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HIV/HBV co-infection is a significant risk factor for liver fibrosis in Tanzanian HIV-infected adults

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Abstract

Background—In sub-Saharan Africa, the burden of liver disease associated with chronic hepatitis B (HBV) and HIV is unknown. We characterized liver disease using aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 in patients with HIV, HBV, and HIV/HBV co-infection in Tanzania.

Methods—Using a cross sectional design, we compared the prevalence of liver fibrosis in treatment-naive HIV mono-infected, HBV mono-infected, and HIV/HBV co-infected adults enrolled at Management and Development for Health (MDH)-supported HIV treatment clinics in Dar es Salaam, Tanzania. Risk factors associated with significant fibrosis (APRI>0.5 and FIB-4 >1.45) were examined.

Results—267 HIV-infected, 165 HBV-infected and 63 HIV/HBV co-infected patients were analyzed [44% male, median age 37 (IQR 14), BMI 23 (7)]. APRI and FIB-4 were strongly correlated (r = 0.78, p = < .001, R2 0.61). Overall median APRI scores were low [HIV/HBV [0.36 (IQR 0.4)], HIV [0.23 (0.17)], HBV [0.29 (0.15)] (p <0.01)]. In multivariate analyses, HIV/HBV co-infection was associated with APRI >0.5 [HIV/HBV vs. HIV: OR 3.78 (95% CI 1.91, 7.50)], [HIV/HBV vs. HBV: OR 2.61 (1.26, 5.44)]. HIV RNA per 1 log10 copies/ml increase [OR 1.53

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(95% CI 1.04, 2.26)] and HBV DNA per 1 log10 copies/ml increase [OR 1.36 (1.15, 1.62)] were independently associated with APRI >0.5 in HIV-infected and HBV-infected patients, respectively.

Conclusions—HIV/HBV co-infection is an important risk factor for significant fibrosis. Higher levels of circulating HIV and HBV virus may play a direct role in liver fibrogenesis. Prompt diagnosis and aggressive monitoring of liver disease in HIV/HBV co-infection is warranted.

Introduction

Chronic hepatitis B virus (HBV) infection is a major global health problem infecting over 240 million people worldwide and causing > 600,000 annual deaths [1]. In Tanzania 6–7% of the population is co-infected with HIV and HBV [2]. In patients with chronic HBV, HIV significantly accelerates liver disease and leads to higher rates of liver complications [3]. Few studies have examined rates of liver fibrosis in patients infected with chronic HBV alone and compared that to HIV/HBV co-infected persons to determine the impact of HIV co-infection on liver outcomes. Evaluating liver fibrosis in patients with chronic HBV with and without HIV is crucial for assessing long-term prognosis and, in HBV mono-infected patients, determining the need for antiviral therapy. It is particularly important in sub-Saharan Africa (SSA) where HBV is endemic and additional risks of liver injury exist [4]. In the US, liver biopsy, transient elastography (TE; FibroScan®) and serologic testing such as FibroSure® are commonly used determine the degree of fibrosis in patients with chronic HBV, however these tests are rarely available in SSA. Aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis 4 (FIB-4), are two inexpensive, non-invasive and non-proprietary serum markers of fibrosis that are recommended by WHO for assessing liver fibrosis in low- and middle-income countries (LMICs) [1] when more expensive measures are not available.

We used APRI and FIB-4 to compare the prevalence of liver fibrosis in treatment- naive HIV, HBV and HIV/HBV co-infected individuals in Dares Salaam, Tanzania. The goal of our study was to improve the current gap in understanding of liver disease associated with HBV and HIV in a setting where a high burden of both infections exists.

