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High Prevalence of Liver Fibrosis Associated with HIV Infection: A Cross-Sectional Study in Rural Rakai, Uganda

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Abstract

Background—Liver disease is a leading cause of mortality among HIV-infected persons in the US and Europe; however, data regarding effects of HIV and anti-retroviral therapy (ART) on liver disease in Africa remains sparse.

Methods—500 HIV-infected participants in an HIV care program in Rakai, Uganda were frequency-matched by age, gender and site to 500 HIV-uninfected participants in a population cohort. All participants underwent transient elastography (FibroScan®) to quantify liver stiffness measurements (LSM) and identify participants with significant liver fibrosis, defined as LSM ≥9.3 kPa (≈ Metavir F ≥2). 962 (96 %) of participants had valid LSM data. Risk factors for liver fibrosis were identified by estimating adjusted prevalence risk ratios (adjPRR) and 95% confidence intervals (CI) using modified Poisson multivariate regression.

Findings—The prevalence of significant fibrosis was 17% among HIV-infected and 11% in HIV-uninfected participants (p =0.008). In multivariate analysis, HIV infection was associated with a 50% increase in liver fibrosis (adjPRR 1.5, 95%CI 1.1–2.1; p=0.010). Fibrosis was also associated with male gender (adjPRR 1.4, 95% CI 1.0–1.9; p=0.045), herbal medicine use (adjPRR 2.0, 95%CI 1.2–3.3; p=0.005), heavy alcohol consumption (adjPRR 2.3, 95% CI 1.3–3.9; 0.005), occupational fishing (adjPRR 2.5, 1.2–5.3; p=0.019), and chronic HBV infection (adjPRR 1.7, 95% CI 1.0–3.1; p=0.058). Among HIV-infected participants, ART appeared to reduce fibrosis risk (adjPRR 0.6, 95% CI 0.4–1.0; p=0.030).

Interpretation—The burden of liver fibrosis among rural Ugandans is high, particularly among persons with HIV infection. These data suggest that liver disease may represent a significant cause

Contributors

LS, SRJ, TCQ, PO and GK oversaw the design and conduct of the study. LS, GDK and AN participated in data-analysis and interpretation of data. AN supervised data-management; SJR and IB supervised laboratory studies. PO, VK, SJR and LS supervised field-work. OL, PO, DLT, CT, RG, MW, and VK provided additional technical assistance and contributed to the interpretation of data. All authors took part in the preparation of the paper and approved the final version.

Conflicts of Interest

We declare that there were no conflicts of interest.

of HIV-related morbidity and mortality in Africa; clarifying the etiology of liver disease in this population is a research priority.

Keywords

HIV; fibrosis; hepatitis co-infection; liver; Uganda

Introduction

With the introduction of antiretroviral therapy (ART), the overall mortality associated with HIV has steeply declined in Europe and the United States. Death from opportunistic infections has decreased significantly, but with improved survival conferred by ART, liver disease has emerged as a leading cause of morbidity and mortality in several western HIV cohorts (1, 2). Most of the increased liver-related morbidity and mortality has been reported among HIV-infected persons co-infected with hepatitis B and C viruses (HBV and HCV) (1, 3).

In the United States and Europe, other co-factors (e.g., alcohol, hepatitis delta infection, obesity, some first generation antivirals) have also been linked to the development of liver disease among HIV-infected persons (1, 4, 5). However, data regarding the effects of HIV, ART and other cofactors on liver disease in Africa remain sparse, and most prior reports are limited to studies of liver enzyme elevation (6, 7). Liver disease staging based on liver biopsy or more recently developed non-invasive approaches have not been reported from African HIV-infected populations.

While liver biopsy is considered the gold standard to diagnose and stage liver disease, invasive biopsy studies are difficult to conduct in resource-limited settings. Therefore, in the current study, we applied novel, non-invasive transient elastography methods to ascertain the prevalence and to identify correlates of liver fibrosis among 500 HIV-infected and 500 HIV-uninfected rural Ugandans.

