



## The prevalence of hepatitis B co-infection in a South African urban government HIV clinic

Cynthia Firnhaber, Anne Reyneke, Doreen Schulze, Babaty Malope, Mhairi Maskew, Patrick MacPhail, Ian Sanne, Adrian Di Bisceglie

**Objective.** There are an estimated 350 million hepatitis B carriers worldwide. In South Africa the prevalence of mono-infection with hepatitis B has been estimated to range from 1% in urban areas to approximately 10% in rural areas. The exact prevalence of hepatitis B in the HIV-infected population has not been well established. Hepatitis B screening is not standard practice in government HIV clinics. Co-infection with hepatitis B and HIV can influence antiretroviral treatment and prognosis of both diseases. The purpose of this study was to evaluate the prevalence of hepatitis B/HIV coinfection.

**Design.** This is believed to be the first prospective observational report on the prevalence of hepatitis B/HIV co-infection in South Africa. Patients on whom hepatitis B serological tests could not have been done previously were recruited from an HIV clinic in a regional hospital in Johannesburg. Standard hepatitis B serological tests were performed.

**Results.** Five hundred and two participants were screened. The cohort's average age was  $37 \pm 9$  years and the average CD4 count was 128 cells/ $\mu$ l. Twenty-four (4.8%) were hepatitis B surface antigen positive. Nearly half (47%) of the participants showed some evidence of hepatitis B exposure. The risk of hepatitis B co-infection was not significantly different when analysed in terms of sex, race, CD4 count or age. Liver function tests were not a good predictor of hepatitis B infection.

**Conclusion.** The rate of hepatitis B infection, as defined by hepatitis B surface antigen positivity, in HIV-infected individuals in urban South Africa was 5 times the rate in people who were not HIV-infected. A 5% rate of hepatitis B/HIV co-infection is a reason to increase the accessibility of tenofovir/emtricitabine (Truvada) for first-line treatment for this population.

*S Afr Med J* 2008; 98: 541-544.

There are an estimated 350 million hepatitis B carriers worldwide. Hepatitis B transmission is similar to that of HIV; therefore, co-infection with HIV and hepatitis B is not unusual. The prevalence of mono-infection with hepatitis B in South Africa has been estimated as approximately 10% in the rural population and 1% in urban areas.<sup>1,2</sup> The exact prevalence of hepatitis B in the HIV population has not been accurately established.

The guidelines for the South African HIV Comprehensive Care, Management and Treatment (CCMT) programme do not include viral hepatitis studies.<sup>3</sup> Hepatitis B serological tests are done only if serum aminotransferases are elevated in the absence of another known cause (e.g. tuberculosis and concomitant medications). We found three studies that

documented the South African prevalence of HIV/ HBV coinfection: a retrospective unmatched control laboratory-based study;<sup>4</sup> a prospective study looking at HIV patients admitted to hospital;<sup>5</sup> and a retrospective study of a cohort emanating from South African goldmines.<sup>6</sup> The rate of co-infection varied from 6% to 17%. No prospective study has evaluated the rate of hepatitis B virus (HBV) infection in a CCMT outpatient antiretroviral (ARV) clinic in South Africa.

Lamivudine is used in the treatment of both HIV and hepatitis B<sup>7,8</sup> and is widely used as first-line ARV therapy in most African settings. Hepatitis flares have been reported both on initiation of lamivudine and on its discontinuation in HIV-seropositive patients.<sup>9,10</sup> Lamivudine's safety and tolerability in HBV/HIV co-infection have not been described in resource-limited settings. Our study describing the baseline prevalence of HIV/hepatitis B co-infection in a Johannesburg CCMT clinic forms part of a PEPFAR ([USA] President's Emergency Plan for AIDS Relief) evaluation to examine the prevalence of co-infection and the 6-month safety and tolerance of lamivudine in this co-infected population.

*Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg*

Cynthia Firnhaber, MD

Anne Reyneke, RN

Doreen Schulze, Diploma in Health Administration

Babaty Malope, BSc, MSc

Mhairi Maskew, MB BCh

Patrick MacPhail, PhD, FCP, FRCP

Ian Sanne, MB BCh, FCP (SA)

*Department of Hepatology, School of Medicine, Saint Louis University, St Louis, Minn., USA*

Adrian Di Bisceglie, MD, FACP

*Corresponding author: C Firnhaber (cfirnhaber@witshealth.co.za)*

### Methods

#### Subjects

Patients from an outpatient PEPFAR-supported HIV clinic in a regional academic hospital in Johannesburg were invited to participate in this study. Patients who were about to



initiate ARV therapy according to the SA CCMT guidelines were informed about hepatitis B and HIV coinfection (CD4 counts  $<200/\mu\text{l}$  or World Health Organization (WHO) III or IV staging). A total of 502 people agreed to undergo hepatitis B screening and gave written informed consent. The study was approved by the University of the Witwatersrand ethics committee and the Saint Louis University Institutional Review Board. The patients had to be willing to start an ARV regimen containing lamivudine. Reasons given for not participating in the study included wanting additional time to listen to the education on hepatitis B or to sign consent, poor understanding of the study, not wanting an extra blood sample taken, and feeling too ill.

