HIV, Hepatitis B, and Hepatitis C in Zambia

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ABSTRACT

Objectives: Epidemiologic data of HIV and viral hepatitis coinfection are needed in sub-Saharan Africa to guide health policy for hepatitis screening and optimized antiretroviral therapy (ART). **Materials and Methods:** We screened 323 HIV-infected, ART-eligible adults for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) at a tertiary hospital in Lusaka, Zambia. We collected basic demographic, medical, and laboratory data to determine predictors for coinfection. **Results:** Of 323 enrolled patients, 32 (9.9%; 95% CI=6.7–13.2%) were HBsAg positive, while 4 (1.2%; 95% CI=0.03–2.4%) were HCV Ab positive. Patients with hepatitis B coinfection were more likely to be <40 years (84.4% vs. 61.4%; *P*=0.01) when compared to those who were not coinfected. Patients with active hepatitis B were more likely to have mild to moderately elevated AST/ALT (40–199 IU/L, 15.8% vs. 5.4%; *P*=0.003). Highly elevated liver enzymes (>200 IU/L) was uncommon and did not differ between the two groups (3.4% vs. 2.3%; *P*=0.5). We were unable to determine predictors of hepatitis C infection due to the low prevalence of disease. **Conclusions:** HIV and hepatitis B coinfection was common among patients initiating ART at this tertiary care facility. Routine screening for hepatitis B should be considered for HIV-infected persons in southern Africa.

Key words: Africa, Hepatitis B, Hepatitis C, HIV, Prevalence, Zambia

INTRODUCTION

Since 2004, the Zambian government's program for antiretroviral therapy (ART) has expanded rapidly in the public sector.[1,2] Because of severe resource constraints, however, the routine screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) has not been incorporated into the country's HIV treatment guidelines. Understanding the extent of these dual epidemics is critical to the optimization of HIV treatment. Several antiretroviral drugs – most notably nevirapine and lopinavir – are associated with liver failure among patients with HBV or HCV infection.[3-7] Conversely, tenofovir and lamivudine have been shown to inhibit HBV replication and could be used to improve long-term clinical outcomes.

Studies of HBV surface antigen (HBsAg) prevalence among HIV-infected adults have provided varying estimates in Zambia. In a 1996 survey, Oshitani and colleagues detected HBsAg in the serum samples of 24 of 340 (7.1%) HIV-infected pregnant women.[8] In 2002, Kasolo *et al.* estimated HBsAg seropositivity in 31.3% among HIV-infected adults hospitalized at a tertiary care institution.[9] To our knowledge, there are no studies examining co-infection rates among adults starting ART in a primary care setting, nor are there published data on HCV-HIV coinfection prevalence in Zambia.

MATERIALS AND METHODS

We conducted a cross-sectional study of adults seeking HIV care and treatment at the University Teaching Hospital (UTH), a 2500-bed tertiary care center in Lusaka. The UTH Department of Internal Medicine manages one of the country's oldest ART programs, founded in 2001

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by the Ministry of Health.[10] Individuals who present to the clinic are screened for ART eligibility based on the Zambian national guidelines that are similar to those of the World Health Organization (WHO): CD4+ cell count <200 cells/μL, or WHO disease stage IV, or CD4+ cell count <350 cells/μL and WHO disease stage III.[11] Unlike the neighboring primary care centers of the Lusaka district that rely heavily on mid-level clinicians,[12] care at UTH is provided by physicians.

We recruited adolescents and adults >16 years of age with confirmed HIV infection who were identified as ART eligible. Trained study staff approached potential candidates, described study procedures, and obtained informed consent for the hepatitis survey. Only adults who were ART naïve were considered, unless the previous ART use was deliberately transient, as with postexposure prophylaxis or perinatal HIV prevention. All participants were asked to complete a 28-question survey, administered in the language of their choice: English, Nyanja, or Bemba. Questions covered demographic characteristics, medical history, socioeconomic history, and risk factors for hepatitis B and/or C acquisition.

Blood specimens were drawn for viral hepatitis screening. We used the enzyme immunoassays to detect HBsAg for acute HBV (Axsym HBsAg™, version 2; Abbott Max-Planck, Wiesbaden, Germany) and anti-HCV antibodies for HCV infection (Axsym HCV™, version 3; Abbott Max-Planck, Wiesbaden, Germany). Baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were analyzed using an automated chemistry analyzer (Cobas Integra 400™; Roche, Mannheim, Germany). Liver enzyme elevation was based on guidelines set forth by the Division of AIDS, U.S. National Institutes of Health.[13] We graded liver enzyme elevations according to the highest results between ALT or AST as follows: ALT and/or AST of 50–100 U/L mild elevation; 101-200 U/L moderate elevation; >200 U/L severe elevations.