Methods

Study design and participants

This cross-sectional study was conducted in the Rakai District of rural southwestern Uganda. 500 unselected HIV-infected patients of the Rakai Health Sciences Program (RHSP) HIV care program were recruited from five clinics. These HIV-infected participants were frequency-matched by age, gender and community to 500 HIV-uninfected participants identified from the population-based Rakai Community Cohort Study (RCCS). Since 1994, RCCS has conducted censes and surveys in over 12,000 adults aged 15–49 years at 12–18 month intervals (8). All participants provided informed consent. Data collection included a structured interview focused on exposures potentially associated with liver disease, collection of venous blood and a transient elastography (FibroScan®, Echosense, Paris, France) examination to quantify liver fibrosis.

Laboratory assays

HIV-1 serology was determined by two HIV-1 enzyme immuno-assays (EIAs) namely Vironostika HIV-1 (OrganonTeknika, Charlotte, North Carolina, USA) and Cambridge Biotech (Worcester, Massachusetts, USA). EIA discordant and all concordant-positive results were confirmed by western blot (HIV-1 Western Blot; Bio-Merieux-Vitek, St. Louis, Missouri, USA). For HIV-infected participants, the most recent CD4 count (within 12 months) and CD4 count nadir were abstracted from the RHSP HIV Care Program database.

CD4 counts were measured by FACSCalibur flow cytometer (software version 1.4, Becton Dickinson, San Jose, California, USA). HBV surface antigen (HBsAg) and antibodies to HBV core (anti-HBc) status was determined using ELISA (ETI-EKB s Plus and ET-AB-COREK Plus, respectively; Diasorin, Vercelli, Italy). Antibodies to schistosomiasis were tested using a soluble egg antigen ELISA (Schisto-96; IVD Research Inc, Carlsbad, California, USA). Liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were tested using standard methods (COBAS CII; Roche, Basel, Switzerland); hepatotoxicity was defined by ALT elevations and classified according to ACTG criteria(6).

Transient elastography

Following formal training and certification from the manufacturer, two RHSP study nurses conducted all transient elastography scans as recommended by the manufacturer. A conservative liver stiffness measurement (LSM) cutoff of >9.3 kPa from a prior validation study in a community cohort of Americans of African descent was used to define significant fibrosis (equivalent to Metavir F ≥2) (9). According to manufacturer recommendations, scans with high variability defined as an interquartile range (IQR) greater than 30% of the median LSM value from an individual examination (IQR/LSM<30%) were not considered valid and were excluded from the analysis. Participants with invalid scans on an initial attempt were repositioned and rescanned up to 4 times to achieve a valid scan.

Statistical analysis

Demographic, behavioral and clinical characteristics were compared by HIV status. Differences in continuous variables were assessed using t-tests and Wilcoxon-Mann-Whitney test. Categorical variables were compared using Pearson's chi squared test. Because odds ratios can overestimate the magnitude of association between covariates if the outcome of interest is common, univariate and adjusted prevalence risk ratios (PRR) with 95% confidence intervals (95% CI) were estimated using modified Poisson regression (10). Covariates included in multivariate models were based upon univariate associations ($p<0.10$) and biological plausibility. Age was included in all models and nadir CD4 cell count and ART status were included in models restricted to HIV-infected participants. Stata version 11.0 (Stata Corp, College Station, TX) was used for statistical analysis.

The study was approved by IRBs of the National Institute of Allergy and Infectious Diseases, Johns Hopkins Medical Institutions, Western IRB (Olympia WA), the Scientific and Ethics Committee of the Uganda Virus Research Institute and the Uganda National Council for Science and Technology. This study is registered on clinicaltrials.gov (#NCT00782158).

Role of the Funding Source

The funding source had no role in study design, data interpretation and analysis or in preparation of this manuscript.

