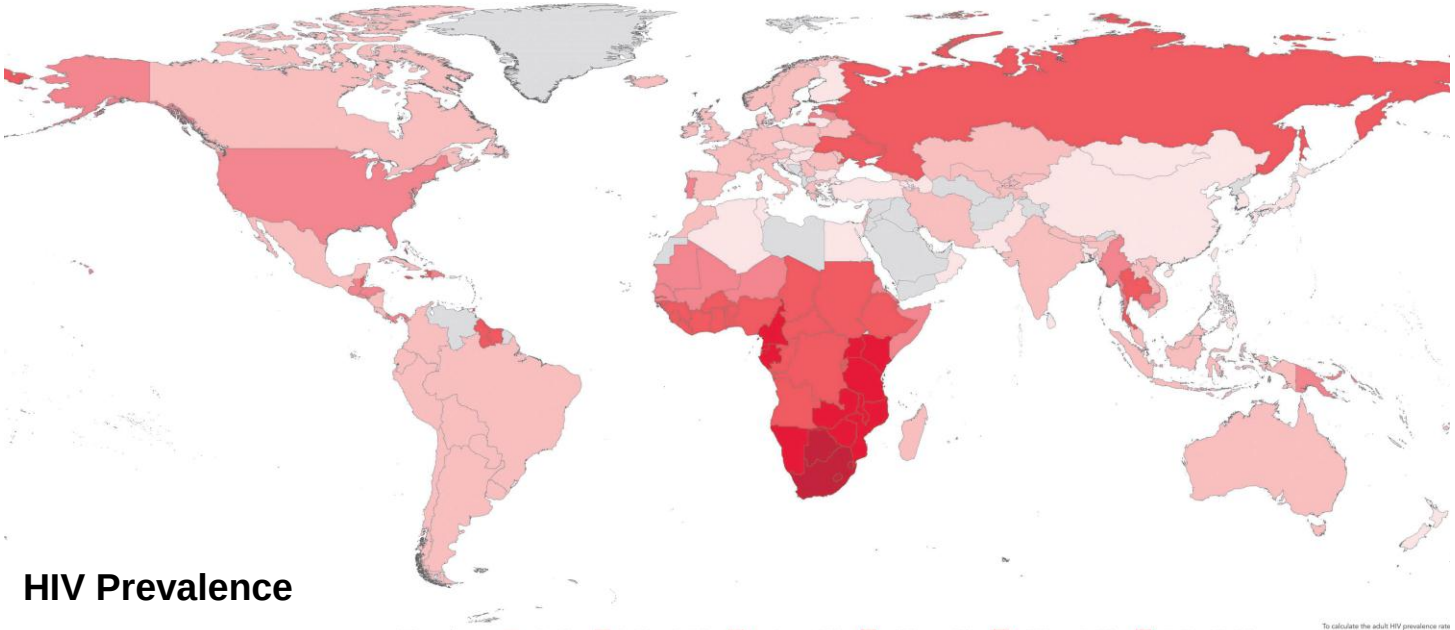

Atlantic Ocean
Pacific Ocean
Indian Ocean
Prevalence of Hepatitis B Surface Antigen
High ≥8%
Intermediate 2% - 7%
Low <2%


HIV Prevalence
Source: UNAIDS
No data
<0.1%
0.1% – <0.5%
0.5% – <1.0%
1.0% – <5.0%
5.0% – <15.0%
15.0% – 28.0%

Background

- Estimated 2 - 4m HIV/HBV co-infected people worldwide; most of these people in Africa
- Rates of HBV co-infection in HIV+ population range from between 4%-23% in Africa (10-17% in West Africa)
- Improved survival (with ART roll-out) means complications of chronic HBV infection likely to become increasingly common in these countries
- Longer duration of HBV infection (acquired in childhood) in Africans may increase complications

Implications of HBV/HIV co-infection

- HIV infection accelerates liver disease: co-infected patients 19x increased mortality than patients with HBV infection alone
- Complicates ART by increasing drug-related hepatocellular toxicity (either direct or via IRIS), or flares following withdrawal of 3TC, FTC or tenofovir
- Little evidence of detrimental effect of HBV infection on HIV progression
- But little known about interaction between the two infections or responses to ART in patients with occult HBV

