Changes in liver stiffness after ART initiation in HIV-infected Nigerian adults with and without chronic HBV

Jennifer L. Grant^{1*}, Patricia Agaba^{2,3}, Placid Ugoagwu², Auwal Muazu², Jonathan Okpokwu², Samuel Akpa², Stephen Machenry², Godwin Imade^{2,4}, Oche Agbaji^{2,5}, Chloe L. Thio⁶, Robert Murphy¹ and Claudia Hawkins¹

¹Department of Medicine, Division of Infectious Diseases, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; ²HIV Care and Treatment Centre, Jos University Teaching Hospital, Jos, Nigeria; ³Department of Family Medicine, University of Jos and Jos University Teaching Hospital, Jos, Nigeria; ⁴Department of Obstetrics and Gynaecology, University of Jos and Jos University Teaching Hospital, Jos, Nigeria; ⁵Department of Medicine, University of Jos and Jos University Teaching Hospital, Jos, Nigeria; ⁶Department of Medicine, Division of Infectious Diseases, Johns Hopkins University, Baltimore, MD, USA

*Corresponding author. Present address: Department of Medicine, Division of Infectious Diseases, NorthShore University Health System, Evanston, IL, USA. Tel: +1 847 657 5959; Fax: +1 847 657 5764; E-mail: jgrant@northshore.org

Received 5 November 2018; returned 9 December 2018; revised 6 February 2019; accepted 11 March 2019

Background: There are limited data from sub-Saharan Africa on long-term liver fibrosis changes in HIV- and HIV/HBV-infected individuals.

Objectives: To assess the effects of ART on liver stiffness measurement (LSM) using transient elastography (TE) in HIV- and HIV/HBV-infected Nigerian adults and examine factors associated with fibrosis regression.

Methods: We included ART-naïve HIV- and HIV/HBV-infected adults (≥ 18 years) enrolled in a prospective, longitudinal study of liver disease between July 2011 and February 2015 at Jos University Teaching Hospital HIV Care and Treatment Centre in Nigeria. Patients initiated ART and had TE at baseline and follow-up (year 3). LSM cut-offs for Metavir scores were 5.9, 7.6 and 9.4 kPa for moderate fibrosis, advanced fibrosis and cirrhosis, respectively. We used multivariable regression to identify factors associated with TE (≥ 1 Metavir) stage decline.

Results: A total of 106 HIV- and 71 HIV/HBV-infected patients [70.5% female and median age=34 years (IQR=29–42 years)] were studied. Baseline LSM and median LSM decline were significantly higher in HIV/HBV- versus HIV-infected patients; 41% of HIV/HBV-infected patients regressed ≥ 1 Metavir stage versus 17% of HIV-infected patients ($P < 0.01$); LSM scores at year 3 were not significantly different between HIV- and HIV/HBV-infected patients. In multivariable analyses, patients with baseline CD4+ T cells ≥ 200 (versus < 200) cells/mm³ and lower BMIs were more likely to experience LSM stage decline.

Conclusions: HBV coinfection does not attenuate LSM declines in HIV-infected patients after ART initiation despite being a risk factor for more advanced liver disease prior to therapy. The inverse association between BMI and TE stage decline needs further investigation.

Introduction

In Nigeria, ~9%–15% of 3.6 million patients living with HIV are coinfecting with HBV.^{1–3} HIV significantly accelerates the course of chronic HBV, resulting in higher rates of end-stage liver disease, hepatocellular carcinoma (HCC) and death.⁴ Until recently there has been a relative paucity of data from sub-Saharan Africa (SSA) on the burden of liver disease in HIV/HBV coinfection. The few studies that have been conducted in this region, including our own, have reported high rates of significant liver fibrosis and cirrhosis (Metavir fibrosis stage $\geq F2$), using a variety of non-invasive fibrosis measures in HIV/HBV-infected populations, ranging from 5.3% to 17.2%.^{5–9} Traditional risk factors such as excess alcohol

consumption and advanced immunosuppression, and high HIV and HBV viral loads appear to accelerate this risk.