Methods

Study design, site and population

This cross-sectional study was conducted among adult (age ≥ 18 years) patients enrolled in eight HIV Care and Treatment Clinics (CTCs) and a single HBV clinic in Dares Salaam, Tanzania (HIV prevalence ≈4.7% in 2015 [5]) which are supported by Management and Development for Health (MDH) under the President's Emergency Plan For AIDS Relief (PEPFAR). Antiviral therapy naïve, HIV-infected, HBV-infected and HIV/HBV co-infected adults evaluated between April 2014- November 2015 were considered eligible for enrollment. Patients with active tuberculosis (TB) or who were pregnant, anti-HCV seropositive, or had a known history of hepatocellular carcinoma (HCC) or clinical evidence of advanced liver disease (jaundice, hepatic encephalopathy, ascites, abnormal bleeding) were excluded. Chronic hepatitis B was defined as HBsAg sero-positive on at least one occasion within the past 6 months. Patients were recruited for participation and enrolled in

MDH-supported CTCs following written informed consent, which was subject to ethical reviews by the National Institution of Medical Research, Dares Salaam, Tanzania, and Northwestern University.

Study procedures

HIV-infected patients receive free access to antiretroviral treatment (ART), monthly clinical visits, and semi-annual virological monitoring according to Tanzanian National HIV Guidelines [5]. HBV mono-infected patients are evaluated monthly and receive free access to lamivudine, which is initiated in all patients. Laboratory tests performed for the study included: CD4+ T cell count, HIV RNA quantification (Cobas® Amplicor HIV-1 monitor test v2.0; Roche Diagnostics Corp., Indianapolis, IN; lower limit of detection (LLD) < 20 copies/mL); platelets, AST, ALT, creatinine, HBeAg/anti-HBe (EIA assay Cobas e411); HBV DNA (COBAS® Ampliprep Taqman 96, v2.0, Roche Diagnostics GmbH, Mannheim, Germany; LLD <20 IU/ml). All laboratory tests were conducted at the MDH supported Temeke Research Laboratory. Demographic, clinical, laboratory and therapeutic data were collected on National Care and Treatment Center forms (CTC 2) and supplementary forms which are entered into a secure computerized database. Alcohol consumption was defined as 'yes' or 'no' in a response to a question asking about current alcohol use. Daily alcohol consumption was also quantified but these data were not included because the numbers were too small for any meaningful analyses.

Assessment of liver fibrosis

APRI and FIB-4 were calculated using standard definitions: APRI (AST/ULN ×100)/platelet count 10^9/L, FIB-4 (age (yr)×AST (IU/L))/ (platelet count (10^9/Lx [ALT (IU/L)$^{1/2}$] [6, 7]. Cut-off values of 0.5 and 1.45 were used for APRI and FIB4 respectively. These are the lower cut-offs proposed by the WHO for significant fibrosis (METAVIIR ≥ F2), which have a high sensitivity for ruling out F2 and above. We also conducted our analyses using the higher APRI cutoffs for significant fibrosis 1.5 and 3.25, which at this higher level are more specific for the diagnosis of fibrosis [1]. Results using APRI > 0.5 are presented given the low prevalence of APRI scores > 1.5 in our cohort.

Statistical Analysis

Univariate and multivariate (MV) logistic regression analysis was used to examine the association between APRI, FIB-4 (primary outcomes) and HBV co-infection as well as other HIV and HBV factors. In MV analyses, covariates were identified through stepwise regression and retained if their P value < 0.20. P values < 0.05 were considered statistically significant. All of the analyses were repeated using higher APRI (≥1.5) and FIB4 (> 3.25) cutoffs respectively. Concordance between baseline APRI and FIB-4 values was assessed using Pearson's correlation coefficient. All statistical analyses were performed using SPSS, v22.0; IBM, Armonk, NY.

Results

Baseline characteristics (Table 1.)

All 267 HIV mono-infected, 63/68 HIV/HBV-co-infected and 165/168 HBV mono-infected patients who were enrolled in the study were included in the final analysis [median age 37 yrs (interquartile range (IQR) 14), median BMI 23 (IQR 7.0), 44% male]. The 5 HIV/HBV- and 3 HBV-infected patients were excluded because complete HBV virologic and HBeAg/anti-HBe serologic testing revealed no evidence of chronic HBV infection. HBV mono-infected patients were more likely to be male [67% (HBV) vs. 48% (HIV/HBV) and 29% (HIV)], younger [32 yrs (HBV) vs. 37 (HIV/HBV) and 39 (HIV)] and have a higher median BMI [25 (IQR 7) (HBV) vs. 21 (6.4) (HIV/HBV) and 22 (6.6) (HIV)]. HIV/HBV-co-infected patients were significantly more likely to be HBeAg sero-reactive (37% vs. 10%) and have HBV DNA ≥4.3 log IU/ml (37% vs. 16%) than HBV mono-infected patients. Overall, median APRI scores were 0.27 (IQR 0.19). 80% of the study population had APRI and FIB-4 scores < 0.5 and < 1.45 respectively, scores which are indicative of minimal fibrosis if any. Median APRI scores were similar between HIV [0.23 (IQR 0.17)], and HBV mono-infected patients [0.29 (0.15)] but significantly lower than HIV/HBV-co-infected patients [0.36 (0.4)] (p values for pairwise comparisons < 0.01 (vs. HIV) and 0.07 (vs. HBV), respectively).

