Assessment of Liver Fibrosis by Transient Elastography in Patients With HIV and Hepatitis B Virus Coinfection in Nigeria

Claudia Hawkins,1 Oche Agbaji,1 Placid Ugoagwu,4 Charles Ani,1 Chinedum Okafo,2 Erika Wallender,5 and Robert L. Murphy1

1Northwestern University, Chicago, Illinois; 2Department of Medicine, University of Jos and Jos University Teaching Hospital; 3HIV Clinic, Jos University Teaching Hospital, Nigeria; 4Johns Hopkins University, Baltimore, Maryland; and 5Vanderbilt University Medical Center, Nashville, Tennessee

We describe the prevalence and risk factors for advanced liver fibrosis (≥9.3 kPa) using transient elastography in human immunodeficiency virus (HIV)–monoinfected and HIV/HBV (hepatitis B virus)–coinfected, antiretroviral naive adults in Nigeria. HBV coinfection and HBV DNA levels significantly increased the risk of advanced fibrosis in HIV and HIV/HBV patients, respectively.

Keywords: HIV; HBV; liver fibrosis; Africa.

Human immunodeficiency virus (HIV) significantly accelerates the course of chronic hepatitis B (HBV) disease, resulting in higher rates of liver-related morbidity and mortality in individuals with HIV or HBV alone [1]. There are few data on the burden of liver disease in HIV/HBV–coinfected individuals in sub-Saharan Africa (SSA), where both HIV and HBV are endemic. This is, in part, due to the lack of financial and technological resources needed to investigate liver damage in these populations.

Transient elastography (TE), a noninvasive test that measures liver stiffness through pulsed echo ultrasound, is a promising alternative to liver biopsy and has high sensitivity for determining the presence of advanced liver fibrosis in HBV and HIV/HBV coinfection [2]. Using TE, we compared the prevalence of advanced fibrosis and associated risk factors in a cohort of antiretroviral therapy (ART)–naive, HIV-monoinfected, and HIV/HBV–coinfected individuals in Jos, Nigeria. We also assessed the correlation between HBV serological and virological markers and severity of liver disease in HIV/HBV coinfection. We hypothesized that the prevalence of liver disease would be higher in HIV/HBV–coinfected patients than in HIV-monoinfected patients and that risk factors may differ based on the presence or absence of HBV.

METHODS

This cross-sectional study was conducted at the Harvard PEPFAR (the President’s Emergency Plan for AIDS Relief)/AIDS Prevention Initiative in Nigeria (APIN) and supported by the Jos University Teaching Hospital (JUTH) HIV Care and Treatment Center, Jos, Nigeria. Through the program, patients receive free access to ART as well as baseline assessments; clinical, immunological, and virological monitoring; and prophylaxis and treatment for opportunistic infections according to Nigerian National ART Guidelines and international standards [3]. In this study, we included HIV-infected adults (aged ≥18 years) who were newly enrolled into the program between July 2011 and February 2012, HIV antibody–positive, ART-naive, HCV antibody–negative, and had a known hepatitis B surface antigen (HBsAg) status. A patient was classified as HIV/HBV coinfected if he or she had at least 1 positive HBsAg. All other participants were considered HIV monoinfected. Study patients had TE, CD4+ T cell counts, HIV RNA, hemoglobin, and alanine aminotransferase (ALT) levels measured at enrollment. Hepatitis B e antigen (HBeAg), anti-HBe, and HBV DNA levels were obtained from HIV/HBV–coinfected patients. HBsAg was determined by enzyme immunoassay assay (Sysmex, Kobe, Japan). HIV RNA was determined using the Roche COBAS Amplicor HIV-1 Monitor Test (Roche Diagnostics GmbH, Mannheim, Germany) with a lower limit of detection of 400 copies/mL. CD4+ T-cell count was determined via flow cytometry (Partec GmbH, Munster, Germany). All laboratory tests were performed according to the manufacturer’s specifications. Liver stiffness measurement (LSM; kPa) was performed by 2 physicians trained in use of the TE procedure by the manufacturer. LSM was considered reliable if 10 successful measurements were obtained and the success rate was >60%.

