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Association between hepatitis B infection and elevated liver stiffness among HIV-infected adults in Lusaka, Zambia

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Abstract

Background—In sub-Saharan Africa, liver disease epidemiology among HIV-infected individuals is not well described, in part due to limited access to diagnostic tests for liver fibrosis.

Methods—We recruited HIV-infected adults (≥18 years) at antiretroviral therapy initiation at two facilities in Zambia's capital Lusaka. Using vibration controlled transient elastography we assessed liver stiffness, a surrogate for fibrosis/cirrhosis, and analyzed liver stiffness measurements (LSM) according to established thresholds (>7.0 kPa for significant fibrosis and >11.0 kPa for cirrhosis). All participants underwent standardized screening for potential causes of liver disease including chronic hepatitis B (HBV) and C virus co-infection, herbal medicine, and alcohol use. We used multivariable logistic regression to identify factors associated with elevated liver stiffness.

Results—Among 798 HIV-infected patients, 651 had a valid LSM (median age, 34 years; 53% female). HBV co-infection (12%) and alcohol use disorders (41%) were common and hepatitis C virus co-infection (<1%) was rare. According to LSM, 75 (12%) had significant fibrosis and 13 (2%) had cirrhosis. In multivariable analysis, HBV co-infection as well as male sex, increased age, and WHO clinical stage 3 or 4 were independently associated with LSM >7.0 kPa (all P<0.05). HBV co-infection was the only independent risk factor for LSM >11.0 kPa. Among HIV-HBV patients, those with elevated ALT and HBV viral load were more likely to have significant liver fibrosis than patients with normal markers of HBV activity.

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Conclusions—HBV co-infection was the most important risk factor for liver fibrosis and cirrhosis and should be diagnosed early in HIV care to optimize treatment outcomes.

Keywords

HIV/AIDS; Africa; liver fibrosis; hepatitis B virus; transient elastography; alcohol use disorder

Introduction

In high-income settings advanced liver disease is a leading cause of mortality among HIV-infected individuals, primarily due to chronic viral hepatitis co-infection. In the D:A:D study of HIV-infected patients taking antiretroviral drugs in Europe, Australia, and Argentina, 14.5% of deaths were liver disease-related as a result of decompensated cirrhosis, and/or hepatocellular carcinoma.[1] Among those who died from liver disease, 17% had chronic hepatitis B virus (HBV) and 66% had hepatitis C virus (HCV).[1] In the Multicenter AIDS Cohort Study in the United States, men who were dually HIV- and HBV-infected had 8 times increased liver-related mortality compared to those with HIV alone.[2,3]

HIV-infected individuals in sub-Saharan Africa (SSA) may have an increased risk of developing liver fibrosis and cirrhosis from various factors. In SSA, the prevalence of HBV co-infection reaches 10–15% in the general population and three million individuals are estimated to be dually infected with HIV and HBV.[4] In these settings, chronic HBV is most commonly acquired in early childhood and was inconsistently found to be a risk factor for liver fibrosis.[5,6] Fibrosis may also be caused by environmental exposure to aflatoxins and by certain traditional herbal medicines. In rural Uganda, for example, HIV-infected patients who reported herbal medicine use had 2–5 fold increased rates of liver fibrosis.[7] Schistosomiasis is also endemic in SSA and contributes to the burden of periportal fibrosis and portal hypertension.[8]

Due to limited access to diagnostic tests for liver fibrosis/cirrhosis in SSA, the causes of liver disease are poorly characterized among HIV-infected populations. Although the most advanced cases are diagnosed clinically, the diagnosis historically required a liver biopsy, which is unavailable outside of major referral centers due to its invasive nature, requirement for a pathologist to interpret hepatic histology, and potential risk of complications. To reduce the need for biopsy, blood and imaging tests for liver fibrosis have been developed, including transient elastography (TE, Fibroscan®), which has been used in several recently published studies in Africa[5,9,10] and recommended by the World Health Organization in management of HBV[11] and HCV.[12] Using TE, we measured liver stiffness in a relatively large cohort of HIV-infected, antiretroviral therapy (ART)-naïve Zambian adults and investigated possible risk factors for liver fibrosis/cirrhosis.