Occult HBV Infection

- Defined as HBV infection (HBV DNA+) with *negative* HBsAg test
- May occur due to low level HBV replication (below sensitivity limit of HBsAg assay) or due to diagnostic escape mutants
- Clinical implications of occult HBV infection include:
  - Potential transmission of HBV including by transfusions/organ transplants
  - Reactivation of HBV in immunocompromised patients
  - In HCV co-infection, associated with accelerated fibrosis and poorer response to interferon α
  - Probable increased risk of hepatocellular carcinoma
- Clinical significance of HIV/HBV co-infection in terms of liver disease progression (fibrosis & hepatocellular carcinoma) is unknown
  - No evidence of adverse response to ART in Ghana *(Chadwick et al AIDS 27: 139-141, 2013)*

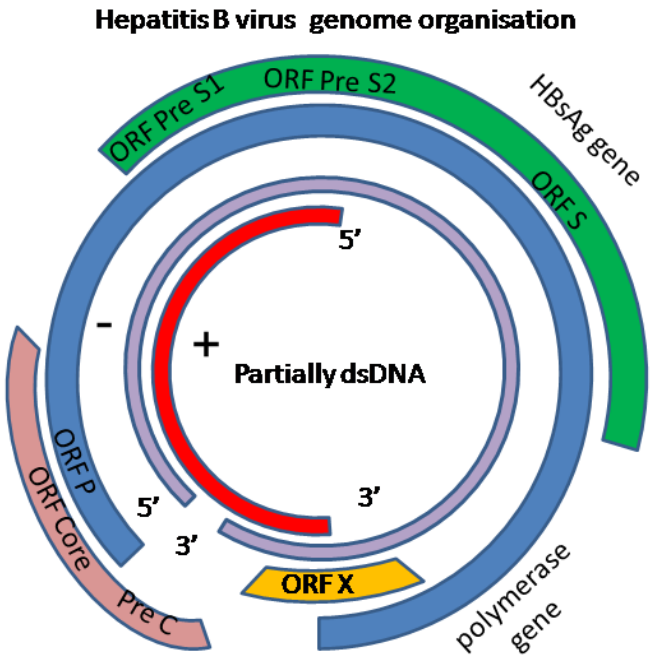
Table 1. Typical serological profiles in patients with hepatitis B infection

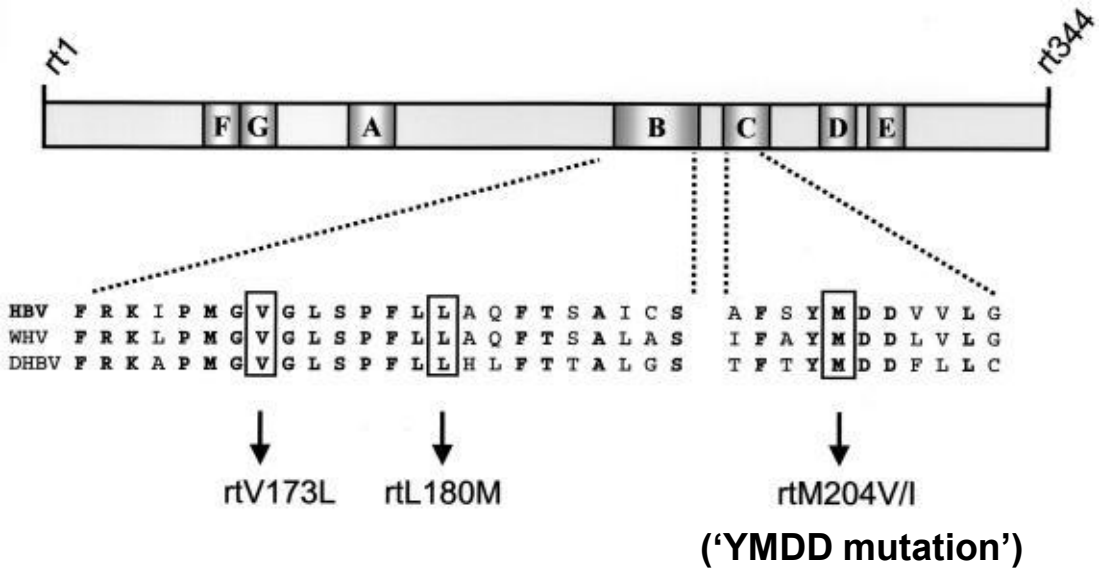
Serological tests	Hepatitis B immunisation	Acute HBV	Recovered from HBV	Chronic hepatitis B	Healthy or inactive carrier	Occult hepatitis B
HBsAb	+	−	+	−	−	−/+
HBcAb total	−	+	+	+	+	−/+
HBeAb	−	−	+	−	+	−/+
HBsAg	−	+	−	+	+	−
HBeAg	−	+	−	+	−	−/+
HBV DNA	−	+	−	+, $>10^5$ copies	+, $<10^5$ copies	+, $<10^3$ copies

