Long-term changes in liver fibrosis in HIV and HIV/HBV infected Nigerians on ART

Jennifer Grant[1]; Oche Agbaji[2]; Muazu Muhammad[3]; Placid Ugoagwu[2]; Ifeanyi MacHenry[2]; Chloe Thio[4]; Patricia Agaba[3]; Robert Leo Murphy[1]; Claudia Hawkins[1]

[1]Division of Infectious Diseases, Northwestern University, Chicago, Illinois
[2]Department of Medicine, University of Jos and Jos University Teaching Hospital and [3]HIV Clinic, Jos University Teaching Hospital, Jos, Nigeria
[4]Johns Hopkins University, Baltimore, Maryland

NORTHWESTERN UNIVERSITY

#564

Background

- Chronic hepatitis B (HBV) is a major global health problem causing >600,000 annual deaths worldwide
- In Sub-Saharan Africa (SSA), approximately 8-25% of HIV-infected patients are co-infected with HBV
- In a recent cross sectional study we conducted in ART-naive HIV and HIV/HBV co-infected Nigerians, advanced liver fibrosis (liver stiffness measurement (LSM) ≥ 9.3 kPa) was present in 22% of HIV/HBV co-infected and 5% of HIV mono-infected patients, respectively
- Other studies from SSA have demonstrated similar findings, however data on the long-term effects of antiretroviral therapy (ART) on liver disease progression in these populations is lacking

Objectives

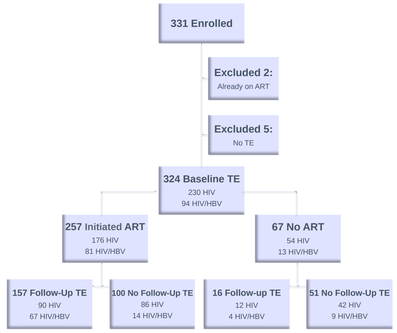
- To determine changes in liver fibrosis in HIV mono-infected and HIV/HBV co-infected Nigerians after initiation of HBV-active ART
- To assess HIV and HBV-related risk factors associated with liver fibrosis regression

Methods

- **Study design & population:**
  - Prospective cohort study of ART-naive HIV and HIV/HBV patients
  - Enrolled at Jos University Teaching Hospital (JUTH) from 7/2011 – 2/2012
  - Transient elastography (TE) at enrollment and at 36 months
  - ART initiation per GoN and WHO 2010 HIV treatment guidelines (updated 2013)
- **Inclusion criteria**: ≥18 years; HIV antibody–positive; ART-naïve; HCV antibody–negative; known hepatitis B surface antigen (HBsAg) status
- **Exclusion criteria**: decompensated liver disease and/or hepatocellular carcinoma
- **Clinical protocols:**
  - ART provided through Harvard PEPFAR/APIN program
  - ART: AZT or TDF + 3TC/FTC + NNRTI or PI; TDF + 3TC/FTC recommended in all HIV/HBV co-infected in 2012
  - Monthly scheduled clinic visits for ART refills; study visits annually
- **Data collection**:
  - Baseline demographics
  - CD4+ T-cell counts, HIV RNA, Hgb, platelets, AST (enrollment only), ALT, creatinine; HBV DNA, HBeAg and anti-Hbe (HIV/HBV co-infected)
  - HIV RNA: assay lower limit of detection (LLD) of 200 copies/mL (Roche Cobas AmpliPrepTaqMan, Roche Diagnostics GmbH, Mannheim, Germany)
  - HBV DNA: assay LLD of 116 copies/mL (Roche Cobas AmpliPrepTaqMan)
- **Outcome and definitions:**
  - TE cut-offs for METAVIR fibrosis stages: moderate fibrosis (F2) ≥ 5.9 kPa, advanced fibrosis (F3) ≥ 7.6 kPa, and cirrhosis (F4) ≥ 9.4 kPa
  - Fibrosis regression defined as a dichotomous outcome: decrease of ≥ 1 METAVIR fibrosis stage based on TE results (i.e. F4 → F3, etc.)
- **Statistical analysis**:
  - χ^2 or Fisher's Exact test (baseline categorical) and Mann-Whitney-U (baseline continuous); Related-samples marginal homogeneity test (repeated categorical) and Wilcoxan Signed Rank test (repeated continuous)
  - Univariate (UV) logistic regression (outcome = fibrosis regression)
  - Multivariable logistic regression for variables with p<0.20 in UV model (SPSS, v22.0; IBM, Armonk, NY)

Results

Figure 1: Study Flow Chart



Median time from baseline to follow-up TE: 33 (IQR 21-43) months
ART, antiretroviral therapy; **TE**, transient elastography

