CHANGES IN LIVER STIFFNESS MEASUREMENT IN HIV AND HIV/HBV COINFECTED NIGERIANS

Patricia Agaba[1]; Ado Rivera[2]; Placid Ugoagwu[1]; Muazu Awal[1]; Jonathon Okpokwu[1]; Stephen MacHenry[1]; Godwin Imade[1]; Oche Agbaji[1]; Chloe Thio[3]; Robert Leo Murphy[4]; Claudia Hawkins[4]

[1]Department of Medicine, University of Jos and Jos University Teaching Hospital
[2]IPHAM Center for Education in Health Sciences, Northwestern University, Chicago, Illinois
[3] Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland4
[4]Division of Infectious Diseases, Northwestern University, Chicago, Illinois

NORTHWESTERN UNIVERSITY

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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 previous 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
- Data on the long-term effects of antiretroviral therapy (ART) on changes in non-invasive fibrosis markers in these populations is lacking

Objectives

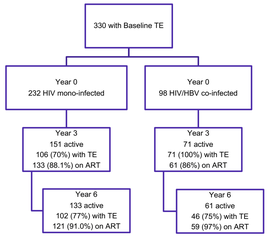
- To determine long-term changes (6 years) in TE score in HIV mono-infected and HIV/HBV co-infected Nigerians after initiation of HBV-active ART
- To assess HIV and HBV-related risk factors associated with ≥30% decline in TE scores

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, Year 3 and Year 6
  - 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:**
  - Liver stiffness measurement (LSM) 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 ≥30% decline in TE score
- **Statistical analysis**:
  - X^2 or Fisher's Exact test (baseline categorical) and Student t-test or Mann-Whitney-U (baseline continuous)
  - Univariate (UV) cox proportional hazards (CPH) regression (outcome = fibrosis regression) and Multivariable CPH regression for variables with p<0.20 in UV model (R 3.5.2)
  - Linear mixed effects model for assessing TE scores over time

Results

Figure 1: Study Flow Chart



ART, antiretroviral therapy; **TE**, transient elastography

Table 1: Baseline Patient Characteristics

Variable	Total	HIV (n = 232)	HIV/HBV (n = 98)	p-value
Age, years	36 (9.4)	36 (9.2)	35 (9.8)	0.42
Male (n,%)	**95 (28.8)**	**55 (23.7)**	**40 (40.8)**	**<0.01**
BMI, kg/m^2	24.38 (6.2)	24.62 (6.6)	23.82 (5.2)	0.29
Alcohol use, yes (n, %)	85 (25.8)	58 (25.0)	27 (27.6)	0.73
CrCl, ml/min	103.6 (43.1)	102.3 (42.6)	106.5 (44.1)	0.42
Platelet count (x100 k/ul)	247 (94.3)	246 (89.4)	248 (105.7)	0.85
ALT, IU/L	**35 (60.4)**	**29 (46.7)**	**48 (83.3)**	**0.01**
HgB, g/dL	12 (2.0)	12 (1.9)	12 (2.1)	0.95
HIV RNA, $\log_{10}$ copies/mL	4.61 (4.1, 5.1)	4.65 (4.0, 5.1)	4.81 (4.3, 5.3)	0.07
CD4+ T-cells/mm^3	**366 (196)**	**398 (200)**	**288 (163)**	**<0.01**
HBV DNA, $\log_{10}$ copies/mL	1.66 (0.00, 5.52)	-	1.66 (0.00, 5.52)	-
HBeAg reactive (n, %)	20 (6.1)	-	20 (20.4)	-
Liver stiffness measure (kPA)	**6.5 (5.5)**	**5.9 (5.3)**	**7.9 (5.7)**	**<0.01**
***ART regimen at initiation #TDF+FTC/3TC+NNRTI**	**122 (37.0)**	**55 (31.4)**	**67 (78.8)**	**<0.01**
AZT+3TC+NNRTI (n,%)	**138 (41.8)**	**120 (68.6)**	**18 (21.2)**	
ART duration (months)	40 (22,45)	39 (22, 45)	40 (23, 44)	0.84

All values median (IQR) unless specified
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
#154 (58.8%) of 262 on TDF+FTC/3TC containing regimen at last visit (Yr 6)