To compare categorical variables, we used Pearson's chi-square test and Fisher's exact test, as appropriate. For continuous variables, statistical comparisons were made using Wilcoxon's rank sum tests. Our sample size was based on an estimated HBV prevalence of 31%,[9] with a precision ±5%. All analyses were performed using SAS™, version 9.1.3 (SAS Institute, Cary, NC, USA). This analysis was approved by the Institutional Review Boards of the University of Zambia (Lusaka, Zambia) and the University of Alabama at Birmingham (Birmingham, AL, USA).

RESULTS

From December 12, 2007 to June 13, 2008, we enrolled 323 ART-naïve adolescents and adults >16 years of age into our study. The median age was 37 years (IQR=32, 44); median CD4+ cell count was 118 cells/μL (IQR=59, 199); and 174 (54%) were women. Of the 323 participants, 32 (9.9%; 95% confidence interval [CI]: 6.7–13.2%) were HBsAg positive while four (1.2%; 95% CI: 0.03–2.4%) were anti-HCV antibody seropositive. No one was coinfected with hepatitis B and C.

Patients with active HBV and HIV coinfection were more likely to be <40 years of age (84.4%) when compared to those who were not coinfected (63.9%; *P*=0.02). No differences in prevalence were noted according to sex, baseline WHO stage, or CD4+ cell count. A history of blood transfusion, that of tattooing, reported sexual partners in the past year, and past history of sexually transmitted infections were also not associated significantly with HBV [Table 1]. Mild to moderately elevated liver transaminases (AST or ALT) were more likely to be observed among patients with HBV coinfection (*P*=0.003). A severe elevation of liver enzymes (≥200 IU/L) was uncommon in this population (7 of 290; 2.4%) and similar between the HIV/HBV coinfected and non-co-infected groups (3.4% vs. 2.3%; *P*=0.5). No statistically significant predictors of hepatitis C infection were identified, though our statistical power to observe differences was very low with only four HCV infected persons (data not shown).

DISCUSSION

As the HIV epidemic in Zambia moves forward in the ART era, new data on hepatitis coinfection are clearly needed to guide health policy. In this cross-sectional study, we found that active HBV coinfection (HBsAg seropositivity) occurred in 9.9% of ART-naïve HIV-infected patients. In contrast, HCV occurred in only 1.2% of HIV-infected persons, a finding consistent with the primarily heterosexual transmission of HIV and low intravenous drug use in our setting.

Our estimate of HBV prevalence was lower than the 31% reported in 2003 at UTH, a figure upon which our sample size had been based. In that study, Kasolo and colleagues had targeted hospitalized patients and this likely contributed to the unusually high prevalence observed among HIV-positive adults.[14] Our results are more consistent with studies in South Africa (4.8%),[15] Nigeria (11.9%),[16] Senegal (16.8%),[17] and Tanzania (17.3%)[18] that targeted HIV-eligible patients in an outpatient setting. It

Table 1: Univariate predictors of active hepatitis B infection among HIV-infected adults eligible for antiretroviral therapy