In Nigeria, treatment with ART that includes at least two NRTIs with activity against HBV is now recommended in all HIV/HBV-coinfecting individuals.¹⁰ Tenofovir in combination with lamivudine or emtricitabine has been shown in several studies from high-income countries (HIC) to reverse liver disease progression and improve survival.^{11,12} In SSA, long-term studies of liver disease progression in both HIV- and HIV/HBV-infected populations on ART are lacking. Evaluating the effects of ART on liver fibrosis progression in this region is important given the high burden of both HBV

and HIV infection, higher frequency of advanced immunosuppression and presence of competing causes of liver injury such as race, hepatotoxic medications and other liver-specific coinfections, all of which could negatively impact responses to therapy.

In this study, we assessed the effects of ART on longitudinal changes in liver stiffness measurement (LSM) in HIV- and HIV/ HBV-infected Nigerians using transient elastography (TE), an inexpensive and accurate non-invasive marker of liver fibrosis, and examined predictors of TE stage decline.¹³

Methods

Study design and population

This prospective, longitudinal cohort study was conducted at the AIDS Prevention Initiative in Nigeria (APIN)-supported HIV Care and Treatment Centre at Jos University Teaching Hospital (JUTH) in Jos, Nigeria (local prevalence of HIV = 16.7% and HBV = 10.3%).^{14,15}

Patients were recruited from a longitudinal cohort study of liver disease in 236 HIV-infected and 94 HIV/HBV-coinfected [at least one positive hepatitis B s antigen (HBsAg) test; Alere Determine™ HBsAg] patients who were enrolled at the APIN-supported HIV Care and Treatment Centre at JUTH between July 2011 and February 2012. For this analysis, patients were included if they were ≥18 years old, HIV antibody seropositive, ART-naïve, HCV antibody-negative, had a known HBsAg status and underwent successful baseline and follow-up (year 3) TE. Patients were excluded if they had evidence of ascites, decompensated liver disease and/or known HCC. We obtained written informed consent and the study was approved by the JUTH Ethics Committee and the Northwestern University Institutional Review Board.

Clinical protocols

Clinical care of all HIV-infected patients at JUTH follows Nigerian and WHO guidelines.^{16,17} As part of standard care, patients are evaluated monthly to every 3 months in the clinic after initiation of ART. At each visit, they are provided with ART refills and treatment adherence counselling. Laboratory testing, including haemoglobin (g/dL), CD4+ T cell count (cells/mm³), ALT (IU/L) and HIV RNA [Roche Diagnostics, GmbH, Germany; lower limit of detection (LLOD) <200 copies/mL], is performed every 6–12 months. Study participants in the existing longitudinal cohort are followed at annual study visits. At each study visit, patients receive a clinical assessment, TE (baseline and every 3 years), and additional laboratory studies including HBV DNA (Roche Diagnostics, GmbH; LLOD <20 IU/mL), hepatitis B e antigen (HBeAg) and anti-HBe (Abbott Architect i2000 kits, Abbott Laboratories). One trained technician performs TE using the M probe on all patients (FibroScan™, Echosens, France) to obtain LSM. This is considered reliable if 10 successful measurements are obtained with a success rate >60% and IQR/median LSM ≤30%.¹³ Patients who did not meet the criteria for successful measurement were asked to come back for a repeat scan or were excluded from the study. Recommended ART at the time of study enrolment (2011) included the combination of tenofovir or zidovudine plus lamivudine or emtricitabine and an NNRTI, and was initiated in participants according to criteria in the Nigerian and WHO guidelines.^{16,17}

Definitions, outcomes and statistical analysis

We classified LSM scores into Metavir fibrosis categories based on validated cut-offs previously used in studies of HIV/HBV-coinfected patients: moderate (F2) fibrosis ≥5.9 kPa, advanced (F3) fibrosis ≥7.6 kPa and cirrhosis (F4) ≥9.4 kPa.^{13,18,19} The primary outcome of interest was change in LSM. Secondary outcomes were LSM stage decline, defined as a ≥1 fibrosis stage decline from baseline to 36 month follow-up in patients with ≥F2 fibrosis at

baseline; changes in ALT; and HIV and HBV virological suppression (defined as <LLOD).