HbsAb=hepatitis B surface antibody; HBcAb=hepatitis B core antibody; HBeAb=hepatitis B e antibody; HBsAg=hepatitis B surface antigen; HbeAg=hepatitis B e antigen

- Antiretroviral therapy with 3TC, FTC or tenofovir in occult HBV co-infection may lead to negative HBV DNA, hence prevent identification of occult infection
- Current BHIVA guidelines do not suggest routine screening for occult HBV co-infection in HBsAg- patients

RT Domain of HBV *pol* gene





- RT mutations in HBV, secondary to use of NRTIs such as lamivudine, may be associated with diagnostic escape mutants
- Hence lamivudine monotherapy for HBV (common in many first-line ART combinations in Africa) may lead to HBsAg- (occult) HBV infection

Occult HBV: Prevalence in HIV-infected Cohorts

Study	Country	Sample size	Patient type	HBsAg+ Prevalence	Occult HBV Prevalence	Median HBV DNA (IU/mL)
Lukwaheni *et al* (2009)	S. Africa	148	All patients starting ART	23%	22.9%	?
Mphahlele *et al* (2006)	S. Africa	167	Not stated	16.2%	22.1%	?
Firnhaber *et al* (2009)	S. Africa	502	All clinic patients	4.4%	7.6%	4,100
N'dri-Yoman et al (2011)	Cote d'Ivoire	495	ART-naïve HBc/sAb+	13%	10%	158
Geretti *et al* (2010)	Ghana	834	All clinic patients	16.7%	9.9%	994
		342	ART-naive	17.8%	25.8%	
Bloquel *et al* (2010)	France	383	ART-naïve HBc/sAb+	?	4%	?
Morsica *et al* (2009)	Italy	175	ART-naïve HBc/sAb+	?	15%	?
Nebbia *et al* (2007)	UK	343	HBcAb+ patients	5.3%	14%	72
Shire *et al* (2009)	USA	909	All clinic patients	3%	1.3%	?

Aims

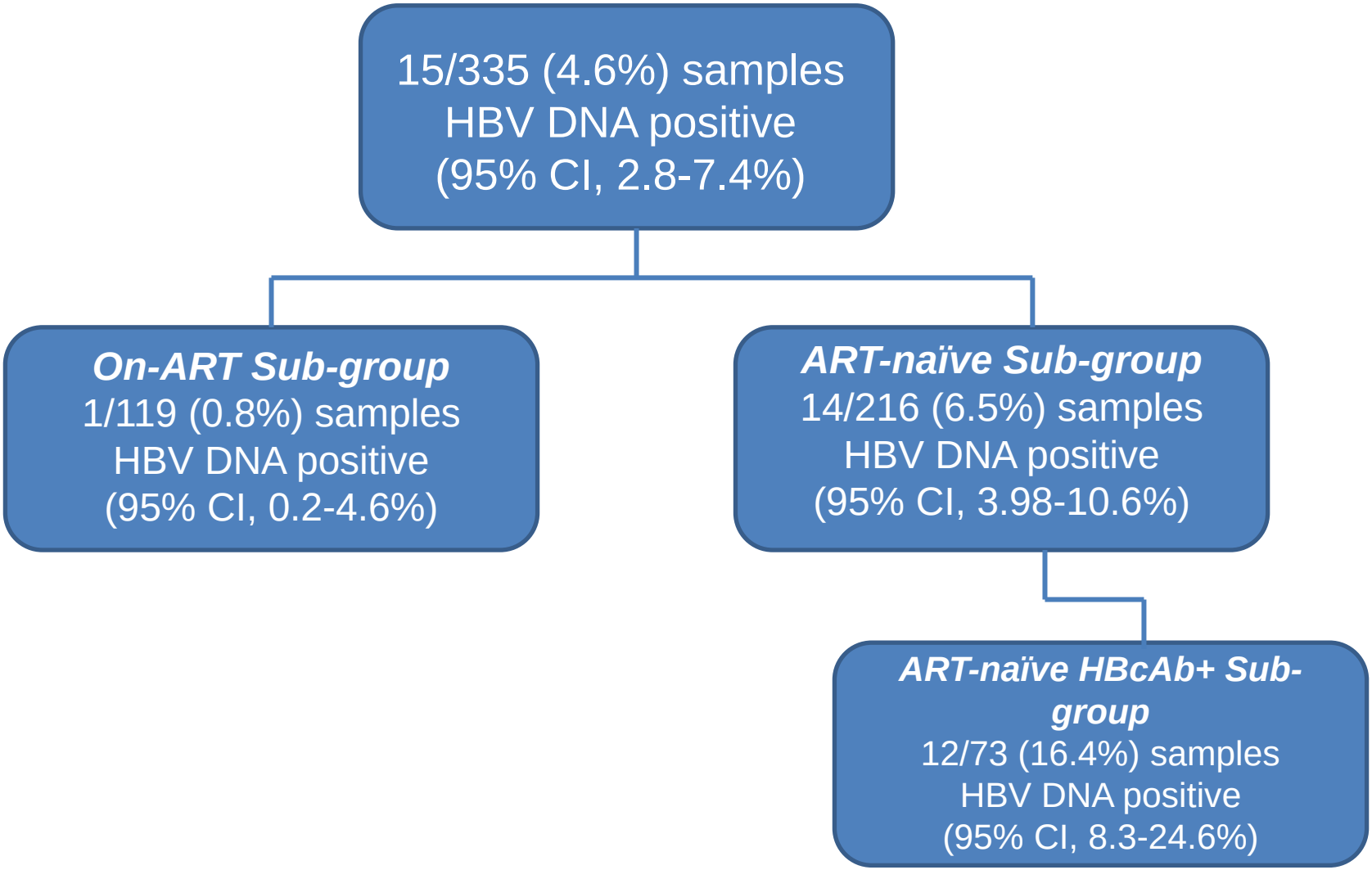
1) To determine the prevalence of occult HBV infection in HIV-infected African migrants to the UK, including subgroups