### Laboratory analysis

Serological testing included hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs) and hepatitis early (e) antigen (HBeAg) and antibody (anti-HBe) using the AxSYM assay with the MEIA methodology (Abbott Laboratories, Ill., USA). Hepatitis B viral DNA (HBV DNA) was measured using the Roche Cobas Amplicor quantitative assay (Roche Diagnostic Systems, Branchburg, NJ). Patients who were seropositive to HBsAg were considered positive, enrolled in the next phase of the study and initiated on highly active antiretroviral treatment (HAART) of lamivudine, stavudine and efavirenz, the first-line ARV regimen in the South African CCMT programme. Blood was drawn at the enrolment visit for HBeAg and anti-HBc, HBV DNA, hepatitis C and D antibody, full blood count, serum electrolytes, serum aminotransferases, urinalysis, CD4 cell count and HIV viral load.

### Results

The study comprised 502 participants, 354 (71%) females and 148 (29%) males, with a mean age ( $\pm$  significant deviation

(SD)) of  $37\pm 9.1$  years. Female subjects were significantly younger than male subjects ( $35.8\pm 8.5$  years v.  $39.9\pm 9.7$  years,  $p<0.0001$ ). The female-to-male ratio and the average age of the participants reflect the demographics of the larger clinic, which mirrors the demographic pattern of the South African HIV epidemic. The mean CD4 count was  $128.6\pm 84.4$ , and was similar in males and females ( $p>0.84$ ). The majority (94.6%) of the 502 patients were black; the rest (27) were either coloured or white (Table I). As shown in the table, 24 (4.8%) of the 502 patients screened were seropositive for HBsAg. Fifty-three (10.5%) of the patients had isolated core antibodies without any other markers of HBV infection. Forty-seven per cent of the cohort demonstrated some exposure to hepatitis B. Only 2.6% of the cohort had serological findings consistent with vaccination (anti-HBs alone).

The risk for hepatitis B infection was not significantly different when analysed in terms of sex (odds ratio (OR) 0.7 (95% confidence interval (CI) 0.3 - 1.6),  $p>0.4$ ) or racial group (OR (95% CI) 1.3 (0.2 - 10.1),  $p>0.7$ ). There was no statistical difference in hepatitis B serological results in terms of CD4 count, age or gender, except that men were statistically more likely to have an isolated core antibody ( $p<0.054$ ) (Table I) and were 1.6 times more likely to be positive overall to any hepatitis B serological test (positive for anti-HBs or anti-HBc or HBsAg combined) (OR (95% CI) 1.6 (1.1 - 2.3),  $p<0.012$  (Table I)).

Of the 24 subjects who were seropositive to HBsAg, 19 qualified for the observational study. The baseline demographics of the smaller cohort were not statistically significantly different from the main cohort in terms of mean baseline CD4 count and age.

We compared the standard laboratory results with HBeAg-negative and HBeAg-positive patients who were HBsAg positive. E antigen is thought to be a marker of hepatitis B replication. Of the 19 who were HBsAg positive, 9 were e-

Table I. Demographic and baseline information of all subjects screened for HBV

		Screening			
		All (502)	Female (354)	Male (148)	Significance
Demographic information	Age (mean ( $\pm$ SD))	37.0 (9.1)	35.9 (8.6)	39.9 (9.7)	$p<0.0001$
	CD4 counts (mean ( $\pm$ SD))	128.6 (84.4)	129.1 (78.6)	127.4 (97.1)	$p=0.84$
	Race				
	Black (f:m ratio 2.5:1)	475	338 (71.2)	137 (28.8)	$p<0.0001$
	Other (mixed race or Caucasian) (f:m ratio 1.4:1)	27	16 (59.3)	11 (40.7)	$p=0.33$
HBV seropositive markers	HB surface antigen positive	24 (4.8)	15 (4.2%)	9 (6.1%)	
	HB surface antibodies only	13 (2.6%)	7 (2.0%)	6 (4.1%)	
	HB core antibodies only	53 (10.6%)	29 (8.2%)	24 (16.2%)	$p=0.053$
	Both HB surface and core antibodies	124 (24.7%)	88 (24.9%)	36 (24.3%)	
	Negative to all	288 (57.4%)	215 (60.7%)	73 (49.3%)	
Positive to any marker	Positive	214 (42.6%)	139 (39.3%)	75 (50.7%)	$p=0.019$