We compared clinical characteristics using the Wilcoxon rank-sum test (continuous) and the χ^2 test (categorical). We analysed variables over time using the Wilcoxon signed rank test (continuous) and the related-samples marginal homogeneity test or the McNemar test (categorical). We performed univariate and multivariable regression to identify factors associated with fibrosis stage decline after ART initiation. A *P* value of <0.05 was deemed statistically significant. Calculations were performed using SPSS v24.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristics (Table 1)

A total of 177 patients were analysed; 106 (59.9%) HIV monoinfected and 71 (40.1%) HIV/HBV coinfected. HIV/HBV-coinfected patients were more likely to be male, and have lower baseline CD4+ T cell counts and higher baseline ALT levels (Table 1). The majority of HIV/HBV-coinfected patients were HBeAg seronegative and 23 (32.4%) had an HBV DNA level ≥2000 IU/mL. 160 (90.4%) patients initiated ART; HIV/HBV-coinfected patients were more likely than HIV-monoinfected patients to initiate TDF-based regimens (82% versus 28%; *P* < 0.01). There were no significant differences in baseline characteristics between patients who initiated ART and the 17 patients who did not (data not shown).

Changes in liver stiffness (Table 2)

The overall median LSM declined between baseline and follow-up [median = 33 months (30–34 months)] from 5.5 (4.4–6.8) kPa to 4.9 (4.2–6.1) kPa; *P* < 0.01. Median declines were higher in HIV/HBV-coinfected versus HIV-monoinfected patients [−1.1 (−2.7 to 0.3) kPa versus −0.2 (−1.2 to 0.8) kPa; *P* < 0.01]. At the end of follow-up, LSM was similar between HIV/HBV-coinfected and HIV-monoinfected patients. Declines were similar irrespective of ART regimen (tenofovir versus non-tenofovir) and when excluding 17 patients who did not initiate ART (data not shown). Among HIV/HBV-coinfected patients, median declines in LSM were higher in patients with baseline HBV DNA ≥3.3 log₁₀ IU [−1.7 (−7.9 to −0.9) kPa] compared with patients with HBV DNA <3.3 log₁₀ IU [−0.8 (−2.1 to −0.5) kPa]; *P* = 0.02. Overall, 47/177 (26.6%) patients had ≥1 fibrosis stage decline [18 (17%) HIV versus 29 (41%) HIV/HBV; *P* < 0.01].

Factors associated with ≥1 fibrosis stage decline (Table 3)

In multivariable analyses, among all patients, those with lower BMIs and higher baseline CD4+ T cells (≥200 cells/mm³) were more likely to experience fibrosis stage decline. Similar findings were observed when analysing HIV/HBV-coinfected patients alone. There were no significant associations between baseline or follow-up HIV RNA, HBV DNA or HBeAg status and LSM stage decline. Neither months on ART nor use of tenofovir-based ART was associated with LSM stage decline in either group.

HIV and HBV virological outcomes

A total of 124/169 (73.4%) patients achieved an undetectable HIV RNA (<200 copies/mL), with no statistically significant difference

Table 1. Baseline patient characteristics, by coinfection status

Characteristic	All	HIV	HIV/HBV	P
Total no., n (%)	177	106 (59.9)	71 (40.1)	–
Age (years), median (IQR)	34 (29–42)	35 (31–43)	33 (28–41)	0.241
Female, n (%)	124 (70.5%)	80 (76.2)	44 (62)	0.043
Alcohol use, yes, n (%)	48 (27.1%)	29 (27.4)	19 (26.8)	0.930
BMI (kg/m ²), median (IQR)	24.1 (21.2–27.8)	24.4 (21.5–28.1)	23.4 (20.6–27.3)	0.257
HIV RNA (log ₁₀ copies/mL), median (IQR)	4.6 (4.1–5.1)	4.7 (4.0–5.1)	4.6 (4.2–5.3)	0.632
CD4+ T cell count (cells/mm ³), median (IQR)	334 (220–470)	386 (241–481)	268 (185–403)	0.004
ALT (IU/L), median (IQR)	20 (15–32)	19 (13–30)	2 (17–37)	0.013
ALT ≥2× ULN ^a , n (%)	14 (8.1)	5 (4.9)	9 (12.9)	0.058
Platelet count (×10 ⁹ /L), median (IQR)	226 (175–282)	231 (178–274)	220 (173–298)	0.916
CL _{CR} (via Cockcroft–Gault formula) (mL/min/1.73 m ²), median (IQR)	70 (57.4–86.1)	71 (59.5–87.9)	67.5 (55.2–85.9)	0.281
HBV DNA (log ₁₀ IU/mL), median (IQR)	–	–	1.7 (0–5.5)	–
HBV DNA ≥2000 IU ^b , n (%)	–	–	23 (32.4)	–
HBeAg positive ^c , n (%)	–	–	10 (14.9)	–
Initiated ART ^d , n (%)	160 (90.4)	93 (87.7)	67 (94.4)	0.142
Initial ART regimen, n (%)				<0.001
ZDV+3TC+NNRTI	77 (48.1)	67 (72)	10 (14.9)	
TDF+3TC/FTC+NNRTI	81 (50.6)	26 (28)	55 (82)	
other ^e	2 (1.3)	0 (0)	2 (3)	

