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Prevalence and Associations with Hepatitis B and Hepatitis C infection Amongst HIV-infected Adults in South Africa

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Abstract

We assessed prevalence and factors associated with hepatitis B in a cross-section of HIV-infected primary care and anti-natal clinic patients in South Africa and evaluated a rapid hepatitis B surface antigen (HBsAg) assay. We enrolled 998 patients; 88% were women, median age was 29 years, and median CD4 count was 354 cells/mm^3. HBsAg ELISA, anti-hepatitis B core (HBc) antibodies, and hepatitis C virus antibody were positive among 4.2%, 37%, and 0.1% of subjects, respectively. Univariate and multivariate associations were assessed using logistic regression. Anti-HBc antibodies were associated with alcohol use, traditional medicines, and higher CD4. HBsAg positivity was associated with lower CD4. Compared to the HBsAg ELISA, a rapid HBsAg test had a sensitivity of 75.0% and specificity of 99.6%. In conclusion, we identified a moderate prevalence of both HBsAg and anti-HBc. Importantly, we found subjects with HBsAg positivity had lower CD4 counts.

Keywords

HIV/AIDS; HBV; HBsAg; HCV; rapid test; Africa

Background

Chronic hepatitis B (CH-B) is hyperendemic in parts of Africa and Asia where it is the leading cause of liver-related death and liver cancer (1). Co-infection with HIV increases mortality rates and risks for liver related complications beyond that of either HIV or CH-B alone (2). The increased risk of liver related complications appears to persist even in the setting of HAART (3). Prevention of HBV through preventing perinatal transmission by use of hepatitis B immune globulin and vaccination and prevention of childhood or adult transmission through vaccination are important long-term steps to reduce the burden of CH-B. However, among the 5–15% of HIV-infected individuals already chronically infected with CH-B, specific therapies, such as lamivudine, tenofovir, or tenofovir co-formulated with emtricitabine may reduce the morbidity from HIV-CH-B co-infection (4;5).

In South Africa the HIV prevalence was 18% in 2008 and 17% in 2002 amongst adults 15–49 years old (6). Antiretroviral therapy rollout started in South Africa in 2004; prior to that time little therapy was available. The prevalence of chronic hepatitis B is less well

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characterized in South Africa. However, infant hepatitis B vaccination was started on a national level in 1996. No routine adult HBV vaccination has been instituted, partly due to the assumption that the majority of HBV transmission occurring in South Africa occurs during infancy (7). Developing prevention strategies and assessing treatment needs requires understanding the epidemiology of C-HB, other chronic viral hepatitis infections, and risks for infection. However, factors associated with transmission, prevalence by region, and interactions between HIV and CH-B, including the impact on CD4 count, are incompletely characterized in Africa. In addition, rapid hepatitis B surface antigen tests have recently become commercially available and could be useful tools in clinical settings, but performance characteristics in HIV-infected populations are unclear. We sought to describe prevalence and associations with CH-B infection and HCV infection among HIV-infected adult South Africans, to investigate associations between CH-B and CD4 count, and to assess the performance of a point-of-care hepatitis B surface antigen (HBsAg) test among HIV-infected individuals.

Methods

In 2002, before the introduction of antiretroviral therapy in this population, we recruited a sample of HIV-infected adults ≥18 years old who were anti-retroviral therapy naïve and receiving antenatal or primary care in an urban area in South Africa (Soweto). None of these individuals received HBV vaccination as part of the infant vaccination program as it was only initiated in 1996. Antenatal subjects were included to provide a population-based sample of individuals not receiving care for medical illness. After obtaining informed consent, a structured questionnaire was administered by trained study assistants. The questionnaire included questions regarding age, sex, receipt of blood transfusions, incarceration history, history of present or past self described heavy alcohol use (defined as intoxication two or more times a month), and history of present or past use of traditional medications. Traditional medications were defined as any herbal or mineral preparation ingested, inhaled, or applied to the skin (often via a small incision). Point-of-care immunochromatographic HBsAg screen (Determine Abbot Laboratories, Sao Paulo, Brazil), laboratory-based HBsAg ELISA and hepatitis B core antibody (anti-HBc) (both, Axym Assay, Abbott Laboratories, USA), hepatitis C antibody (Core Combo, Core Diagnostics, Birmingham UK), alanine aminotransferase (ALT), and CD4 count (Beckman Coulter, Fullerton CA) were performed on all subjects. Hepatitis B e antigen (HBeAg) was assayed on participants with positive HBsAg serology (Abbott Axym). The normal range for the ALT assay was 5–40 IU/L. All laboratory tests were performed by an accredited clinical laboratory in South Africa.