Results

500 HIV-infected and 500 HIV-uninfected participants were enrolled; 468 (94%) of HIV-infected and 494 (99%) of HIV-uninfected participants had valid elastography scans and were included in the analysis. Two-thirds (67%) of participants were females and this was identical by HIV status (Table 1). The median age was similar by HIV status (37 and 38 years); the difference of less than one year in median age was due to frequency matching by age-group. HIV-infected participants had lower BMI compared to those without HIV infection. Regular alcohol use was reported more commonly by HIV-infected participants.

The prevalence of chronic HBV infection was similar by HIV status (5% vs. 3%) with neither group displaying substantial liver enzyme elevations. At study enrollment, HIV-infected participants had a median CD4 count of 449 cells per μL (IQR, 320–642) and 60% were receiving ART with a median duration of 19 months (IQR, 9–38). Demographics of the HIV-infected group were similar to that of the over-all RHSP HIV Care Program which is currently 65% female with 64% on HAART and has a median CD4 count of 480 cells per μL.

Overall, 14% of participants had liver stiffness measures indicative of significant fibrosis. The prevalence of fibrosis was higher among HIV-infected (17%) than HIV-uninfected participants (11%; p=0.008). In multivariate analysis, HIV infection was associated with a 50% increase in liver fibrosis (adjPRR 1.5, 95%CI 1.1–2.1; p=0.01). Liver fibrosis was also significantly associated with male gender (adjPRR 1.4, 95% CI 1.0–1.9; p= 0.045), herbal medicine use (adjPRR 2.0, 95%CI 1.2–3.3; p=0.005), heavy liquor drinking defined as ≥ 1.25L/week (adjPRR 2.3, 95% CI 1.3–3.9; p=0.005), occupational fishing (adjPRR 2.5, 1.2–5.3;p= 0.019), and chronic HBV infection (adjPRR 1.7, 95% CI 1.0–3.1;p= 0.058) (Table 2).

In multivariate analysis, among HIV-infected participants (Table 3), occupational fishing (adjPRR 2.9, 95% CI 1.4–6.2; p=0.005) and chronic HBV infection (adjPRR 2.0, 95% CI 1.1–3.9; p=0.033) remained significantly associated with liver fibrosis. There was also a trend for increased liver fibrosis associated with herbal medicine use (adjPRR 2.0, 95% CI 0.9–4.4; p= 0.078) and heavy liquor use (adjPRR 2.2, 95% CI 1.0–4.8; p=0.059). ART was protective against liver fibrosis (adjPRR 0.6, 95% CI 0.4–1.0; p= 0.030), but the association of fibrosis with CD4 nadir <100 cells per μL was not statistically significant (adjPRR 1.5, 95% CI 0.9–2.6; p=0.126).

Discussion

Our data reveal a high burden of liver fibrosis in rural Southwestern Uganda, especially among HIV-infected persons. HIV infection was associated with 50% increase in prevalence of fibrosis after controlling for the expected association of liver disease with male gender, chronic HBV infection, and heavy alcohol consumption. These data suggest that liver disease may be a significant cause of morbidity and mortality among HIV-infected persons in sub-Saharan Africa, as has been recently observed in many more developed regions of the world (1, 2).

To our knowledge, systematic assessment of liver fibrosis among HIV-infected persons has not been reported from sub-Saharan Africa. Prior data on liver disease in HIV-infected populations from Uganda or Africa have largely been restricted to studies using liver enzyme elevation as a marker of liver disease (6, 7), and have suggested relatively low levels of hepatotoxicity. However, liver enzyme elevations are poor markers of liver fibrosis or cirrhosis, especially in HIV-infected populations (11, 12). And of note, in Uganda, although previous studies of liver fibrosis in the community have not been done, liver cancer rates appear to be increasing in recent years, although the etiology for this increase remains unclear (13).