ZDV, zidovudine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine.

^aULN=31 IU/mL.

^b2000 IU/mL=3.3 log₁₀.

^cExcludes five patients with both concurrent HBeAg and anti-HBE at study enrolment.

^dART initiated at a median time of 2 months (IQR=0.6–8 months) after initial TE.

^eOther regimens are TDF/ZDV/3TC and ZDV/3TC/lopinavir/ritonavir.

Table 2. Patient outcomes, by coinfection status^a

Characteristic	All, n=177	HIV, n=106	HIV/HBV, n=71	P
Baseline LSM (kPa), median (IQR)	5.5 (4.4–6.8)	5.1 (4.2–5.8)	6.4 (4.7–9.0)	<0.001
LSM at follow-up (kPa), median (IQR)	4.9 (4.2–6.1)	4.9 (4.2–5.8)	5.2 (4.1–6.6)	0.163
Change (kPa), median (IQR)	–0.4 (–1.5–0.6)	–0.2 (–1.2–0.8)	–1.1 (–2.7–0.3)	<0.001
Baseline LSM ≥9.4 kPa, n (%)	19 (10.7)	2 (1.9)	17 (23.9)	<0.001
LSM ≥9.4 kPa at follow-up, n (%)	9 (5.1)	1 (0.9)	8 (11.3)	0.002
Decrease in LSM ≥1 stage ^b , n (%)	47 (26.6)	18 (17)	29 (40.8)	<0.001
ALT ≥2× ULN at follow-up ^c , n (%)	3 (2)	1 (1.1)	2 (3.6)	0.285

^aIncludes 17 patients who did not initiate ART.

^bDecrease of at least one stage (i.e. F3 to F2) in patients with at least F2 at baseline.

^cULN=31 IU/mL.

observed between HIV-monoinfected and HIV/HBV-coinfected patients [73/98 (74.5%) versus 51 (71.8%); $P=0.64$]. Among HIV/HBV-coinfected patients, 52 (67.5%) achieved an undetectable HBV DNA level (<20 IU/mL).

Discussion

We present findings from one of the few studies using TE to assess long-term (>1 year) changes in LSM in both HIV- and HIV/HBV-infected patients in SSA. Similar to other studies from SSA,^{5–9,20}

relatively high rates of LSM-classified significant liver fibrosis and cirrhosis prior to ART initiation were observed in both HIV-infected and HIV/HBV-coinfected patients. After ART initiation, significant declines in LSM and the proportion of patients with LSM ≥9.4 kPa were observed in both patient groups, correlating with declines in HIV and HBV viral load. The larger decline in HIV/HBV-coinfected patients (–1.1 kPa) was not unexpected given the higher baseline LSM in these patients. Our findings are similar to other studies of HIV-infected and HIV/HBV-coinfected populations from SSA and Europe that have used TE and other non-invasive markers to