Descriptive statistics were performed using Student's t-test or chi-square tests. Associations with HBsAg status were assessed using logistic regression. As a sensitivity analysis, we repeated ALT and CD4 count analyses stratified by whether or not women were pregnant because of the potential effects of pregnancy on ALT and CD4 count (hemodilution). We calculated the sensitivity, specificity, positive predictive value and negative predictive value for the rapid HBsAg test using the laboratory-based HBsAg ELISA as the gold standard. The study was approved by the University of the Witwatersrand's ethics board.

RESULTS

998 HIV-infected adults were screened and agreed to participate; 88% were women of whom 26% were pregnant (Table 1). The median age was 29 years (interquartile range (IQR): 25–34), the median CD4 count was 354 (IQR: 198–537), and all subjects were black Africans. Based on self-report using the structured questionnaire, 9.2% ever received a

blood transfusion, 17.9% had ever used traditional medicines, 9.6% had ever been incarcerated, and 30.8% had a history of heavy alcohol use.

Of the 998 subjects enrolled, 981 had results from HBsAg ELISA testing; the other 17 had insufficient serum or errors in laboratory processing. Only the 981 with test results were included for subsequent analysis. Overall 41 of 981 (4.2%; 95% confidence interval (CI): 2.9–5.4) tested positive for HBsAg using the laboratory-based ELISA HBsAg assay and 367 of 990 participants (37%, 95% CI: 34.1–40.1) were anti-HBc positive. Of 34 subjects positive for HBsAg and tested for HBeAg, 18 (52.9%, 95% CI: 35–71) were eAg positive. One subject tested positive for HCV antibodies.

In assessing for associations with anti-HBc we observed what appeared be increasing prevalence with advancing age, however, this was not a statistically significant trend (p trend >0.05). Between the age range of 17–25 years the prevalence was 34.6 (95% CI: 28.4–40.9), 26–35 years it was 37.1% (95% CI: 33.0–41.2), 36–45 years it was 39.2 (95% CI: 32.1–46.2), and among those >45 years old it was 40.0 (95% CI: 21.4–58.6). Using logistic regression, we assessed for associations with anti-HBc status. Anti-HBc was positivity associated with heavy alcohol use (OR: 1.6), traditional medicine use (OR: 1.7), and higher CD4 count strata (Table 2). We found no associations between incarceration or blood transfusion and HBV serostatus (p>0.1).

In reverse of anti-HBc, individuals positive for HBsAg had a lower median CD4 count than those negative (312 versus 358 cells/mm^3, p=0.04). This difference held true when limiting the sample to pregnant women: median CD4 was 264 cells/mm^3 (IQR: 187–363) among pregnant women positive for HBsAg versus 344 cells/mm^3 (IQR: 248–526) among pregnant women negative for HBsAg. Median ALT was higher, 21 IU/L (IQR: 16–32) versus 16 IU/L (IQR: 12–23, p=0.002) and 22.0% compared to 6.6% had values of ALT above the upper limit of the reference range among individuals positive versus negative for HBsAg. We found no association with alcohol use or traditional medications and HBsAg status (Table 2).

Using the Determine rapid HBsAg assay, 34 of 973 (3.5%) tested positive. The sensitivity, specificity, and positive and negative predictive values for the test were 75.0 (95% CI: 58.5 – 86.8), 99.6 (95% CI: 98.8 – 99.9), 88.2 (95% CI: 71.6 – 96.1), and 98.9 (95% CI: 97.9 – 99.4), respectively.