Table 1: Baseline Patient Characteristics

N (%) or Median (IQR)	HIV (N=230)	HIV/HBV (N=94)	*p*-value
Female	173 (75.2%)	57 (60.6%)	**0.01**
Age, years	35 (31-42)	33.5 (29-41)	0.28
BMI, kg/m^2	23.8 (20.4-27.3)	23.4 (30.1-26.1)	0.44
Alcohol use, yes	60 (26.2%)	25 (26.6%)	0.93
CrCl, ml/min	95.1 (74-120)	101.8 (84-122)	0.27
Platelet count (x100k/ul)	241 (188-291)	221 (175-303)	0.53
AST, IU/L	24 (19.5-31.5)	33 (24.5-42.5)	**<0.01**
ALT, IU/L	20 (14-34)	24 (16-38)	**0.04**
Hgb, g/dL	12 (11-13)	12 (11-13)	0.71
HIV RNA, log$_{10}$ copies/mL	4.6 (4-5.1)	4.8 (4.3-5.4)	0.06
CD4+ T-cells, cells/mm^3	385 (264-506)	265 (167-386)	**<0.01**
Initiated ART*	176 (76.5%)	81 (86.2%)	0.05
Initial ART regimen TDF + FTC/3TC + NNRTI AZT + 3TC+ NNRTI	55 (31.2%) 121 (68.8%)	66 (81.5%) 14 (17.3%)	**<0.01**
ART regimen at last visit TDF + FTC/3TC + NNRTI AZT + 3TC + NNRTI	76 (43.2%) 100 (56.8%)	75 (92.6%) 5 (6.2%)	**<0.01**
HBV DNA, log$_{10}$ IU/mL	-	1.6 (0-5.5)	-
HBV DNA ≥ 3.3 log$_{10}$ IU/mL**	-	31 (33%)	-
HBeAg Reactive	-	20 (21.3%)	-

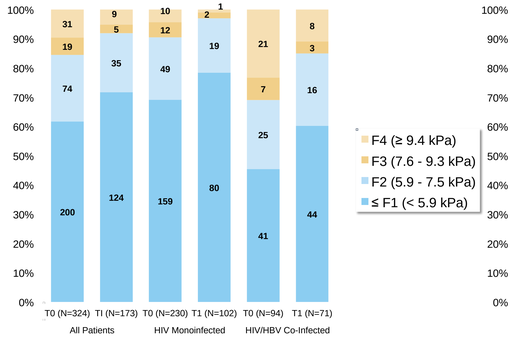
CrCl, creatinine clearance (via Cockcroft-Gault formula); **AST**, aspartate transaminase; **ALT**, alanine transaminase; **Hgb**, hemoglobin; **ART**, antiretroviral therapy; **TDF,** tenofovir; **FTC,** emtricitabine; **3TC**, lamivudine; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **AZT**, zidovudine; **HBeAg**, hepatitis B e-antigen
*ART initiated a median time of 2 months (IQR 0.6-8 mos) after initial TE
**Log$_{10}$3.3 = 2000 IU/mL

Table 2: Liver Stiffness at Baseline and Follow-Up

	HIV Monoinfected			HIV/HBV Co-infected		
	Baseline N=230	36 Months[§] N=102	*p*	Baseline N=94	36 Months[§] N=71	*p*
Median LSM (IQR), kPa	5.1 (4.4-6)	4.9 (4.1-5.8)	0.21	6.2 (4.7-8.7)	5.0 (4.1-6.6)	<0.01
Fibrosis Category[†] n, (%)						
None/Mild (F0/F1)	159 (69.1)	80 (78.4)		41 (43.6)	44 (62)	
Moderate (F2)	49 (21.3)	19 (18.6)	0.31	25 (26.6)	16 (22.5)	<0.01
Advanced (F3)	12 (5.2)	2.0 (2)		7 (7.4)	3 (4.2)	
Cirrhosis (F4)	10 (4.3)	1.0 (1)		21 (22.3)	8 (11.3)	

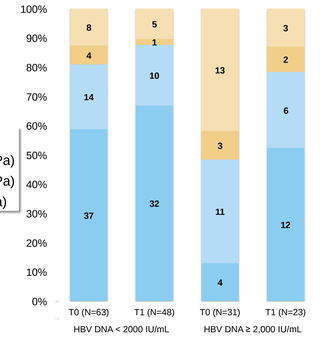
[§] Median time from baseline to follow-up TE of 34 months (IQR 33-36) in HIV and 31 months (IQR 28-33) in HIV/HBV, p <0.01. [†]F0/F1,<5.9 kPa; F2, 5.9-7.5 kPa; F3, 7.6-9.3 kPa; F4, ≥9.4 kPa
LSM, liver stiffness measurement