Univariate methods were used to compare demographic and baseline clinical characteristics between HIV- and HIV/HBV-
coinfected individuals. Variables with a P value of ≤ .20 or that were considered clinically relevant were selected for inclusion in multivariate logistic regression modeling, which was conducted to further evaluate factors potentially related to advanced liver fibrosis (LSM ≥ 9.3 kPa) in all study patients and HIV/HBV patients alone. This cutoff value has been validated in previous studies that included HIV-infected patients of African descent with and without viral hepatitis coinfection [4]. All analyses were conducted using Stata version 10.1 (College Station, TX).

All patients provided written informed consent. The institutional review boards at JUTH and Northwestern University approved this study.

RESULTS

Baseline Characteristics

A total of 232 HIV and 93 HIV/HBV patients were enrolled during the study period. Baseline characteristics are presented in Table 1. The prevalence of advanced liver fibrosis (LSM ≥ 9.3–< 12.3 kPa) and cirrhosis (LSM ≥ 12.3 kPa) was 7/232 (3.0%) and 4/232 (1.7%) among HIV patients and 5/93 (5.4%) and 16/93 (17.2%) among HIV/HBV patients, respectively. The prevalence of advanced fibrosis (LSM ≥ 9.3 kPa) was significantly lower in HIV/HBV patients with HBV DNA levels <3.3 log IU/mL (the cutoff above which treatment is recommended in some HBV populations) compared with HIV/HBV patients with HBV DNA levels ≥3.3 log IU/mL (10.3% vs 43.0%, respectively; P < .01).

Risk Factors for Significant Liver Fibrosis

In multivariate analyses, the only factor associated with advanced liver fibrosis (LSM ≥ 9.3 kPa) was HBV coinfection (adjusted odds ratio [OR], 5.5; 95% confidence interval [CI], 2.5, 12.3; Table 2). This association was largely unchanged when adjusted for ALT and HIV RNA (data not shown). ALT, CD4+ T-cell count, HIV RNA, and alcohol were not found to be predictive of advanced fibrosis in multivariate models. To determine factors associated with advanced fibrosis among HIV/HBV patients, we constructed separate multivariable models and found that HBV DNA ≥3.3 log IU/mL was significantly associated with advanced fibrosis (adjusted OR, 6.1; 95% CI, 2.0, 18.9; P = .002), although HBeAg status was not (adjusted OR, 2.7; 95% CI, .8, 9.3; P = .11). The magnitude of association between HBV DNA level and advanced fibrosis was similar when higher HBV DNA cutoffs were used (≥4.3 log IU/mL vs <4.3 log IU/mL; adjusted OR, 6.4; 95% CI, 2.1, 19.6; P < .001).

DISCUSSION

In one of the few studies to assess liver fibrosis using TE in SSA, we found that among HIV-infected patients, HBV coinfection significantly increases the risk of advanced liver fibrosis. Furthermore, among HIV/HBV patients, high HBV DNA was significantly associated with advanced liver fibrosis.

To our knowledge, only 1 other study from Africa has assessed liver fibrosis using TE in HIV- and HIV/HBV–coinfected patients [4]. In that study, which was conducted in Uganda, 17% of HIV-infected patients had liver stiffness measures indicative of significant fibrosis that were much higher than the 5% observed in our HIV-monoinfected cohort. The prevalence of liver fibrosis in our HIV/HBV patients was also lower than in a recent study of African HIV/HBV patients with mostly HBeAg-negative disease, of whom 36% had advanced fibrosis (metavir 3 or 4) [5].

Table 1. Comparison of Baseline Characteristics of Study Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV Patients (n = 232) n (% or IQR)</th>
<th>HIV–HBV Patients (n = 93) n (% or IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median</td>
<td>35.5 (31, 42.5)</td>
<td>33.0 (29.5, 41.0)</td>
<td>.24</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57 (24.6)</td>
<td>37 (39.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married (%)</td>
<td>146 (62.9)</td>
<td>56 (60.2)</td>
<td>.65</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.9 (20.4, 27.3)</td>
<td>23.4 (20.2, 26.1)</td>
<td>.44</td>
</tr>
<tr>
<td>CD4+ T-cell count (cells/mm³)</td>
<td>383.5 (269.0, 506.0)</td>
<td>264.0 (172.0, 380.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV RNA (log copies/mL)</td>
<td>4.65 (4.03, 5.1)</td>
<td>4.81 (4.3, 5.3)</td>
<td>.04</td>
</tr>
<tr>
<td>Platelet count (×100 k/µL)</td>
<td>242.5 (188.0, 291.5)</td>
<td>221 (177.5, 304.0)</td>
<td>.25</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.0 (11.5, 13.0)</td>
<td>12.5 (11.4, 13.5)</td>
<td>.23</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>20 (14.5, 33.0)</td>
<td>24.5 (16.5, 38.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Alcohol consumption (any) (%)</td>
<td>60 (25.9)</td>
<td>25.0 (26.9)</td>
<td>.85</td>
</tr>
<tr>
<td>HBV DNA (log IU/mL)</td>
<td>NA</td>
<td>2.40 (0.2, 6.35)</td>
<td>NA</td>
</tr>
<tr>
<td>Hepatitis B e antigen positive (%)</td>
<td>19 (20.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency; IQR, interquartile range; NA, not applicable.