DISCUSSION

We identified a relatively low prevalence of HBsAg among an urban HIV-infected population in South Africa and the virtual absence of anti-HCV antibodies. These findings differ from much of the African continent, but are consistent with results from a smaller study in a different urban setting in South Africa in terms of both CH-B and HCV prevalence (8). The consistency of these findings with the smaller study that was limited to antiretroviral therapy initiators is re-assuring, especially as our study was not limited to a population specifically seeking care for HIV or with advanced HIV disease, as that could introduce confounding.

We identified an association between heavy alcohol use and anti-HBc positivity, suggesting increased HBV exposure. This is an important finding and, as far as we know, new for southern Africa. This finding suggests adolescent/adult transmission of HBV among HIV-infected individuals possibly as a result of increased high risk sexual activity that often parallels heavy alcohol use (9;10). It is also possible that an unmeasured factor is associated with both infant HBV exposure and later alcohol use. Further exploration of timing of HBV infection and potential risk factors is important as adult transmission of HBV has previously

been considered rare in Africa and disease can be prevented by vaccination. We also found an association between traditional medicine use and increased anti-HBc prevalence. It is unclear whether the exposure occurred during childhood or adulthood as adults who use traditional medicines may also be more likely to have used traditional medicines as children. Traditional medicines are plausibly linked to HBV exposure as small cutaneous incisions are made while administering some traditional treatments. In addition, studies from West Africa have also found an association between traditional medicine use and HBV (11;12).

Importantly, we found a higher prevalence of HBsAg with lower CD4 count. Few studies have had the opportunity to evaluate the impact of HBsAg on the absolute CD4 count using a wide range of CD4 values as previous studies have assessed patients initiating antiretroviral therapy (usually with CD4 <200 cells/mm^3). Some of these studies have reported an association between HBsAg and CD4 count while others have not (13–15). However these previous studies have been focused on ART initiators which may mask an association between CD4 count and CH-B and are susceptible to confounding by an unmeasured factor influencing both CH-B risk and timing of presentation for antiretroviral therapy. For example, in Africa people living in rural areas have a higher HBsAg prevalence (16) and may be more likely to present to care with more advanced HIV and lower CD4 counts than urban dwellers. Pregnant women, presenting for antenatal care, as in our study, are less susceptible to this confounding. Thus, our finding of lower CD4 count even among pregnant women with HBsAg is important and novel. Several plausible biological hypotheses may explain our finding. One is that HBV infection causes a non-progressive absolute decrease in CD4 count, this is suggested by studies in HIV-uninfected individuals (13;14). A second explanation may be that reactivation of HBsAg is occurring at lower CD4 counts, a phenomenon reported in HIV-infected and other highly immunosuppressed populations (17). Finally, individuals with greater immunosuppression are more likely to progress to CH-B following acute HBV infection (18). This could be an explanation if a significant amount of adult transmission is occurring. Further work examining the impact of CH-B on CD4 count would be valuable to identify whether an immune interaction is leading to lower CD4 counts, significant adult transmission is occurring, or if HBV is re-activating. This has important implications for recommendations for prevention of C-HB and management of HIV-HBV co-infection. Finding the opposite association with anti-HBc seropositivity, of higher prevalence at higher CD4 counts, may be a result of a loss of antibodies with waning immunity.

We also found a low prevalence of HCV - one antibody positive subject. This is consistent with a study of individuals mostly from rural regions and a study from Johannesburg (8;19). Because of the sensitivity of HCV antibody testing, we doubt that we failed to identify a significant number of individuals with chronic HCV infection (20). Our findings do differ from findings from east Africa where HCV antibody screening has been positive for 1–12% (21;22). The finding suggests very low circulating HCV within the population, low rates of injection drug use, and low rates of nosocomial transmission. Given our finding of rare HCV infection, routine HCV screening among HIV-infected individuals is probably not indicated in South Africa.