Methods

Study setting and patients

In two public sector HIV treatment facilities in Zambia's capital Lusaka we recruited HIV-infected adults (18+ years old) who were eligible for ART into a prospective cohort study.

According to local guidelines at the time, patients were ART eligible if they had WHO clinical stage 3 or 4 disease and/or a CD4+ count of <350 cells/mm^3 prior to April 2014 after which eligibility expanded to all patients with a CD4+ count <500 cells/mm^3.[13] Patients who intended to transfer care to a facility outside of Lusaka within 12 months of ART initiation were excluded from participation. This study was implemented within the framework of the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA), a large regional network of HIV treatment programs that pools and analyzes standardized and anonymized datasets.[14] The ethics committees of the University of Zambia (Lusaka, Zambia) and University of North Carolina at Chapel Hill (North Carolina, USA) approved this study (clinicaltrials.gov identifier NCT02060162) and all patients provided informed consent prior to participation.

Laboratory measurements

In addition to WHO staging and CD4+ testing at enrollment, we measured height, weight, ALT, AST, creatinine, and platelet count. Using rapid point-of-care tests in the clinic we screened patients for hepatitis B surface antigen (HBsAg; Determine HBsAg, Alere Inc., Massachusetts, USA) using finger prick sampling and for anti-hepatitis C antibody (Oraquick HCV, Orasure Technologies, Pennsylvania, USA) using an oral swab kit. Patients were defined as HBV co-infected if the HBsAg test was positive. Among HBV co-infected individuals, we measured hepatitis B e antigen (HBeAg) and HBV DNA levels (Roche COBAS AmpliPrep/COBAS TaqMan HBV Test version 2.0; limit of detection, 20 IU/ml). We also determined HBV genotype using an in-house Sanger sequencing assay.[15–17] Nucleotide sequences were analyzed with Sequencher version 5.0 (Gene Codes Corporation, Michigan, USA) and the Geno2Pheno (www.geno2pheno.org) platform was used to predict HBV genotypes.

Assessment of liver stiffness

Liver fibrosis/cirrhosis was assessed in non-pregnant patients using TE according to manufacturer guidelines (Echosens, Paris, France). With patients lying supine with their right arm abducted, at least 10 valid liver stiffness measurements (LSM) were made of the right lobe of the liver. Measurements were made by 1 of 3 operators who received manufacturer-recommended training. We classified TE as very reliable if the interquartile range divided by median (IQR/M) was <0.1, reliable if IQR/M was 0.1–0.3, and poorly reliable if IQR/M was >0.3.[18] We defined significant hepatic fibrosis (corresponding to Metavir stages F2–F4) as median LSM >7 kPa and cirrhosis (Metavir stage F4) as median LSM >11 kPa. These thresholds were suggested in the WHO guidelines for treatment of hepatitis B virus in resource-limited settings.[11] In secondary analyses we considered high LSM thresholds (>9.3 kPa for significant fibrosis and >12.3 kPa for cirrhosis) that were used in other liver fibrosis studies in SSA and based on validation studies in Europe and the U.S.[5,9]

Other study procedures

Using a standardized questionnaire we screened for potential causes of elevated liver stiffness including anti-tuberculosis treatment, current herbal medicine use, regular exposure to freshwater lakes or rivers (a surrogate for schistosomiasis), and alcohol use. We assessed

current and recent alcohol consumption using the World Health Organization's Alcohol Use Disorders Identification Test consumption questions (AUDIT-C),[19] an instrument that has been used in other African settings.[20] Each alcoholic beverage was standardized to a local beer that contained 10 grams of alcohol per 12-ounce bottle. We defined a possible alcohol use disorder as an AUDIT-C score of ≥3 points for women and ≥4 for men.[19]

Statistical analyses

Among patients with a valid TE result, we compared baseline characteristics between HBsAg positive and negative participants using Wilcoxon rank sum tests for continuous variables and Chi square tests for categorical ones. We categorized body mass index as <18.5, 18.5–25, and >25 and CD4+ count as <100, 100–199, 200–350, and >350 cells/mm^3. We investigated the association between HBsAg-positivity and significant fibrosis and cirrhosis using multivariable logistic regression, adjusted for all factors associated with fibrosis or cirrhosis in univariable analyses as well as those identified *a priori* from literature review. Among HIV-HBV co-infected patients, we described the proportion with hepatic fibrosis and cirrhosis according to HBV viral load and ALT level. We used Stata version 12 (Statacorp, College Station, Texas) for data analysis.