Liver biopsy has been the gold standard for the assessment of liver fibrosis, but for practical and technical reasons, biopsy is used minimally in most of sub-Saharan Africa. Transient elastography has been validated as an effective, non-invasive tool for staging liver fibrosis in persons with HBV or HCV infection, non-alcholic steatohepatitis, and alcohol-related liver disease (9, 14), with similar performance characteristics in persons with and without HIV infection (15). Elastography is quick, painless and highly acceptable to patients and

providers, making it a reasonable tool for the evaluation of liver disease in resource-limited settings.

The prevalence of significant liver fibrosis observed in this HIV-infected population approaches levels reported from European and US HIV cohorts with long-standing HBV or HCV co-infection (9, 16). HIV infection is known to accelerate HBV and HCV-related liver fibrosis and liver-related mortality (1, 3). Liver disease now represents one of the leading causes of mortality in European and US HIV-infected populations, largely associated with viral hepatitis co-infection. In contrast, viral hepatitis does not appear to account for a large portion of liver fibrosis in this Ugandan cohort. Chronic HBV infection was associated with a 2-fold higher prevalence of fibrosis, but the prevalence of HBsAg postivity was only 5% among HIV-infected participants. Although participants were not specifically tested for HCV infection, a previous study found no HCV viremia among 365 Rakai repository samples (17).

The effect of HIV infection on development of liver disease in those co-infected with viral hepatitis is complex. The mechanism has largely been postulated as immunosuppression and possibly a direct or indirect (microbial translocation) effect of HIV in those co-infected with HCV leading to an accelerated natural course of viral hepatitis infection and more rapidly progressive liver fibrosis and cirrhosis (3, 18–21). Although in our study, viral hepatitis does not appear to play a large role, it is possible that HIV similarly accelerates the development of fibrosis in those with other tropical co-infections or hepatotoxic exposures. Such an association with alcohol and HIV has been previously suggested (3).

In addition to an independent effect of HIV on liver fibrosis, this study showed an estimated 40% protective effect afforded by ART. The role of antiviral therapy in the progression of liver disease is complicated. Liver disease emerged as primary health issue among HIV-infected persons only after the advent of effective ART and subsequent prolonged survival. Although, there have also been some studies demonstrating protective effects of ART on development of liver disease similar to our findings (22, 23), survival bias may confound the association between ART and lower risk of fibrosis. HIV-infected persons without liver disease may live longer and therefore may have been more likely to survive to 2004 when ART became available in this population. Importantly, due to cost constraints, several antiretrovirals (e.g., stavudine, didanosine, zidovudine, nevirapine) previously associated with liver disease in Western cohorts are commonly used in resource-limited settings. Long-term prospective studies will be required to fully address these complex issues and to determine if earlier ART initiation can significantly reduce the progression of liver disease.

Alcohol is a well known cause of liver disease and Ugandans have among the highest reported consumption of alcohol; the WHO estimates that approximately 55% of adult Ugandan men and 33% of Ugandan women regularly consume alcohol (24). In this study, 22% of HIV-infected and 16% of HIV-uninfected persons admitted to drinking alcohol. Regular alcohol consumption was crudely associated with liver disease but was highly correlated with male gender. Heavy liquor consumption was reported infrequently but was associated with a >2-fold higher prevalence of liver fibrosis. Clearly, some misclassification of alcohol exposure could occur due to a social desirability or reporting bias, especially among HIV-infected persons on ART who are counseled to avoid alcohol. It should be noted however that those on ART had a 40% lower prevalence of liver disease.

Herbal medicine use has been reported to be more common than alcohol consumption in Uganda (25). However, we found herbal medicine use to be rarely reported by our study participants, possibly due to counseling directed against using herbs while on ART. Use of herbs was significantly associated with liver disease. While the association of fibrosis with

herb use could represent reverse causality (e.g., persons with symptomatic liver disease might be more likely to use herbal medicines), no participants in the study had been previously diagnosed with liver disease within the formal medicine system or by traditional healers. Systematic investigation of the herbal medicine type, dose and duration will be required to assess specific links of herbs to liver disease.