Risk factors associated with advanced fibrosis (Table 2.)

HIV/HBV co-infection was significantly associated with APRI > 0.5 compared to HIV ($p < 0.01$) and HBV mono-infection ($p=0.01$) in multivariate (MV) analyses. In a subgroup analysis of patients with HIV, both HIV RNA per 1 $\log_{10}$ copies/ml increase [OR 1.53 (95% CI 1.04, 2.26); $p=0.04$] and HBV co-infection [OR 4.29 (1.98, 9.31); $p < 0.01$] were independently associated with APRI > 0.5, whereas CD4 T cell count, WHO stage, age and sex were not. In patients with HBV, co-infection with HIV [OR 2.64 (1.30, 5.34); $p < 0.01$], HBeAg sero-reactivity [3.50 (95% CI 1.60, 7.67); $p < 0.01$] and HBV DNA levels per $\log_{10}$ IU/ml [OR 1.36 (1.15, 1.62); $p < 0.01$] were all associated with APRI > 0.5 in univariate analyses. The magnitude of association between co-infection with HIV and APRI > 0.5 fell to non-significant levels ($p > 0.05$) after adjusting for HBV DNA and HBeAg status (examined independently because of the high degree of collinearity between these variables) in MV models.

Similar results were observed when repeating all of the above analyses using the higher APRI cutoff ≥ 1.5 and the high and low FIB-4 significant fibrosis categories recommended by WHO (≥1.45 and ≥3.25) [data not shown] [1]. Both APRI and FIB-4 were highly correlated ($r = 0.78$, $p =\leq .001$, R^2 0.61). HBV DNA was not predictive of FIB-4 ≥1.45 in HBV-infected patients, presumably due to the slightly lower number of HBV-infected patients in the higher FIB-4 vs. APRI fibrosis categories.

Discussion

We present one of the largest studies to date from SSA comparing the prevalence of liver fibrosis using APRI and FIB-4 in treatment naïve, HIV-, HBV- and HIV/HBV-infected

patients. The use of non-invasive markers APRI and FIB-4 were feasible in this setting and both were highly correlated. Overall, the prevalence of significant liver fibrosis in HIV and HIV/HBV co-infected patients in this study was much lower that that reported in a recent study from Tanzania using an APRI cutoff ≥1.5 (9.1% and 14.2% respectively) [8]. Patients in our cohort reported significantly less alcohol consumption (7.9% vs. 25.2%), had lower median AST levels (25.9 vs. 53 IU/mL) and a higher median CD4 cell count (212 vs. 185 cells/mm^3), which we speculate may have contributed to the differences in APRI score observed between the two studies. In addition, we also excluded patients with active TB.

A significantly higher rate of fibrosis was observed in patients with HIV/HBV co-infection compared to HIV and HBV mono-infection, confirming findings from several other SSA studies [4, 8, 9]. Notably, HIV/HBV co-infected patients had almost three times the risk of APRI > 0.5 compared to patients with HBV alone. In multivariate analyses of HBV-infected patients, HBeAg sero-reactivity and HBV DNA levels ≥4.3 $\log_{10}$ IU/mL explained about 50%–70% of the increased risk of fibrosis due to co-infection with HIV (data not shown). Our findings confirm a relationship between the level of active HBV viral replication and risk of liver disease progression, which has been observed in other studies [10].