Results

From October 2013 to August 2014, we enrolled 798 HIV-infected treatment-naïve adults in the cohort study and 653 had TE at enrollment. The main reasons for a missing TE result were pregnancy as a contraindication (n=25), or enrollment at time when the instrument was unavailable (n=118). TE was invalid in two cases with the remaining 651 (82%) comprising the analysis cohort. Patients excluded from the analyses because of unavailability of TE had similar age, sex, WHO clinical stage, HBsAg status, and CD4+ count compared to those who received the test (all P>0.05).

Within the analysis cohort, the median age of participants was 34 years (interquartile range [IQR] 29–40), 343 (52.7%) were women, and the median CD4+ count was 229 cells/mm^3 (IQR 122–336) at the time of ART initiation. HBsAg-positivity was relatively common (n=98, 12.4%) but anti-hepatitis C antibody positivity was rare (n=1, <1%). No current or recent alcohol consumption (i.e., AUDIT-C score of 0) was reported by 360 (55.1%), moderate consumption (AUDIT-C of 1–2 for women and 1–3 for men) was reported by 25 (3.8%), and 268 (41.2%) reported levels of drinking consistent with a possible alcohol use disorder (58.9% of men versus 25.2% of women, P<0.001). Current use of at least one herbal medicine was reported by 103 (15.8%) participants. A full description of the characteristics of the analysis cohort is displayed in Table 1.

Among HBV co-infected patients, 19 (29.7%) were hepatitis B e antigen positive, the median HBV viral load was 3.7 (2.1–6.4) $\log_{10}$ IU/ml, and 53.6% had HBV viral loads >2,000 IU/ml. HBV genotype was A1 for 29 patents, E for 28 patients, and 1 patient had mixed infection with A1 and E. Compared to their HBsAg-negative counterparts, HBV co-infected patients were more likely to be male, to have alcohol use disorder, had higher median ALT but similar median CD4+ counts. Age and sex distribution were similar in both study groups (Table 1).

Across the 651 assessments of liver stiffness, based on IQR/M, TE was very reliable in 357 (54.8%), reliable in 289 (44.4%), and poorly reliable in 5 (0.8%). Median LSM was 5.1 kPa (IQR 4.4–6.1), 75 (11.5%) had LSM >7 kPa consistent with significant hepatic fibrosis, and 13 (2.0%) had LSM >11 kPa consistent with cirrhosis. The proportion with significant fibrosis according to patient demographics and selected clinical characteristics are displayed in Figure 1. Patients who reported hazardous levels of alcohol consumption had similar median LSM (5.2 kPa) and a similar percentage with LSM >7.0 (11.7%) compared to non-drinkers (median LSM, 5.0 kPa; 11.2%). In multivariable analyses, HBsAg-positivity was associated with the presence of significant liver fibrosis (adjusted odds ratio [AOR] 2.84; 95% confidence interval [CI], 1.48–5.46). Other risk factors for LSM >7 kPa included age 40+, male sex, and WHO clinical HIV stage 3 or 4 (all $P<0.05$). HBsAg-positivity was the only statistically significant predictor of cirrhosis (AOR 7.31; 95% CI, 2.14–24.59; Table 2). At thresholds of LSM >9.3 for significant fibrosis and >12.3 for cirrhosis, point estimates in the models were similar (Supplementary table), but only HBsAg-positivity remained significantly associated with the outcomes.

Among HBV co-infected patients, significant fibrosis was more common in those with elevated ALT (23.6% versus 8.8%, P=0.083), positive HBeAg (42.1% versus 22.2%, P=0.08), or HBV viral loads >20,000 IU/ml (31.2% versus 20.4%, P=0.32). When stratified by ALT levels (normal or elevated) and HBV viral load (≤20, 20–2,000, or >2,000 IU/ml), we observed a significant trend toward higher liver stiffness level with increases in both (P=0.04; Figure 2).