Figure 2a: Changes in liver fibrosis stage by HBV infection status



T0, baseline (study enrollment); **T1**, follow-up: median follow-up 33 months

Figure 2b: Changes in liver fibrosis stage by HBV DNA Level[§]



[§]HIV/HBV co-infected patients only

Table 3: Factors Associated with Fibrosis Regression

		Univariate Analysis		Multivariable Analysis*	
	Covariate**	**OR (95% CI)**	***p***	**aOR (95% CI)**	***p***
ALL PATIENTS	BMI (per 1 kg/m^2)	0.87 (0.80-0.95)	<0.01	0.86 (0.78-0.96)	0.01
	HBV positive (ref=negative)	3.26 (1.61-6.59)	<0.01		
	EtOH, yes (ref=no)	0.89 (0.42-1.9)	0.76		
	Baseline LSM, (per 1 kPa)	1.44 (1.23-1.68)	<0.01	1.41 (1.2-1.7)	<0.01
	HIV RNA (per 1 log$_{10}$ copies/mL)	0.83 (0.53-1.31)	0.43		
	CD4+T-cells <200 cells/mm^3 (ref=≥200)	0.5 (0.19-1.3)	0.16		
	ART duration (per 1 month)	1.03 (0.99-1.08)	0.11		
	HIV RNA <200 copies/mL at 36 mo (ref=≥200)	2.69 (1.05-6.92)	0.04	6.5 (1.7-24.3)	0.01
HIV/HBV[¥] PATIENTS	BMI (per 1 kg/m^2)	0.82 (0.71-0.93)	<0.01	0.76 (0.63-0.92)	0.01
	CD4+T-cells <200 cells/mm^3 (ref=≥200)	0.20 (0.05-0.78)	0.02	0.09 (0.02-0.55)	0.01
	HIV RNA <200 copies/mL at 36 mo (ref=≥200)	3.21 (0.94-11)	0.06	7.2 (1.3-37.5)	0.02

*Multivariate analysis adjusted for baseline LSM. **Variables are baseline, unless otherwise indicated. [¥]Other HBV-specific covariates assessed in HIV/HBV patients found to be not statistically significant (not shown) are HBV DNA at baseline and 36 months and HBeAg (+); **OR,** odds-ratio; **aOR**, adjusted odds-ratio; **BMI**, body-mass-index, **EtOH**, alcohol use, **LSM**, liver stiffness measurement, **ART**, antiretroviral therapy; **mo**, months.

Summary

- Improvements in median liver stiffness measurement (LSM) were observed in HIV mono- and HIV/HBV co-infected patients who had TE performed at enrollment and follow up
- The largest changes in LSM were observed in HIV/HBV co-infected patients and patients with higher LSM at baseline
- In multivariate analyses, after adjusting for baseline LSM:
  - HIV RNA < 200 copies/mL at 36 months was associated with a 6-7x higher odds of fibrosis regression
  - Higher BMI was associated with lower odds of fibrosis regression
  - In HIV/HBV patients, baseline CD4+ T-cell count <200 cells/mm^3 was strongly associated with a lower odds of fibrosis stage decline
  - HBV DNA levels and HBeAg status were *not* associated with fibrosis stage decline in HIV/HBV patients

Conclusions

- ART was associated with improvement in liver fibrosis scores in the majority of HIV/HBV co-infected and HIV mono-infected patients
- HBV co-infection 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
- Early ART initiation and virologic control of HIV are important in protecting against further liver damage
- The negative association between BMI and a decline in fibrosis stage may represent the presence of other non-viral factors contributing to liver disease i.e. nonalcholic fatty liver disease (NAFLD), and warrants further investigation

Acknowledgements

- 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 Asian Studies
- This work was funded in part by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with APIN (PS 001058). The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

References

- Miailhes 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(1): 61-9
- Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine **2012**; 30(12): 2212-9.
- Stabinski L, O'Connor S, Barnhart M, Kahn RJ, Hamm TE. Prevalence of HIV and hepatitis B virus co-infection in sub-Saharan Africa and the potential impact and program feasibility of hepatitis B surface antigen screening in resource-limited settings. J Acquir Immune Defic Syndr **2015**; 68 Suppl 3: S274-85.
- Stockdale AJ, Geretti AM. Chronic hepatitis B infection in sub-Saharan Africa: a grave challenge and a great hope. Trans R Soc Trop Med Hyg **2015**; 109(7): 421-2.
- World Health Organization (WHO). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva, Switzerland. March, 2015.

Division of Infectious Diseases, Northwestern University Feinberg School of Medicine; 645 N. Michigan Ave, Suite 900; Chicago, Illinois, 60611; ph: 312-695-5085, email: jennifer-grant@northwestern.edu