Table 3. Predictors of TE (≥ 1 Metavir) stage decline^a

Covariate	Univariate analysis		Multivariable analysis ^a	
	OR (95% CI)	P	adjusted OR (95% CI)	P
All patients				
age (per 1 year) ^b	0.99 (0.95–1.05)	0.96		
male (versus female)	0.39 (0.14–1.13)	0.08		
HBsAg positive (versus negative)	0.92 (0.32–2.63)	0.87		
LSM (per 1 kPa) ^b	1.00 (0.92–1.10)	0.94		
time between TE (months)	1.05 (0.90–1.23)	0.52		
BMI (per 1 kg/m ²) ^b	0.87 (0.78–0.97)	0.01	0.71 (0.55–0.93)	<0.01
alcohol intake, yes (versus no) ^b	0.82 (0.27–2.47)	0.72		
HIV RNA (per 1 log ₁₀ copies/mL) ^b	0.78 (0.50–1.22)	0.28		
CD4+ T cells ≥ 200 cells/mm ³ (ref: <200) ^b	3.27 (1.0–10.66)	0.05	15.04 (2.69–83.97)	<0.01
started ART, yes (ref: no)	2.25 (0.30–17.12)	0.43		
months on ART (per 1 month)	1.07 (1.01–1.12)	0.02		
HIV RNA at 36 months <20 copies/mL (ref: ≥ 20)	3.76 (1.16–12.13)	0.03	3.87 (0.98–15.2)	0.08
HIV/HBV patients				
age (per 1 year) ^b	0.99 (0.94–1.05)	0.81		
male (versus female)	0.34 (0.09–1.26)	0.11		
LSM (per 1 kPa) ^b	0.99 (0.91–1.09)	0.95		
time between TE (months)	1.03 (0.84–1.27)	0.80		
BMI (per 1 kg/m ²) ^b	0.80 (0.68–0.95)	0.01	0.71 (0.55–0.93)	0.01
alcohol intake, yes (ref: no) ^b	0.69 (0.18–2.68)	0.59		
HIV RNA (per 1 log ₁₀ copies/mL) ^b	0.46 (0.18–1.16)	0.10		
CD4+ T cells ≥ 200 cells/mm ³ (ref: <200) ^b	4.82 (0.95–24.32)	0.06	19.57 (1.96–195.8)	0.01
started ART, yes (ref: no)	2.15 (0.13–37.19)	0.60		
months on ART (per 1 month)	1.05 (0.99–1.11)	0.10		
HIV RNA at 36 months <20 copies/mL (ref: ≥ 20)	3.60 (0.86–15.1)	0.08	6.34 (0.73–54.8)	0.09
HBV DNA (per 1 log ₁₀ copies/mL) ^{b,c}	1.03 (0.83–1.27)	0.80		
HBeAg positive (versus negative) ^b	0.44 (0.09–2.10)	0.29		
HBV DNA at 36 months <20 IU/mL (ref: ≥ 20)	0.87 (0.22–3.61)	0.87		

^aBackward stepwise logistic regression including only patients starting at F2 or higher; HBV-specific variables in block 2 of 2.^bBaseline variable.^cRegression model also run using HBV DNA ≥ 3.3 log₁₀ IU/mL as a categorical variable with no significant difference in findings.

measure changes in liver fibrosis after ART initiation.^{7,21} Where TE has been used, median overall declines in LSM vary between -0.2 and 1.2 kPa, depending on the population (HIV versus HIV/HBV) and length of follow-up.^{9,18,19,22}

In this study, a significant association between baseline immune status and LSM stage decline after ART was observed. Among all patients, after adjusting for baseline TE score, patients with CD4 counts ≥ 200 cells/mm³ were ~ 15 times more likely to have a ≥ 1 fibrosis stage decline at follow-up. Our findings are consistent with several other studies that have shown strong associations between advanced immune suppression and elevations in fibrosis scores both at baseline and at follow-up.^{7,9,20–22} It is thought that advanced immunosuppression may accelerate liver fibrosis through its effects on the inflammatory milieu, although low CD4 counts may also be an independent marker of liver dysfunction.²³ In this study, importantly, there was no association between HIV/HBV coinfection and fibrosis regression, despite HIV/HBV-infected patients having overall lower CD4+ T cell counts at

baseline. This suggests that any independent effects of HBV on reduced immunity at baseline do not persist after ART initiation.