1) To explore associations between occult HBV co-infection (OHBVHC) and demographic or clinical factors in this population

Methods

- Unlinked anonymised point prevalence study in 3 HIV clinics: Royal Free, Middlesbrough and Newcastle
- Patients of African origin (>16 years) identified with negative HBsAg and no positive test previously
- Data extracted from notes or electronic records including demographics, lab results and ART
- Stored serum or plasma samples identified from Virology lab – linked to data.
- Data and lab samples anonymised and samples tested using real-time PCR for HBV DNA (LLD – 1.4 IU/mL)
- Prevalence of OHBVHC in entire group and sub-populations calculated
- Associations of OHBVHC with different demographic and clinical covariates explored by logistic regression

Results


15/335 (4.6%) samples
HBV DNA positive
(95% CI, 2.8-7.4%)
On-ART Sub-group
1/119 (0.8%) samples
HBV DNA positive
(95% CI, 0.2-4.6%)
ART-naïve Sub-group
14/216 (6.5%) samples
HBV DNA positive
(95% CI, 3.98-10.6%)
ART-naïve HBcAb+ Sub-group
12/73 (16.4%) samples
HBV DNA positive
(95% CI, 8.3-24.6%)

Characteristics of Population at Time of Sampling

		HBV DNA Positive (n=15)	HBV DNA Negative (n=320)
Age (median, yrs)		40	36
Female (%)		8 (53)	226 (71)
CD4 count (median, cells/ml)		281	330
Nadir CD4 (median, cells/ml)		278	275
HBV DNA (median IU/ml)		8	
HIV viral load (median log cpml)		4.42	4.58
HBcAb+ (n, %)		12 (80)	106 (33)*
HBsAb+ (n, %)		10 (66)	179 (56)
HCV IgG+ (n, %)		0 (0)	6 (2)
ALT elevated (%)		2 (13)	37 (11)
ALT (mean, u/L)		24.1	22.1
ART-naïve (%)		14 (93)	118 (37)*
African Region	South	7 (47)	177 (55)
(n, %)	Central	1 (7)	8 (3)
	East	5 (33)	58 (18)
	West	2 (13)	76 (24)

*p<0.05 by Chi-squared test. HBcAb: hepatitis B core antibody. HBsAb: hepatitis B surface antibody. HCV: hepatitis C virus. ART: antiretroviral therapy. ALT – alanine transaminase

Univariate Analysis of Factors Associated with Occult HBV/HIV Co-infection

	OR	*p*
Age (per 10 years older)	0.97	0.42
Sex (female)	0.41	0.14
CD4 (per 100 cells/μl increase)	0.996	0.45
HIV viral load (per 1 log cpml increase)	1.04	0.22
HBcAb+	7.4	0.003
HBsAb+	2.66	0.11

Conclusions

1) Occult HBV infection not uncommon in HIV+ Africans, although not as common as expected
2) Screening should be considered in sub-populations with higher risk of OHBVHC, such as Africans, Asians, HBcAb+ or patients with raised transaminases at diagnosis
3) As HBV DNA levels low in patients with OHBVHC, risk of progression of liver disease probably low but further research needed, including risk of hepatotoxicity of ART and HBV resistance

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