We found some evidence that schistosomiasis may contribute to liver disease in our study population. The Rakai District borders Lake Victoria and schistosomiasis is endemic in communities near the lake. An occupational history of fishing was a strong and independent risk factor for liver disease. Schistosomiasis antibody was not significantly associated with liver disease, however this assay is a poor marker of active infection and of the liver disease associated with schistosomiaisis (26).

In exploratory models evaluating the attributable fraction of liver disease in this population, the associations of liver disease with HIV, hepatitis B infection, and alcohol while strong and consistent, cannot fully account for the prevalence of liver fibrosis (data not shown). Even when also including herbs, alcohol and fishing as potential etiological agents (recognizing that evidence for causality is tenuous at best), we found that three-quarters of liver disease remained unexplained both in the overall and in the HIV-infected study population.

There is a need for etiologic studies of liver disease in African settings, including other tropical infections (e.g., parasitic eosinophil-mediated liver disease) and environmental exposures such as aflatoxin(27). In addition, syndromes of liver disease reported from African settings (e.g., Bantu siderosis, intrahepatic idiopathic portal hypertension) could also contribute to liver disease in Africa. However, Bantu siderosis is unlikely to occur in Uganda because local alcohol is usually brewed in clay as opposed to iron pots and intrahepatic idiopathic portal hypertension has not been closely examined since first documented in Kenya in the 1980s (28, 29). Further, the role of HIV in the pathogenesis of liver disease in the setting of these hepatotoxic exposures and tropical liver disease syndromes is unknown.

There are limitations to this study. Transient elastography was used to identify liver fibrosis, because the “gold standard” of liver biopsy was impractical on a large scale in this setting. Transient elastography has not been validated previously in Uganda, however a previous study in Burkina Faso, showed that transient elastography was a reliable tool for the detection of liver disease among HBV-infected persons (30). In addition, in this study we used a conservative cutoff score validated in a previous study of persons predominately of African descent to prevent over-diagnosis of liver fibrosis. Another limitation of the study is that it is cross-sectional and thus temporality of associations cannot be established. Finally, as described above, self-reported data especially on alcohol consumption may be susceptible to reporting bias and should be interpreted with caution.

In conclusion, we found a heavy burden of liver disease among rural HIV-infected Ugandans that approaches the extent of disease observed in many western HIV cohorts with substantially higher prevalence of viral hepatitis co-infection. Potential etiologic factors for liver disease in this population and in sub-Saharan Africa need to be clearly elucidated. Many of these potential causative factors could be eliminated or reduced with limited resources and at relatively low-cost (i.e., praziquantel for schistosomiasis). In the context of generalized HIV epidemics and scaling up of ART programs throughout sub-Saharan Africa, liver disease represents an emerging but potentially surmountable public health challenge to HIV care. Recognition of the underlying causative factors of liver disease and

understanding of potential interactions with HIV could allow appropriate interventions to be developed.

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Table 1

Characteristics of study participants

	HIV-Infected (n=500)	HIV-Uninfected (n=500)	p value
Characteristic*	n (% or IQR)	n (% or IQR)	
Median Age, years	38 (IQR 31–44)	37 (IQR 32–44)	0.0250
Female	334 (67)	336 (67)	0.893
BMI >25	74 (15)	122 (24)	<0.001
On TB treatment	10 (2)	1 (0.2)	0.006
Current herb use	10 (2)	36 (7)	<0.001
Current alcohol use	112 (22)	79 (16)	0.008
Heavy liquor use (≥1.25 L/week)	12 (2)	12 (2)	0.651
Lifetime occupational fishing	5 (1)	1 (0.2)	0.101
HBsAg positive	23 (5)	14(3)	0.133
Anti-HBc positive	223 (45)	155 (31)	<0.001
Schistosoma antibody positive	71 (14)	46 (9)	0.014
Median ALT	22 (IQR 16–31)	19 (IQR 15–25)	<0.001
Median AST	27 (IQR 22–35)	23 (IQR 20–27)	<0.001
ACTG ALT hepatoxicity criteria(%)			
No Elevation	446 (89)	472 (94)	0.003
Grade1 (1–2.5 X ULN)	44 (9)	26 (5)	0.026
Grade 2 (2.5- ≥5 X ULN)	10 (2)	2 (0.4)	0.020
CD4 count (cells per μL)	449 (IQR 320–642)	-	-
Nadir CD4 count (cells per μL)	214 (130–350)	-	-
Receiving ART	302 (60)	-	-
ART duration (months)	19 (9–38)	-	-