Patient characteristics	HBsAg+ (N=32)	HBsAg− (N=291)	P-value
Age, median years (IQR)	32.5 (28.0–37.0)	37.5 (32.0–44.0)	0.002
Sex			
Men, *n* (%)	16 (50.0)	132 (45.8)	0.65
Women, *n* (%)	16 (50.0)	156 (54.2)	
Education			
No formal education, *n* (%)	1 (3.1)	3 (1.0)	0.35
Formal education, *n* (%)	31 (96.9)	285 (99.0)	
Income per month			
ZMK <500,000, *n* (%)	19 (59.4)	150 (52.1)	0.43
ZMK ≥500,000, *n* (%)	13 (40.6)	138 (47.9)	
WHO stage			
I or II, *n* (%)	7 (22.6)	86 (30.6)	0.35
III or IV, *n* (%)	24 (77.4)	195 (69.4)	
CD4+ cell count/μL, median (IQR)	152 (82–224)	114 (57–199)	0.25
<200 cells/μL, *n* (%)	22 (73.3)	205 (75.1)	0.83
≥200 cells/μL, *n* (%)	8 (26.7)	68 (24.9)	
Highest ALT or AST value, median (IQR)	45 (37–55)	36 (25–52)	0.04
<50 U/L, *n* (%)	14 (48.3)	194 (71.3)	0.03
50–100 U/L, *n* (%)	13 (44.8)	58 (21.3)	
101–200 U/L, *n* (%)	1 (3.4)	14 (5.1)	
>200 U/L, *n* (%)	1 (3.4)	6 (2.2)	
Previous hepatitis B vaccinations			
Completed course, *n* (%)	0 (0)	0 (0)	1.00
Started but did not complete, *n* (%)	0 (0)	3 (1.0)	
Not previously vaccinated, *n* (%)	32 (100)	283 (98.2)	
Cannot recall, *n* (%)	0 (0)	2 (0.7)	
Sexual partners over past 12 months			
0	6 (18.8)	62 (21.5)	0.40
1	20 (62.5)	194 (67.7)	
≥2	6 (18.8)	29 (10.8)	
Uses condoms			
Yes, *n* (%)	6 (18.8)	92 (33.4)	0.11
No, *n* (%)	26 (81.2)	192 (67.6)	
History of STD			
Yes, *n* (%)	11 (34.4)	122 (42.4)	0.38
No, *n* (%)	21 (65.6)	166 (57.6)	
History of blood transfusion			
Yes, *n* (%)	2 (6.2)	43 (15.0)	0.28
No, *n* (%)	30 (93.8)	244 (85.0)	
History of tattooing			
Yes, *n* (%)	6 (60.0)	55 (78.6)	0.24
No, *n* (%)	4 (40.0)	15 (21.4)	

Missing responses are not included in the table. HBsAg=hepatitis B surface antigen; ZMK=Zambian kwacha; ALT=alanine aminotransferase; AST=aspartate aminotransferase

severely elevated aminotransferase levels. Prior studies have found that among HBV-infected individuals, HIV coinfection is actually associated with lower ALT levels but higher risk of progression to cirrhosis.[19,20] This finding may be related to the impairment of immunity in advanced HIV, which – despite higher rates of HBV replication – results in less inflammation and necrosis. Indeed, in HIV-infected patients, HBV coinfection is an independent predictor for cirrhosis,[21] hepatocellular carcinoma,[22] and mortality.[23]

To prevent this excess morbidity and mortality associated with HIV/HBV coinfection, treatment guidelines in upper-income nations recommend screening all HIV-infected adults for viral hepatitis.[24] Recently updated guidelines from the WHO recommend that all patients who require treatment for HBV coinfection initiate ART, regardless of the CD4 count or WHO clinical stage.[25] Such an approach has also been adopted by the Zambian Ministry of Health.[26] HBsAg is now recommended as part of eligibility screening for ART. For HBsAg-positive individuals with CD4 counts higher than 350 cells/μL, ART can be initiated if liver transaminases are elevated or if HBsAg positivity remains persistent for at least 6 months. Although this represents an important step forward in health policy, the limited availability of hepatitis B screening countrywide – particularly in rural areas – represents a significant challenge to its implementation.

With knowledge of HBV-HIV coinfection, ART regimens could be tailored to treat both conditions. Screening information could also be helpful early in the course of ART, to better understand the development of the immune reconstitution inflammatory syndrome. Validated algorithms to triage high-risk patients for HBV screening could help improve the cost-efficiency of screening programs, but our data suggest that there may be few well-performing demographic or medical predictors. For example, 16 out of 29 (55%) of HBV coinfected patients would be missed if mildly elevated liver enzymes alone were used to triage screening. In contrast with HBV screening, the low disease prevalence of HCV-HIV coinfection suggests that universal screening for HCV is not likely to be cost-effective in our setting.

Several antiretroviral drugs for HIV treatment are known to inhibit HBV replication, including lamivudine, emtricitabine, and tenofovir.[27,28] As tenofovir–lamivudine and tenofovir–emtricitabine "backbones" gain a widespread use in Africa – as they have in Zambia[29] – a large proportion of co-infected patients will receive "empiric" treatment for HBV regardless of formal diagnosis. In this scenario, the initial ART regimen could be used as a criterion to triage HBV

also approximated disease prevalence among HIV-infected pregnant women in Zambia (7.1%).[8]

With the initiation of antiretroviral therapy and subsequent immune reconstitution, a concern is a paradoxical exacerbation of inflammatory-related pathology in persons with HBV who may not know their status. In our HIV-infected population, patients with HBV coinfection were more likely to have moderately elevated ALT but not