Discussion

Among HIV-infected patients in Lusaka, Zambia, HBsAg-positivity was a strong predictor of liver fibrosis and cirrhosis at the time of ART initiation and this association increased with markers of HBV severity. Increased age, male sex, and advanced clinical stage of HIV infection were also linked with elevated liver stiffness. These data suggest that HBV co-infection should be diagnosed early during HIV care and that interventions to identify and manage liver disease in HIV programs in SSA could be tailored to specific groups.

Our findings are consistent with those of other African studies. At a public facility in Nigeria, 325 HIV-infected adult patients (including 93 with HIV-HBV) underwent a cross-sectional assessment of liver fibrosis using TE.[5] HIV-HBV co-infected patients had 5 times the odds of significant fibrosis compared to those with HIV alone. Similar to our findings, HBV viral load was a strong correlate of elevated stiffness measurement, supporting recommendations that HIV-HBV patients be treated with ART regimens that contain tenofovir, the most potent anti-HBV drug available.[21] More recently, among 106 HIV-HBV patients taking lamivudine-based ART in Ghana, 24 (22.6%) had advanced fibrosis or cirrhosis by TE. Most patients were switched to a tenofovir-containing regimen and during 8 months of follow-up, levels of liver stiffness decreased,[10] suggesting a potential role for TE in longitudinal assessment of liver disease where the device is available.

In addition to HBV, we observed that men were more likely to have elevated liver stiffness. Women may have had relatively lower liver stiffness because of the protective effects of

estrogen in hepatic fibrogenesis.[22] Although alcohol abuse disorders were not linked to LSM in the study, men were more likely to report alcohol use and this could explain their doubling of fibrosis compared to women. Worldwide alcohol is a leading cause of cirrhosis; however, in our cohort an elevated AUDIT-C score was not linked with liver stiffness for several potential reasons. First, in our experience, quantifying an individual's alcohol intake in Zambia can be challenging because the most common form of alcohol, maize/sorghum beer, can have variable alcohol concentration and drinks are shared within a group.[23] Further, in our study, assessment of alcohol use was done at the time of ART initiation and we suspect that many recent drinkers had abstained for a period of weeks to months as they were HIV tested, linked to care, and assessed for ART eligibility. Therefore, the hepatic effects of heavy drinking such as steatohepatitis may have receded prior to our assessment of liver fibrosis. Despite these results, screening for alcohol use disorders remains an important intervention as heavy drinking was highly prevalent.

This study had a number of strengths. First, we demonstrated the feasibility of screening for liver fibrosis and cirrhosis using TE, a relatively novel non-invasive test that has been used in a very limited number of studies in SSA.[5,9,10,24] Despite limited availability in SSA, WHO guidelines for HBV[11] and HCV[12] treatment in LMIC recommend TE for fibrosis staging when available. Our sample was recruited among treatment naïve patients at two large clinics in Lusaka and the data are likely representative of other urban populations in the region. Another strength of the study was comprehensive screening of hepatitis C virus, traditional/herbal medicine use, and alcohol abuse disorders. Finally, detailed analyses of the virologic and serologic characteristics of HBsAg-positive individuals added to the limited available literature on HIV-HBV in this region.

Our study also had weaknesses. Because of pregnancy and unavailability of TE, nearly 20% of our cohort did not have a baseline assessment of LSM. However, we do not expect this to have significantly biased our analyses as there were no major differences in the baseline characteristics of these patients compared to those analyzed. Although it is widely recommended for liver fibrosis assessment, TE is imperfect and has not been validated in HIV-infected cohorts in SSA. Rather than focus our analysis on the prevalence of fibrosis/cirrhosis, we investigated risk factors for high LSM, considering various thresholds. We believe this approach provided evidence regarding the usefulness of TE in SSA settings. For settings where TE is not available, more investigation is needed into blood indices that depend on low cost tests, such as AST-to-platelet ratio,[6,25] FIB-4,[26] and GGT-to-platelet ratio.[27] Finally, we did not comprehensively assess patients for other potential causes of liver fibrosis such as hepatosplenic schistosomiasis or aflatoxin exposure.