BMI=body mass index, TB=tuberculosis, HBsAg= hepatitis B surface antigen, Anti-HBc=antibody to hepatitis B core, ALT= alanine transaminase, AST= aspartate transaminase, ACTG= AIDS Clinical Trial Group, ART=antiretroviral therapy, ULN= upper limit of normal (Female 39.9 U/L, Male 43.3 U/L).

* Data are n (%) or median (IQR).

Table 2

Correlates of significant liver fibrosis among all study participants

	Univariate Prevalence Ratio	p value	Multivariate Prevalence Ratio	p value
Age, years	1.0 (1.0-1.0)	0.135	1.0 (1.0-1.0)	0.401
Male gender	1.6 (1.2–2.2)	0.004	1.4 (1.0–1.9)	0.045
BMI >25	0.7 (0.5–1.1)	0.131	-	-
On TB treatment	0.7 (0.1–4.6)	0.708	-	-
Current herb use	1.9 (1.2–3.3)	0.010	2.0 (1.2–3.3)	0.005
Heavy liquor use (≥1.25 L/week)	3.3 (2.0–5.5)	0.000	2.3 (1.3–3.9)	0.005
Lifetime cccupational fishing	3.6 (1.6–8.1)	0.002	2.5 (1.2–5.3)	0.019
HBsAg positive	2.0 (1.1–3.4)	0.017	1.7 (1.0–3.1)	0.058
Anti-HBc positive	1.2 (0.9–1.7)	0.192	-	-
Schistosoma antibody positive	1.4 (0.9–2.1)	0.141	-	-
HIV infection	1.5 (1.1–2.1)	0.009	1.5 (1.1–2.1)	0.010

BMI=body mass index, TB=tuberculosis, HBsAg= hepatitis B surface antigen, Anti-HBc=antibody to hepatitis B core, ART=antiretroviral therapy.

Table 3

Correlates of significant liver fibrosis among HIV-infected participants

	Univariate Prevalence Ratio	p value	Multivariate Prevalence Ratio	P value
Age, years	1.0 (1.0-1.0)	0.535	1.0 (1.0-1.0)	0.727
Male gender	1.5 (1.0–2.3)	0.038	1.3 (0.9–2.0)	0.208
BMI >25	0.8 (0.4–1.4)	0.406	-	-
On TB treatment	0.6 (0.1–4.1)	0.635	-	-
Current herb use	2.6 (1.2–5.7)	0.012	2.0 (0.9–4.4)	0.078
Heavy liquor use (≥1.25 L/week)	2.4 (1.1–5.2)	0.031	2.2 (1.0–4.8)	0.059
Lifetime occupational fishing	3.6 (1.7–7.5)	0.001	2.9 (1.4–6.2)	0.005
HBsAg positive	2.1 (1.2–3.9)	0.014	2.0 (1.1–3.9)	0.033
Anti-HBc positive	0.9 (0.7–1.5)	0.917	-	-
Schistosoma antibody positive	1.1 (0.7–2.0)	0.621	-	-
Nadir CD4 count <100 cells per μL	1.3 (0.8–2.0)	0.282	1.5 (0.9–2.6)	0.126
Receiving ART	0.8 (0.5–1.1)	0.168	0.6 (0.4–1.0)	0.030

BMI=body mass index, TB=tuberculosis, HBsAg= hepatitis B surface antigen, Anti-HBc=antibody to hepatitis B core, ART=antiretroviral therapy.