Studies have also reported a significant association between high HIV RNA levels and liver fibrosis scores prior to ART initiation, probably the result of pro-inflammatory effects of HIV on the liver.^{5,24,25} Although there was no statistically significant association between HIV RNA and TE score or fibrosis change in this study, we did observe a trend towards suppressed HIV RNA and fibrosis regression in both HIV-monoinfected and HIV/HBV-coinfected patients. Similarly, in a study of fibrosis changes in HIV-infected and HIV/HBV-coinfected individuals from Zambia, HIV RNA <40 copies/mL at 1 year was significantly protective against significant fibrosis and cirrhosis at 1 year.¹⁸ These findings provide further evidence of an important role for HIV in fibrogenesis.

In this study, HBV DNA was not associated at either baseline or follow-up with fibrosis changes. In the long term, elevated HBV DNA levels have been associated with high risk of adverse liver outcomes such as HCC and cirrhosis in patients with chronic HBV;

however, HBV factors have not been consistently shown to be predictors of changes in fibrosis scores early after ART initiation in patients with coinfection,^{11,18,21} suggesting that HIV may be a more important contributor to early elevations in fibrosis score and liver inflammation than HBV.

A notable finding was the negative association between higher BMIs and TE stage decline in both HIV-infected and HIV/HBV-coinfected individuals. Our preliminary data could indicate evidence of metabolic syndrome in fibrosis progression although it should be noted that metabolic conditions besides obesity (such as diabetes, lipid levels or hepatic steatosis) were not measured. In France, HIV/HBV-coinfected patients with liver fibrosis progression after tenofovir disoproxil fumarate (TDF) initiation had significantly higher levels of fasting glycaemia at the end of follow-up, while those with regression had significantly lower levels of triglycerides at TDF initiation. BMI was also higher in those with progression, although the finding was not significant.²¹ Fatty liver and hepatic steatosis in conjunction with the metabolic syndrome has been increasingly described in HIV-infected individuals in HIC. Currently there is a paucity of data on fatty liver in SSA, although the prevalence of obesity, dyslipidaemia and metabolic disorders such as diabetes is significantly increasing.^{26,27}

This study provides some of the first long-term data on liver fibrosis changes in this setting, and is unique because of the longer duration of follow-up and the interval between TE measurement than other studies. One limitation of this study is the lack of complete TE data at follow-up, which could have resulted in biased selection of the healthiest individuals in our analysis of the primary outcome. Although patients who underwent repeat TE were more likely to have higher BMIs and initiate ART than those who did not ($n=153$), they were also more likely to be HBV coinfecting. The use of TE in the longitudinal measurement of liver fibrosis changes has also not been properly evaluated during antiviral treatment in chronic HBV. Decreases in LSM in this context may be more reflective of declines of hepatic necroinflammation as a result of viral suppression rather than regression of liver fibrosis, early after ART initiation.^{28,29} This hypothesis may be supported by the finding of a significant decrease in the proportion of patients with ALT $\geq 2 \times$ upper limit of normal (ULN) (8.1% to 2%; $P=0.02$) during follow-up and robust declines in HIV viral load. However, some of these changes in LSM may still partially reflect fibrosis regression as demonstrated in a recent study by Wu *et al.*³⁰ Although LSM by TE performs well in staging liver fibrosis in HBV infection, there are fewer data in HIV/HBV coinfection, and various cut-offs for fibrosis stages have been proposed.³¹ Our more conservative cut-offs, which have been used in HIV/HBV-infected patients in other studies, may overestimate fibrosis in HIV-monoinfected patients; however, validated cut-offs have also yet to be determined in these patients.³² Inaccurate LSM has also been described in obese patients and in non-fasting patients.³³ TE was performed in our population regardless of fasting status, and because of cost constraints an XL probe was not used in 28 (15.8%) patients who were classified as obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). Finally, our cohort included primarily women and younger patients, which may impact generalizability, and some potential confounders were also not examined, including quantification of alcohol intake, coinfection with HDV and use of hepatotoxic medications or herbs, which are common in this setting.

In conclusion, LSM declines were observed in both HIV-infected and HIV/HBV-coinfected patients after initiation of ART,

demonstrating the beneficial effects of ART in this setting. Prompt ART initiation and virological control of HIV are important in protecting against further liver damage. HBV coinfection does not seem to negatively impact fibrosis regression in HIV-infected patients after ART initiation, despite being a risk factor for more advanced liver disease prior to therapy. The apparent association between lower BMIs and fibrosis regression may be the first indication that other non-viral factors, such as fatty liver disease, are contributing to liver damage in this setting, and warrants further investigation.