HIV–infected patients had a similar prevalence of fibrosis to patients with HBV. The presence of liver fibrosis in HIV-infected patients without viral co-infection has been well documented. In Uganda, HIV infection was associated with a 50% increased odds of liver stiffness measurement (LSM) by TE compared to HIV-uninfected individuals [4]. Similar findings have been observed in the US [11]. Several mechanisms underlying the association between HIV and liver fibrosis have been proposed [12]. The strong association between HIV VL and APRI > 0.5 in both HIV and HIV/HBV infected patients that was seen in this study suggests an effect of HIV itself on the liver.

This study provides some of the first data characterizing HBV infection and liver disease risk in HBV mono-infected populations in Tanzania. Most HBV mono-infected patients were HBeAg seronegative and had low levels of HBV DNA. Furthermore, less than 5% had evidence of advanced liver disease. Similar to other SSA studies [9], a higher prevalence of significant fibrosis was observed in patients who were HBeAg seropositive and in patients with high HBV DNA [data not shown]. Our data suggests that the majority of HBV mono-infected patients in this setting are likely to be at very low risk of liver disease progression, however this needs to be confirmed in longitudinal studies.

Strengths of our study include the large number of patients evaluated and inclusion of an HBV mono-infected population recruited from the same community. Although APRI and FIB-4 may be less sensitive for the detection of fibrosis and cirrhosis compared to other measures such as TE [13], our data is consistent with other studies of liver fibrosis in HIV and HBV infected populations in SSA, where more expensive fibrosis measures have been used [9, 14]. Thus, findings in our study would support the use of APRI and FIB-4 in these settings. In addition, there is less concern now about the sensitivity of these measures in HIV/HBV co-infected patients, most of who receive antiviral therapy regardless of any specific HBV treatment criteria. One important potential limitation was the lack of data on important confounders such as use of hepatotoxic medications, recreational drugs and co-

infection with HDV. In a recent study from Tanzania, no confirmed cases of HDV infection in over 200 HIV/HBV-co-infected patients were observed [15].

In conclusion, in this large study of treatment-naïve Tanzanian HIV-, HBV- and HIV/HBV-infected adults, co-infection with HIV/HBV was associated with a significantly higher risk of liver fibrosis than either infection alone. The utility of inexpensive fibrosis markers such as FIB-4 and APRI in this setting was demonstrated. This study highlights the importance of screening all HIV-infected patients for HBV, and early initiation of HBV active antiretroviral therapies in these individuals.

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Table 1

Baseline characteristics of the study population

Characteristic	All patients (n=495)	HIV mono-infected (n=267)	HBV mono-infected (n=165)	HIV/HBV co-infected (n=63)	* p-Value
Male (%)	217 (44%)	77 (29%)	110 (67%)	30 (48%)	**<0.01**
Age Yrs, median (IQR)	37 (14)	39 (15)	32 (13)	37 (11)	**<0.01**
BMI, median (IQR)	23 (7)	22 (6.6)	25 (7)	21 (6.4)	**<0.01**
ALT IU/L, median (IQR)	19.0 (15)	16.6 (11.7)	22 (16.2)	20.3 (21)	**0.01**
AST IU/L, median (IQR)	25.9 (13)	25.8 (12.1)	25.4 (11.2)	30.9 (23)	0.02
Platelets 10^9/L, median (IQR)	252 (126)	290 (157)	225 (66)	246 (139)	**<0.01**
Creatinine clearance, median (IQR)[&]	95.1 (45.9)	94.1 (46.0)	95.9 (37)	95.7 (56.7)	**0.33**
APRI, median (IQR)[#]	0.27 (0.19)	0.23 (0.17)	0.29 (0.15)	0.36 (0.4)	**<0.01**
<0.5 (%)	368 (82.3)	216 (86.4)	119 (82)	33 (63)	**<0.01**
0.51–<1.5 (%)	60 (13.4)	28 (11.2)	19 (13)	13 (25)	
≥1.5 (%)	19 (4.3)	6 (2.4)	7 (5)	6 (12)	
FIB-4, median (IQR)[@]	0.86 (0.63)	0.85 (0.63)	0.81(0.51)	1.09 (1.22)	**<0.02**
<1.45 (%)	359 (80.3)	201 (80.4)	124 (85.5)	34 (65.4)	**<0.01**
1.45–<3.25 (%)	65 (14.5)	39 (16)	16 (11.0)	10 (19.2)	
≥3.25 (%)	23 (4.6)	10 (3.7)	5 (3.4)	8 (15.4)	
Alcohol use, yes (%)	39 (7.9%)	9 (3.4%)	28 (17%)	2 (3.2)	**<0.01**
WHO Stage					
Stage 1 (%)	75 (22.7%)	67 (25.1%)	-	8 (12.7%)	
Stage 2 (%)	64 (19.4%)	55 (20.6%)	-	9 (14.3%)	0.02
Stage 3 (%)	159 (48.2%)	124 (46.4%)	-	35 (55.6%)	
Stage 4 (%)	32 (9.7%)	21 (7.9%)	-	11 (17.5%)	
CD4 cell count, median (IQR)	212 (229)	208 (213)	-	244 (290)	0.53
CD4 <200 cells/ul (%)	(142 (45%)	122 (47%)	-	20 (37%)	0.12
CD4 ≥200 cells/ul (%)	173 (55%)	139 (53%)	-	34 (63%)	
HIV RNA, $\log_{10}$ copies/mL, median (IQR)	5.0 (1.0)	5.02 (0.94)	-	4.83 (1.7)	0.05
HBV DNA, $\log_{10}$ IU/mL median (IQR)	2.80 (2.5)	-	2.8 (1.9)	3.0. (4.5)	0.23