In summary, among treatment naïve HIV-infected adults in Lusaka, Zambia, HBV co-infection was the most important risk factor for elevated liver stiffness. Liver-related mortality among HIV-infected individuals is often preceded by fibrosis and cirrhosis. Therefore, among HIV-HBV patients, liver fibrosis assessment using TE or other non-invasive tests may be considered a viable technique to optimize care of this at risk group.

Acknowledgments

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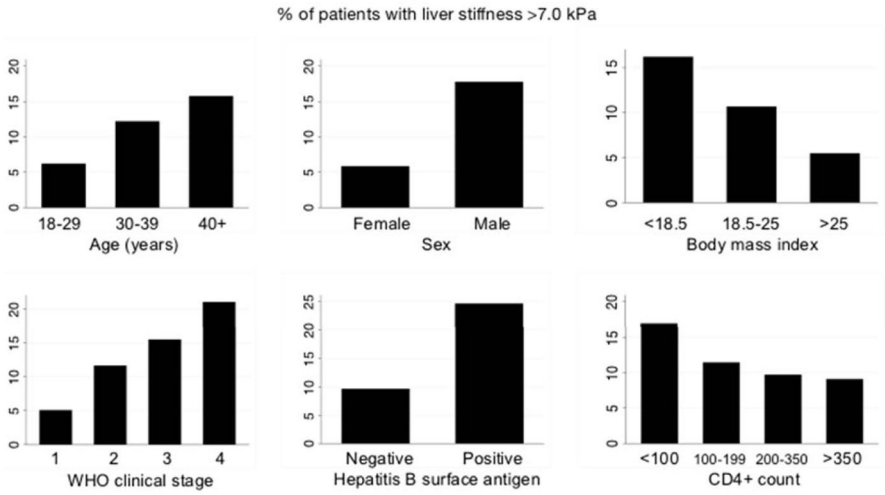

FIGURE 1.

Proportion of individuals with elevated liver stiffness, stratified by baseline characteristics

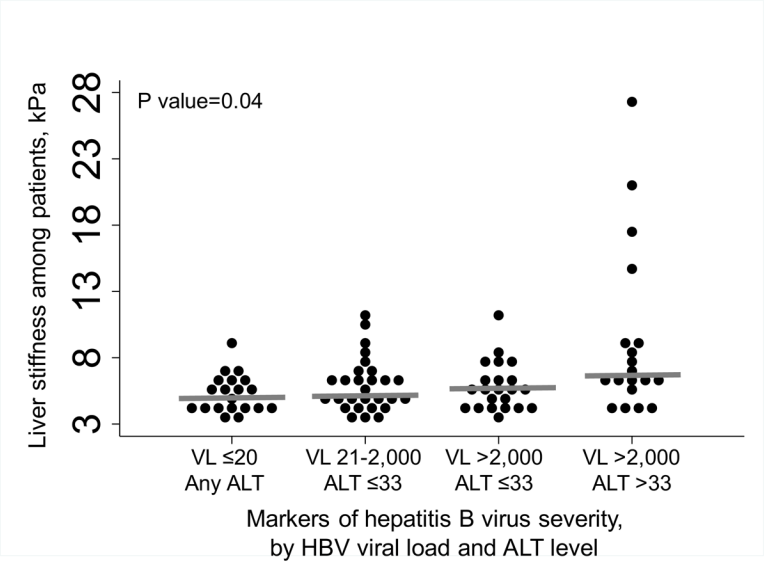

FIGURE 2.