Table 2: Surveys of hepatitis B virus surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) prevalence in HIV-infected persons conducted in Zambia and neighboring sub-Saharan Africa countries, 1996-2011

Author	Publication year	Country	Population	Sample size	HBsAg prevalence (%)	HCV Ab prevalence (%)
Kapembwa *et al.* (current study)	2011	Zambia	Outpatient	323	9.9	1.2
Kasolo *et al.*[9]	2003	Zambia	Inpatient	214	31.3	–
Oshitani *et al.*[8]	1996	Zambia	Antenatal	340	7.1	–
Wester *et al.*[35]	2006	Botswana	Outpatient	160	10.6	–
Rouet *et al.*[36]	2004	Cote d'Ivoire	Antenatal	501	9.0	1.2
Shimelis *et al.*[37]	2008	Ethiopia	Outpatient	305	3.9	–
Mboto *et al.*[38]	2010	The Gambia	Outpatient	1500	–	0.6
Harania *et al.*[39]	2008	Kenya	Outpatient	378	6.1	1.1
Moore *et al.*[40]	2010	Malawi	Outpatient	300	6.7	5.7
Nyirenda *et al.*[41]	2008	Malawi	Inpatient	226	17.5	4.5
Ahmed *et al.*[42]	1998	Malawi	Antenatal	50	13.0	–
Otegbayo *et al.*[16]	2008	Nigeria	Outpatient	1779	11.9	4.8
Pirillo *et al.*[43]	2007	Rwanda	Antenatal	82	2.4	4.9
Diop-Ndiaye *et al.*[17]	2008	Senegal	Outpatient	363	16.8	1.6
Di Bisceglie *et al.*[44]	2010	South Africa	Outpatient	502	4.8	–
Lukhwareni *et al.*[32]	2009	South Africa	Outpatient	192	22.9	–
Firnhaber *et al.*[15]	2008	South Africa	Outpatient	502	4.8	–
Hoffmann *et al.*[45]	2008	South Africa	Outpatient	537	19.7	–
Nagu *et al.*[18]	2008	Tanzania	Outpatient	260	17.3	18.1
Pirillo *et al.*[43]	2007	Uganda	Antenatal	164	4.9	0.6
Kallestrup *et al.*[46]	2003	Zimbabwe	Outpatient	124	–	0.8

screening, so that testing is performed when tenofovir-based regimens are contraindicated or unavailable. While this approach considers only one benefit of HBV screening, such strategies should be considered in settings where universal hepatitis screening is not feasible.

Control strategies for HBV in Zambia have focused on blood bank screening and childhood vaccination. HBV and HCV screening is now universal in transfusion centers across the country, based on guidance from the Ministry of Health. Zambia has also incorporated HBV vaccination into the routine childhood schedule in 2005, and the WHO–UNICEF estimated a coverage of 80% in 2009.[30] Childhood vaccination is especially important given the presumed mode of HBV transmission as horizontal (from family or other close contacts) during early childhood.[31]

Although rates of HIV-HCV coinfection have not been previously published for Zambia, our estimates for anti-HCV antibody positivity were similar to numerous regional surveys conducted over the past decade [Table 2]. Our findings are consistent with the largely heterosexual epidemic, with very few HIV infections caused via injection drug use, tattooing or razors, or medical misuse of contaminated needles (the most efficient means of HCV transmission). The wide range of prevalence estimates seen across sub-Saharan Africa demonstrates the need for ongoing surveillance activities.

We note several limitations to our study. By only testing for a single marker of HBV infection, we were unable to fully describe the epidemiology of the disease in our setting. We cannot comment on lifetime HBV infection rates as we did not measure core or surface antibodies. The inclusion of other serologic markers could also have allowed us to report early or "occult" infections,[32] which may have implications in HIV/HBV coinfected patents as the immune system reconstitutes. Our surveillance of HBV prevalence resulted in far fewer cases than anticipated and limited our ability to investigate independent predictors of coinfection.

CONCLUSION

Active HBV coinfection was diagnosed among nearly 10% of HIV-infected adults eligible for ART at a tertiary care center in Lusaka, Zambia. In contrast, coinfection with HCV was uncommon at approximately 1%. We did not observe any clinically useful predictors for viral hepatitis, suggesting that routine screening should be considered in settings with appropriate resources. Lower cost screening modalities for viral hepatitis are an urgent need to upgrade HIV care in resource-limited settings.[33,34] Antiretroviral drugs with anti-HBV properties could be used preferentially in coinfected persons.

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