Characteristic	All patients (n=495)	HIV mono-infected (n=267)	HBV mono-infected (n=165)	HIV/HBV co-infected (n=63)	* p-Value
≥4.3 $\log_{10}$ IU/mL(%)	49 (22%)	-	26 (16)	23 (37)	**<0.01**
<4.3 $\log_{10}$ IU/mL (%)	177 (78.3%)	-	138 (84%)	39 (63)	
HBeAg reactive (%)	40 (17.6%)	-	17 (10%)	23 (37%)	**<0.01**
Anti-HBe reactive, %	213 (93.4.%)	-	164 (99.4%)	49 (77.8%)	**<0.01**

*p values are for comparison across all groups using Kruskal-Wallis rank test for continuous variables and Pearson X2 test for categorical variables; Mann-Whitney used for comparisons of continuous variables when limiting to within group HIV and HBV comparisons.

$creatinine clearance calculated using **Cockcroft-Gault equation** (((140 - age in years)×(wt in kg))×1.23*) / (serum creatinine in micromol/l). *x0.85 if female

#APRI calculated using [(AST / ULN AST)×100] / Platelets (10^9/ L)

@FIB-4 calculated using (Age×AST) / (Platelets×(sqr (ALT))

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CrCl; creatinine clearance. HBeAg, hepatitis B **e antigen;** anti-HBe, Anti-hepatitis B e Antigen

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Table 2

Factors associated with significant liver fibrosis (APRI>0.5), all patients

Characteristic	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Gender				
Male	1.39 (0.86, 2.3)	0.18	1.19 (0.68, 2.08)	0.54
Female	1		1	
Age				
≤35	1.01 (0.62, 1.66)	0.96	-	
>35	1			
*Current alcohol use				
Yes	0.79 (0.30, 2.11)	0.8	0.73 (0.26, 2.01)	0.54
No	1		1	
Body Mass Index (per 1kg/m^2)	0.99 (0.95, 1.03)	0.58	-	
CrCl (per 1ml/min)	1.00 (0.99, 1.00)	0.22	1.00 (0.99, 1.00)	0.24
HIV status				
HIV/HBV co-infected	3.66 (1.87, 7.15)	<0.001	3.78 (1.91, 7.50)	**<0.01**
HIV mono-infected	1		1	
Hepatitis status				
HIV/HBV co-infected	2.64 (1.30, 5.34)	0.01	2.61 (1.26, 5.44)	**0.01**
HBV mono-infected	1		1	

Abbreviations: Crcl creatinine clearance; OR Odds Ratios; CI confidence intervals

*Current alcohol use retained in all MV models irrespective of p-value at the univariate level