Acknowledgements

We are grateful to the patients and staff of the APIN-supported HIV Care and Treatment Centre at JUTH in Jos, Nigeria.

Funding

This work was supported by the Northwestern University AIDS International Training and Research Program Fogarty International Center/National Institutes of Health (grant # 5D43TW007995-03S1) and funding from the Program for African Studies, Northwestern University. This work was funded in part by the US Department of Health and Human Services, Health Resources and Services Administration (grant # U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with AIDS Prevention Initiative Nigeria (APIN) (grant # PS 001058).

Transparency declarations

None to declare.

Disclaimer

The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

References

- 1 National Agency for the Control of AIDS (NACA), Federal Government of Nigeria. *National Strategic Framework on HIV and AIDS: 2007-2021*. <https://www.childrenandaids.org/sites/default/files/2017-11/NATIONAL-HIV-AND-AIDS-STRATEGIC-FRAMEWORK.pdf>.
- 2 Lesi OA, Kehinde MO, Oguh DN *et al*. Hepatitis B and C virus infection in Nigerian patients with HIV/AIDS. *Niger Postgrad Med J* 2007; **14**: 129–33.
- 3 Ojide CK, Kalu EI, Ogbaini-Emevon E *et al*. Co-infections of hepatitis B and C with human immunodeficiency virus among adult patients attending human immunodeficiency virus outpatients clinic in Benin City, Nigeria. *Niger J Clin Pract* 2015; **18**: 516–21.
- 4 Thio CL, Seaberg EC, Skolasky R Jr *et al*. Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002; **360**: 1921–6.
- 5 Hawkins C, Christian B, Fabian E *et al*. Brief Report: HIV/HBV coinfection is a significant risk factor for liver fibrosis in Tanzanian HIV-infected adults. *J Acquir Immune Defic Syndr* 2017; **76**: 298–302.
- 6 Jaquet A, Wandeler G, Nouaman M *et al*. Alcohol use, viral hepatitis and liver fibrosis among HIV-positive persons in West Africa: a cross-sectional study. *J Int AIDS Soc* 2017; **19**: 214–24.
- 7 Ramírez-Mena A, Glass TR, Winter A *et al*. Prevalence and outcomes of hepatitis B coinfection and associated liver disease among antiretroviral

therapy-naïve individuals in a rural Tanzanian human immunodeficiency virus cohort. *Open Forum Infect Dis* 2016; **3**: ofw162.

8 Stockdale AJ, Phillips RO, Beloukas A et al. Hepatitis B Infection in Kumasi (HEPIK) Study Group. Liver fibrosis by transient elastography and virologic outcomes after introduction of tenofovir in lamivudine-experienced adults with HIV and hepatitis B virus coinfection in Ghana. *Clin Infect Dis* 2015; **61**: 883–91.

9 Hawkins C, Agbaji O, Ugoagwu P et al. Assessment of liver fibrosis by transient elastography in patients with HIV and hepatitis B virus coinfection in Nigeria. *Clin Infect Dis* 2013; **57**: e189–92.

10 Federal Ministry of Health. *National Guidelines for HIV Prevention, Treatment and Care. National AIDS and STIs Control Programme*. Abuja, Nigeria: Federal Ministry of Health, 2016.

11 Martín-Carbonero L, Teixeira T, Poveda E et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. *AIDS* 2011; **25**: 73–9.

12 Rinaldi L, Ascione A, Messina V et al. Influence of antiviral therapy on the liver stiffness in chronic HBV hepatitis. *Infection* 2018; **46**: 231–8.

13 Mialhes P, Pradat P, Chevallier M et al. Proficiency of transient elastography compared to liver biopsy for the assessment of fibrosis in HIV/HBV-coinfected patients. *J Viral Hepat* 2011; **18**: 61–9.

14 National HIV sero-prevalence sentinel survey among pregnant women attending antenatal clinics in Nigeria. *Technical report*. Department of Public Health National AIDS/STI Control Programme, 2010.

15 Sirisena ND, Njoku MO, Idoko JA et al. Carriage rate of hepatitis-B surface antigen (HBsAg) in an urban community in Jos, Plateau State, Nigeria. *Niger Postgrad Med J* 2002; **9**: 7–10.