antigen positive (7 out of 9 had HBV DNA). Ten were e-antigen negative, and 5 of these patients had HBV DNA. There were two statistically different laboratory parameters between the e-antigen-positive and negative patients. The e-antigen-negative patients had higher CD4 counts (189.4 v. 113.11 cells/ $\mu$ l;  $p=0.0316$ ) and higher total proteins. There were no statistical differences in HIV viral load, liver function tests or HBV viral load (although e-antigen-positive patients tended to have higher HBV viral loads) between e-antigen-positive and negative patients. None of the participants was found to be hepatitis C or D positive.

When comparing hepatitis B DNA viral load (HBV) to CD4 count or HIV viral load, there was no statistical difference. The only statistical difference was seen in a slightly higher average in the alanine transaminase (ALT) levels (mean  $46\pm 21.6$ ) in the high detectable HBV viral loads category (Table II). However, liver function tests overall were not good predictors of hepatitis B infection. All of the 19 people who were positive for HBsAg had normal or slightly elevated serum aminotransferases (Table III).

## Discussion

Co-infection with HIV and hepatitis B is not well described in southern Africa, but the rate is anticipated to be high as the viruses have similar modes of transmission. Hepatitis B prevalence in the non-HIV-infected population is about 10% in rural South African areas and about 1% in urban areas.<sup>12</sup> We have shown that the urban South African co-infection rate is five times that found in the non-HIV-infected population. Our serological study also demonstrates that approximately 50% of HIV-seropositive patients have been exposed to hepatitis B. The South African paediatric immunisation programme for hepatitis B started in 1995; this prevention strategy would not be reflected in this cohort.

At present, the SA CCMT guidelines do not recommend routine testing for hepatitis B co-infection. In our study, there were no other markers of hepatitis B infection, and liver function tests were not an adequate indicator of infection. This

**Table III. Liver transaminase results in HIV and hepatitis B co-infected surface antigen-positive patients**

Levels of liver transaminase	Number of patients
AST	
Grade 1 elevation (50 - 100)	8 (42.11)
Normal range (5 - 40)	11 (57.89)
ALT	
Grade 1 elevation (50 - 100)	3 (15.79)
Normal range (5 - 40)	16 (84.21)

AST = aspartate transaminase; ALT = alanine transaminase.

prevalence rate, determined only by surface antigen serology, may be falsely low as HBV DNA has been commonly reported in HIV-seropositive patients with isolated core antibody.<sup>11</sup> If this is the case, the prevalence of co-infection would be closer to 15% in this urban population. Real-time hepatitis B polymerase chain reaction studies on the serum of screened patients with isolated core antibody are currently being done in this cohort.

Hepatitis B can be treated with lamivudine, which is used as first-line treatment in the HIV treatment programme and is well tolerated. However, there are reports of liver complications when treating HIV/hepatitis B co-infection with the addition of antiretroviral therapy for HIV and removal of lamivudine, which can cause liver inflammation and, rarely, liver failure.<sup>10</sup> Another complication is that lamivudine resistance also develops at a quicker rate in HIV-seropositive patients. Therefore, during the first year of lamivudine-containing ARV treatment, most patients will have adequate treatment of their hepatitis B. However, by the second year, approximately 40% of these patients will have developed resistance.<sup>9,12</sup> The WHO guidelines recommend dual therapy in HIV patients: either tenofovir/lamivudine or tenofovir/emtricitabine (Truvada)<sup>12</sup> to reduce the risk of developing resistance, as tenofovir also treats hepatitis B.<sup>13</sup>

Possible limitations of this study were:

1. The low average CD4 count, as these people were attending the educational session to start ARVs as per the

**Table II. HBV viral load v. CD4 count and liver function tests (mean (SD))**

	HBV viral load			<i>p</i> -value
	Undetectable (0)	Low detectable (<200/ $\mu$ l)	High detectable ( $\geq 200$ / $\mu$ l)	
Total (N)=18	5	4	9	
CD4 count result	148.8 (63.8)	209.3 (39.99)	138.1 (95.5)	0.34
Log HIV viral load	11.8 (1.7)	11.9 (1.68)	12.1 (1.1)	0.95
ALP	67.8 (8.5)	75.2 (30.13)	114.2 (78.3)	0.32
AST	30.2 (8.7)	47.0 (19.78)	60.1 (21.3)	0.074
ALT	28 (12.2)	23.4 (12.07)	46.1 (21.6)	0.034*
Albumin	38.2 (4.1)	33.8 (7.37)	32.7 (6.1)	0.267
Haemoglobin	11.7 (2.1)	14.1 (2.47)	11.6 (2.1)	0.159
White cell count	3.3 (0.7)	4.83 (1.58)	4.51 (1.6)	0.24

ALP = alkaline phosphatase; AST = aspartate transaminase; ALT = alanine transaminase.



government programme. How their immune status could affect their serological findings is unknown. With immunodeficiency, there could theoretically be a decrease in production of antibodies to hepatitis B, leading to misdiagnosis of hepatitis B status.