Table 2: Liver Stiffness at Baseline and Follow-Up

	HIV			HIV/HBV		
	Baseline N=232	Year 6[§] N=102	*p*	Baseline N=98	Year 6[§] N=46	*p*
Fibrosis Category[†] n, (%)						
None/Mild (F0/F1)	160 (69)	85 (83)		42 (43)	33 (72)	
Moderate (F2)	50 (22)	12 (12)	0.03	27 (28)	5 (11)	<0.01
Advanced (F3)	11 (5)	4 (4)		8 (8)	3 (7)	
Cirrhosis (F4)	11 (5)	1 (1)		21 (21)	5 (11)	

[§] Median time from baseline to follow-up TE of 36 months (IQR 0-73); HIV/HBV co-infected 34 (28-71), p =0.89
[†]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 2: Estimated Liver Stiffness Over Time by Co-infection status

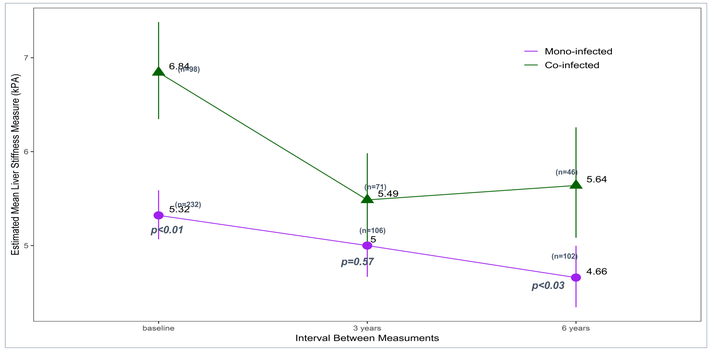


Table 3: Virologic outcomes at follow-up

	HIV		HIV/HBV	
	Year 3	Year 6	Year 3	Year 6
HIV virologic suppression (<200 copies/mL)*	76/102 (75%)	77/107 (72%)	50/70 (71%)	41/55 (75%)
HBV virologic suppression (<116 copies/mL)*	-	-	30/71 (42%)	38/45 (84%)

*n/N based on available viral load data at the time of analysis

Table 4: Factors associated with ≥30% LSM decline

	Odds Ratio (95% Confidence Interval)			
Covariate*	**Univariate analysis**		**Multivariate analysis**	
HBV positive (ref=negative)	2.11* (1.23 to 3.6)	0.007	1.18 (0.63 to 2.22)	0.609
Male vs. Female	1.55 (0.885 to 2.73)	0.125	0.89 (0.47 to 1.69)	0.728
BMI, per 1 kg/m^2	0.913 (0.856 to 0.973)	0.005	**0.93 (0.87 to 0.99)**	**0.035**
Baseline LSM, (per 1 kPa)	7.00 (4.43 to 11.3)	<0.001	**6.12 (3.0 to 11.3)**	**<0.001**
ART duration (per 1 month)	1.31 (0.59 to 2.91)	0.501	1.23 (0.54 to 2.79)	0.619
Alcohol, yes (ref=no)	1.17 (0.64 to 2.12)	0.611	096 (0.50 to 1.84)	0.891
HIV RNA (per 1 $\log_{10}$ copies/mL)	1.000 (0.998 to 1.001)	0.370	-	
CD4+T-cells <200 cells/mm^3 (ref=≥200)	1.28 (0.87 to 1.90)	0.213	-	

*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.

Conclusions

- Significant declines in LSM and equivalent Metavir liver fibrosis stage were observed in both HIV/HBV co-infected and HIV mono-infected subjects following ART initiation, corresponding with high rates of HBV and HIV virologic control.
- Although co-infection with HBV did not seem to negatively impact LSM changes after ART initiation, HIV/HBV co-infected subjects were observed to have higher mean LSM compared to HIV mono-infected throughout follow-up, reiterating the need for close monitoring of liver outcomes in this population.
- The apparent increase in LSM after year 3 among HIV/HBV co-infected subjects is concerning, and similar to that observed in a recent study of HIV/HBV co-infected subjects from France during a median of 39 months on TDF-containing ART. Further follow-up is needed to evaluate the long-term trajectory of LSM changes in this setting and how it impacts risk of liver complications.
- The negative association between BMI and ≥30% LSM decline may represent the presence of other non-viral factors (ie. nonalcholic fatty liver disease (NAFLD) and/or other metabolic abnormalities) that are contributing to liver disease and warrants further investigation

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