16 Federal Ministry of Health. *National Guidelines for HIV and AIDS Treatment and Care in Adolescents and Adults*. Abuja, Nigeria: Federal Ministry of Health, 2010. http://www.who.int/hiv/pub/guidelines/nigeria_art.pdf.

17 WHO. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. *Recommendations for a Public Health Approach*. 2013. <http://www.who.int/hiv/pub/guidelines/arv2013/en/>.

18 Vinikoor MJ, Sinkala E, Chilengi R et al.; IeDEA-Southern Africa. Impact of antiretroviral therapy on liver fibrosis among human immunodeficiency virus-infected adults with and without HBV coinfection in Zambia. *Clin Infect Dis* 2017; **64**: 1343–9.

19 Audsley J, Robson C, Aitchison S et al. Liver fibrosis regression measured by transient elastography in human immunodeficiency virus (HIV)-hepatitis B virus (HBV)-coinfected individuals on long-term HBV-active combination antiretroviral therapy. *Open Forum Infect Dis* 2016; **12**: 3ofw035.

20 Gitau SN, Vinayak S, Silaba M et al. High prevalence of liver fibrosis in patients with human immunodeficiency virus monoinfection and human immunodeficiency virus hepatitis-B co-infection as assessed by shear wave

elastography: study at a teaching hospital in Kenya. *J Clin Imaging Sci* 2016; **6**: 22.

21 Boyd A, Bottero J, Mialhes P et al. Liver fibrosis regression and progression during controlled hepatitis B virus infection among HIV-HBV patients treated with tenofovir disoproxil fumarate in France: a prospective cohort study. *J Int AIDS Soc* 2017; **20**: 214–26.

22 Boyd A, Lacombe K. More long-term assessment of transient elastography is needed for HIV/hepatitis B virus-coinfected patients undergoing treatment with tenofovir. *Clin Infect Dis* 2016; **62**: 128–30.

23 Sullivan T. The implications of low absolute CD4 counts in patients with cirrhosis and human immunodeficiency virus. *Open Forum Infect Dis* 2016; **3**: ofw060.

24 Mohr R, Schierwagen R, Schwarze-Zander C et al. Liver fibrosis in HIV patients receiving a modern cART: which factors play a role? *Medicine (Baltimore)* 2015; **94**: e2127.

25 Kim N, Nance N, Van Rompaey S et al. Poorly controlled HIV infection is a risk factor for liver fibrosis in CNICS cohort. In: *Abstracts of the Twenty-Third Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 2016*. Abstract 558. Foundation for Retrovirology and Human Health, Alexandria, VA, USA. <http://www.croiconference.org/sessions/poorly-controlled-hiv-infection-risk-factor-liver-fibrosis-cnics-cohort>.

26 Sonderup MW, Wainwright HC. Human immunodeficiency virus infection, antiretroviral therapy, and liver pathology. *Gastroenterol Clin North Am* 2017; **46**: 327–43.

27 Hoffmann CJ, Hoffmann JD, Kensler C et al. Tuberculosis and hepatic steatosis are prevalent liver pathology findings among HIV-infected patients in South Africa. *PLoS One* 2015; **10**: e0117813.

28 Chang PE, Goh GB, Ngu JH et al. Clinical applications, limitations and future role of transient elastography in the management of liver disease. *World J Gastrointest Pharmacol Ther* 2016; **7**: 91–106.

29 Bachofner JA, Valli PV, Kroger A et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. *Liver Int* 2017; **37**: 369–76.

30 Wu SD, Liu LL, Cheng JL. Longitudinal monitoring of liver fibrosis status by transient elastography in chronic hepatitis B patients during long-term entecavir treatment. *Clin Exp Med* 2018; **18**: 433–43.

31 Friedrich-Rust M, Ong M-F, Martens S et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008; **134**: 960–74.

32 Morse CG, McLaughlin M, Proschan M et al. Transient elastography for the detection of hepatic fibrosis in HIV-monoinfected adults with elevated aminotransferases on antiretroviral therapy. *AIDS* 2015; **29**: 2297–302.

33 Myers RP, Pomier-Layrargues G, Kirsch R et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. *J Hepatol* 2012; **56**: 564–70.