2. Hepatitis B viral loads were not done on all screened patients owing to limited resources. If the study had had the capacity to perform HBV viral loads, this would have clarified the actual prevalence of hepatitis B exposure and chronic carrier status.

3. Negative or positive e-antigen status did not correlate with HBV replication in our cohort, indicating that e-antigen status may not be an adequate surrogate marker of replicating hepatitis B DNA. Black Africans seroconvert from e antigen to e antibody far earlier than other populations.<sup>14,15</sup> This may be due to the presence of one or more mutations in one of the following areas: the precore/core, the basic core promoter, the Kozak sequence and/or the bulge of the RNA encapsidation signal (personal communication, Professor Michael Kew).

What impact these complications have on ARV treatment programmes in southern Africa is unclear. Monitoring of this cohort for these complications is under way and it is hoped will provide some answers. At present, HIV patients with HBV coinfection should be monitored carefully.

## Conclusions

The rate of co-infection with hepatitis B/HIV as defined by HBsAg is five times the rate of hepatitis B infection in the non-HIV population in urban South Africa; further investigation is necessary to evaluate the possibility of occult hepatitis B infection in patients with an isolated core antibody. A 5% prevalence of co-infection in government ARV urban clinics is a reason to consider evaluating the cost of hepatitis B serological

tests, hepatitis B vaccination (50% of the cohort showed no serological exposure to hepatitis B) and initiating a tenofovir/emtricitabine backbone as an option for first-line ARV therapy in co-infected patients in government ARV clinics.

NIH/Pepfar Targeted Evaluations U01 A1-38858.

## References

1. Burnett RJ, François G, Kew MC, *et al*. Hepatitis B virus and human immunodeficiency virus co-infection in sub-Saharan Africa: a call for further investigation. *Liver Int* 2005; 25(2): 201-213.
2. Di Biseglie AM, Kew MC, Dusheiko GM, *et al*. Prevalence of hepatitis B virus infection among black children in Soweto. *BMJ* 1986; 292: 1440-1442.
3. Tshabalala-Msimang ME, MBewu A, Simelela N, *et al*. *Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*. Pretoria: Department of Health, 2003.
4. Mphahlele J, Azwidowi L, Burnett R, *et al*. High risk of occult hepatitis B virus infection in HIV-positive patients. *South Africa Journal of Clinical Virology* 2006; 35: 14-20.
5. Lodenyo H, Schoub B, Ally R. Hepatitis B and C virus infections and liver function in AIDS patients at Chris Hani Baragwanath Hospital, Johannesburg. *East Afr Med J* 2000; 77(1): 13-15.
6. Hoffman C, Charalambous S, Thio C, *et al*. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007; 21: 1301-1308.
7. Benhamou Y. Antiretroviral therapy and HIV/hepatitis B coinfection. *Clin Infect Dis* 2004; 38: (suppl 2), S98-S103.
8. Nunez M, Puoti M, Camino N *et al*. Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin Infect Dis* 2003; 37: 1678-1685.
9. Soriano V, Massimo P, Maurizio B, *et al*. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005; 19: 221-240.
10. Drake A, Mijch A, Sasdeus J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection despite lamivudine therapy as HAART. *Clin Infect Dis* 2004; 39: 129-132.
11. Shire NJ, Rouster SD, Rajcic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; 36: 869-875.
12. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Geneva: WHO, 2006. [www.who.int/hiv/pub/guidelines/artadultguidelines.pdf](http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf) (accessed 20 October 2007)
13. Dore G, Cooper D, Pozniak A, *et al*. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy – naïve and experienced patients coinfecting with HIV-1 hepatitis B virus. *J Infect Dis* 2004; 189: 1185-1192.
14. Botha JF, Ritchie MJ, Dusheiko GM, Mouton HWK, Kew MC. Hepatitis B virus carrier state in Black children in Ovamboland: Role of perinatal and horizontal infection. *Lancet* 1984; 2: 1209-1212.
15. Kew MC, Kassianides K, Hodkinson J, Coppin A, Paterson AC. Hepatocellular carcinoma in urban-born blacks: Frequency and relation to hepatitis B virus infection. *BMJ* 1986; 293: 1339-1341.

Accepted 23 January 2008.