* Median (IQR) values reported unless otherwise stated.
Higher median CD4+ T-cell counts, lower levels of alcohol consumption, and differences in occupational exposures could explain the comparatively lower rates of liver fibrosis in HIV and HIV/HBV patients in our study.

Similar to the study from Uganda [4], HBV was found to be strongly associated with a higher risk of liver fibrosis. In developed countries, patients with HIV/HBV coinfection have been shown to have decreased immune responses to HBV and higher rates of morbidity and mortality related to liver disease, including fibrosis, end-stage liver disease, and hepatocellular carcinoma [6]. While treatments for HBV have been shown to decrease liver disease progression in these settings [7], it is still unknown whether HBV treatment will have similar effects in SSA where HBV infection is typically acquired much earlier than HIV and has the potential to result in more HBV-associated liver disease over time. Interestingly, HIV viral load and CD4+ T-cell counts were not independently predictive of fibrosis in either HIV- or HIV/HBV–coinfected patients. This is in contrast to previous studies where higher HIV RNA levels and lower CD4+ T-cell counts were shown to be associated with higher TE scores and other surrogate markers of fibrosis [8]. The high baseline median CD4+ T-cell counts in our study could have accounted for the lack of association.

In HIV/HBV patients, higher HBV DNA levels but not HBeAg seropositive status were independently associated with advanced liver fibrosis, which is similar to findings from other studies [9]. The magnitude of association between HBV DNA levels and liver fibrosis was similar at higher (≥4.3 log IU/mL) HBV DNA levels. These data support current recommendations within national guidelines to consider HBV treatment at lower HBV DNA levels (2000 IU/mL) [10]. It is also notable that in our study, the prevalence of advanced fibrosis at HBV DNA levels <3.3 log IU/mL was similar to the prevalence in HIV-monoinfected patients. The small numbers of HBeAg+ patients in this study could have accounted for the lack of independent association between HBeAg status and fibrosis and requires further examination in larger cohorts.

There were some limitations to our study. Interobserver differences in TE measurements, mainly as a result of technique, are common and diagnostic accuracy can be reduced by obesity and severe flares of hepatitis [11]. However, only 2 patients had ALT levels ≥10 ULN (40 IU/L), and the median body mass index in both patient groups was <25 kg/m²; therefore, these factors were probably not significant limitations in our study. Other limitations included the lack of quantifiable data on alcohol consumption and information on potential hepatotoxic confounders such as exposure to aflatoxin or herbs. Due to technical challenges, it was not possible to perform liver biopsies to validate TE findings. We were also unable to measure any surrogate markers of liver disease such as Fibrotest or FIB-4, which have been shown to improve the sensitivity of TE in determining liver fibrosis in HBV patients [12]. Finally, no confirmatory testing of HBsAg was performed to confirm chronic HBV. However, since HBV is usually acquired during childhood in SSA, it is unlikely that acute HBV was acquired recently in any of the patients.

In this Nigerian cohort of HIV-infected individuals, HBV coinfection was independently associated with a higher risk of advanced liver fibrosis. HBV DNA levels were also predictive of these outcomes in HIV/HBV–coinfected patients. Further study is needed to examine the effect of HBV-active ART on liver disease progression in HIV/HBV–coinfected populations.
Notes

Acknowledgments. We acknowledge the support of APIN Ltd./Gte for supporting the care of human immunodeficiency virus (HIV)–infected patients at the Jos University Teaching Hospital HIV Care and Treatment Center.

Financial support. This work was supported by the Northwestern University AIDS International Training and Research Program Fogarty International Center/National Institutes of Health grant 5D43TW007995-03S1.

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References