The sensitivity of the rapid HBsAg test was disappointing for routine clinical use in our population. However this result is similar to a previous report among mostly HIV-infected individuals (23) and lower than a report among HIV-uninfected individuals (24). It is unclear whether HIV serostatus affects test performance. However, HIV co-infected individuals have higher mean HBV DNA levels and HBsAg (25;26), thus lower sensitivity in HIV-infection would appear counter-intuitive and needs further exploration. We would suggest, prior to clinical use of currently available rapid HBsAg tests, that the performance should be assessed in the target population.

This study provides an evaluation of a large cross-section with a large proportion of subjects entering the study for reasons other than medical illness making it a useful addition to the understanding of hepatitis B among HIV infected individuals in Africa. However, the study has several limitations. First, our findings reflect prevalence among individuals seeking antenatal or primary care and is not based on a community survey. Pregnant women are sexually active and may have a higher risk of HBV exposure. Second, we obtained serology at a single time point preventing us from assessing incidence of HBV infection or from diagnosing CH-B (defined as persistence of HBsAg for >6 months). Finally, we did not assess HBV serology in HIV-uninfected individuals, thus we are unable to compare prevalence by HIV status.

This study adds to the understanding of chronic hepatitis infection in South Africa among HIV-infected individuals, including risk factors for HBsAg positivity. Our findings suggest the possibility of adolescent/adult transmission of HBV. If so, adult vaccination may be a useful intervention among HIV-infected individuals. In addition, the finding of a lower CD4 count among individuals with HBsAg is intriguing and needs further investigation.

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Table 1

Characteristics of study subjects

	Women, n (%) or median (IQR)	Men, n (%) or median (IQR)	Combined, n (%) or median (IQR)
Number	879	119	998
Median age, years	28 (25–33)	34 (31–38)	29 (25–34)
Median CD4 count, cells/mm^3	265 (108–445)	368 (209–550)	354 (198–537)
CD4 count strata, cells/mm^3			
<200	205 (23.3)	45 (37.8)	250 (25.0)
200–500	411 (46.8)	51 (42.8)	462 (46.3)
>500	257 (29.2)	23 (19.3)	280 (28.0)
Blood transfusion (ever)	84 (9.6)	8 (6.7)	92 (9.2)
Traditional medicines (ever)	156 (17.7)	23 (19.3)	179 (17.9)
Heavy alcohol use (ever)	222 (25.2)	85 (71.4)	307 (30.8)
Tattoo, piercing, or circumcision	70 (8.0)	24 (20.2)	94 (9.4)
Pregnant at enrollment	228 (25.9)	-	-
Incarcerated (ever)	46 (5.2)	50 (42.0)	96 (9.6)

IQR: interquartile range

Table 2

Univariate and multivariate associations with hepatitis B core antibody and hepatitis B surface antigen positivity.

	Hepatitis B core antibody		Hepatitis B surface antigen	
	Univariate OR (95% CI)	**Multivariate OR (95% CI)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Male (versus female)	1.2 (0.8 – 1.8)		1.46 (0.8 – 2.8)	2.1 (0.9 – 5.2)
Age (per year increase)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)
Ever heavy use of alcohol (versus never)	1.6 (1.2 – 2.0)	1.5 (1.1 – 2.1)	2.2 (1.0 – 4.8)	1.2 (0.6 – 2.5)
Traditional medicine use (versus never)	1.7 (1.2 – 2.4)	1.7 (1.2 – 2.4)	1.3 (0.6 – 2.8)	
CD4 count (cells/mm^3)				
<200	Reference	Reference	Reference	Reference
200–500	1.3 (0.9 – 1.7)	1.4 (1.0 – 2.0)	0.6 (0.3 – 1.2)	0.7 (0.3 – 1.4)
>500	1.4 (1.0 – 2.0)	1.6 (1.1 – 2.4)	0.3 (0.1 – 0.8)	0.3 (0.1 – 0.9)
Ever incarcerated (versus never)	1.3 (0.8 – 1.9)		1.0 (0.4 – 2.9)	
Ever blood transfusion (versus never)	1.2 (0.8–1.8)		1.8 (0.7–4.3)	

OR: odds ratio