Liver stiffness score according to markers of hepatitis B virus (HBV) severity among 81 HIV-HBV co-infected patients

Table 1

Sociodemographic and clinical characteristics of 651 HIV-infected Zambian adults with a valid liver stiffness measurement at the time of antiretroviral therapy initiation

	HBsAg-negative (n=570)	HBsAg-positive (n=81)	P value
Age, years	**34 (30–40)**	**34 (28–39)**	**0.48**
Female sex	307 (53.9)	35 (43.2)	0.07
Education level			
None to grade 6	137 (24.1)	17 (21.2)	0.78
Grades 7–12	422 (74.2)	61 (76.2)	
College/University	10 (1.8)	2 (2.5)	
Body mass index	20 (18–22)	20 (19–23)	0.19
WHO clinical stage			
1 or 2	291 (51.5)	45 (56.2)	0.43
3 or 4	274 (48.5)	35 (43.8)	
Tuberculosis	95 (16.7)	12 (14.8)	0.67
CD4+ count, cells/mm^3	226 (121–331)	233 (128–378)	0.48
Anti-HCV positive	0 (0)	1 (1.2)	—
ALT, U/L	19 (14–27)	23 (13–40)	0.02
AST, U/L	31 (25–41)	35 (26–60)	0.06
HBeAg positive	—	19 (30.0)	—
HBV viral load, log IU/ml	—	3.7 (2.1–6.4)	—
Herbal medicine use	88 (15.4)	15 (18.5)	0.48
Alcohol consumption[b]			
None	324 (56.8)	34 (42.0)	0.04
Moderate	20 (3.5)	5 (6.2)	
Alcohol use disorder	226 (39.7)	42 (51.8)	
Occupational fishing	132 (23.2)	27 (33.3)	0.05

All values are median (interquartile range) or number (%).

[b]Alcohol consumption was defined by consumption questions from Alcohol Use Disorders Identification Test (AUDIT-C). No drinking was defined as AUDIT-C score of 0, moderate drinking was AUDIT-C score of 1–2 for women and 1–3 for men, and alcohol use disorder was AUDIT-C score of 3–12 for women and 4–12 for men.

Abbreviations: HBsAg, hepatitis B surface antigen; WHO, World Health Organization; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus

Table 2

Risk factors for significant fibrosis (>7.0 kPa) and cirrhosis (>11.0 kPa) based on transient elastography among HIV-infected Zambian adults

	Significant fibrosis		Cirrhosis	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Age, years				
18–29	Reference	Reference	Reference	Reference
30–39	2.22 (1.14–4.35)	1.94 (0.91–4.13)	1.46 (0.37–5.72)	2.01 (0.38–10.57)
40+	2.60 (1.27–5.32)	2.80 (1.26–6.24)	1.09 (0.22–5.49)	1.47 (0.21–10.08)
Sex				
Female	Reference	Reference	Reference	Reference
Male	3.43 (2.03–5.79)	2.94 (1.61–5.39)	3.77 (1.03–13.83)	2.81 (0.66–11.96)
Body mass index				
18.5 and above	Reference	Reference	Reference	Reference
<18.5	1.31 (0.77–2.24)	1.26 (0.69–2.31)	2.24 (0.72–6.94)	2.29 (0.63–8.31)
WHO clinical stage				
1 or 2	Reference	Reference	Reference	Reference
3 or 4	1.90 (1.04–3.48)	1.76 (0.97–3.22)	6.31 (1.39–28.68)	4.09 (0.76–21.86)
Tuberculosis	2.04 (1.18–3.51)	1.27 (0.66–2.04)	2.31 (0.70–7.64)	1.74 (0.48–6.32)
HBsAg-positive	2.34 (1.32–4.13)	2.84 (1.48–5.46)	5.82 (1.91–17.70)	7.31 (2.14–24.59)
CD4+ count, cells/mm^3				
200+	Reference	Reference	Reference	Reference
<200	1.54 (0.95–2.49)	1.19 (0.70–2.04)	0.77 (0.25–2.38)	0.40 (0.11–1.44)
Alcohol use disorder	1.04 (0.65–1.68)	0.67 (0.38–1.18)	0.63 (0.19–2.06)	0.36 (0.09–1.39)
Occupational fishing	2.03 (1.23–3.59)	1.57 (0.90–2.75)	2.72 (0.90–8.21)	2.30 (0.70–7.62)
Herbal medicine use	1.26 (0.67–2.38)	1.34 (0.69–2.62)	0.44 (0.05–3.40)	0.37 (0.04–3.17)

Abbreviations: kPa, kilopascals; OR, odds ratio; WHO, World Health Organization