Changes in fibrosis liver scores using AST to Platelet Ratio Index (APRI) after antiviral therapy initiation in Tanzanian adults with HIV, HBV and HIV/HBV co-infection

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Background

- In Sub-Saharan Africa (SSA), 8-25% of persons living with HIV (PLH) are co-infected with chronic hepatitis B (HBV), which is associated with an increased risk of mortality and advanced liver disease compared to mono-infected individuals.
- Little is known about liver fibrosis progression in co-infected patients living in Sub-Saharan Africa treated with antiviral therapy.
- Although liver biopsy is the gold standard method for assessment of liver fibrosis, this is not widely available in low resource settings such as SSA.
- APRI-scores can be used as a surrogate for liver fibrosis which instead rely on routinely collected labs.

Research Objectives

- Compare liver disease progression as assessed by APRI-4 fibrosis scores in HIV, HIV/HBV, and HBV Tanzanians after initiation of HBV-active therapy over three years
- Examine predictors associated with 30% decline in APRI score

Methods

- **Study Design and Population:** Subjects enrolled between 9/2013 and 4/2015 into a longitudinal cohort study of liver disease in HIV, HBV and HIV/HBV co-infection at Management and Development for Health (MDH) supported HIV and HBV clinics in Dar es Salaam, Tanzania were included in this study. Subjects were followed to 36 months at annual study visits, until 4/18.
- **Clinical Protocols:** At each study visit, a comprehensive history and examination and study laboratory testing was performed. HIV mono-infected and HIV/HBV co-infected subjects received tenofovir, lamivudine, and efavirenz (TLE) at study entry. All HBV mono-infected subjects received lamivudine at enrollment and switched to tenofovir disoproxil fumarate (TDF) 1 to 2 years after enrollment when it became available in Tanzania. Laboratory testing included: hemoglobin, platelets, aspartate aminotransferase (AST), Alanine aminotransferase (ALT), creatinine (Roche Cobas Integra® 400+ Analyser), HBeAg/anti-HBe (EIA assay Cobas e411), HBV DNA (COBAS® Ampliprep Taqman 96, v2.0, Roche Diagnostics GmbH, Mannheim, Germany; lower limit of detection (LLD) of 20 IU/mL).
- **Outcome and Definitions:** Liver fibrosis was measured using AST to Platelet Ratio Index (APRI).
- **Statistical Analysis:** Demographics were each described as proportions of the total cohort. Baseline characteristics were characterized using median values and interquartile ranges. APRI at 12, 24, and 36-month follow-up visits were modelled using mixed effects models.
- APRI was defined as [100 X (AST/upper limit of normal)/platelet count (10^9/l)].

Table 1. Baseline characteristics of the study population

Characteristic	All patients (n=489)	HIV/HBV co-infected (n=61)	HBV mono-infected (n=156)	HIV mono-infected (n=272)	P value
Male (%)	209 (42.8)	27 (45.0)	104 (66.7)	78 (28.7)	<0.001
Age, median (IQR)	36 (10)	37 (12)	33 (9)	39 (10)	<0.001
BMI, median (IQR)	23.5 (5.0)	22.4 (4.3)	25.3 (4.8)	22.7 (5.0)	<0.001
Platelets 10^9/L, median (IQR)	277.8 (114.4)	264.6 (128.0)	225.9 (59.3)	309.5 (123.5)	<0.001
AST IU/L, median (IQR)	45.9 (133.40)	51.6 (67.5)	66.9 (227.66)	32.4 (28.8)	0.034
ALT IU/L, median (IQR)	36.6 (129.3)	33.2 (47.6)	63.7 (223.1)	21.8 (19.1)	0.005
APRI, median (IQR)					
Baseline	0.56 (1.71)	1.00 (2.60)	0.77 (2.47)	0.35 (0.50)	0.007
Year 1	0.33 (0.22)	0.32 (0.25)	0.34 (0.16)	0.32 (0.25)	0.643
Year 2	0.32 (0.26)	0.29 (0.18)	0.36 (0.32)	0.30 (0.23)	0.092
Year 3	0.31 (0.20)	0.30 (0.18)	0.33 (0.17)	0.30 (0.21)	0.297
HIV suppressed (<LLD) (%)					
Baseline	4 (1.3)	3 (5.5)	n/a	1 (0.4)	0.026
Year 1	155 (64.3)	33 (75.0)	n/a	122 (61.9)	0.121
Year 2	170 (82.1)	28 (87.5)	n/a	142 (81.1)	0.497
Year 3	173 (85.2)	25 (89.3)	n/a	148 (84.6)	0.714
Baseline CD4, median (IQR)	240.79 (177.3)	258.8 (209.8)	n/a	237.2 (170.3)	0.448
HBV suppressed (<LLD) (%)					
Baseline	49 (22.8)	18 (30.0)	31 (20.0)	n/a	0.166
Year 1	138 (80.2)	35 (81.4)	103 (79.8)	n/a	1
Year 2	120 (82.8)	29 (82.9)	91 (82.7)	n/a	1
Year 3	115 (89.8)	26 (100.0)	89 (87.3)	n/a	0.120

ALT = alanine aminotransferase, AST = aspartate aminotransferase, APRI = AST to platelet ratio index, LLD = lower limit of detection, HBV = hepatitis B virus, IQR = interquartile range

Table 2: Multivariate logistic regression model showing factors associated with 30% or more decline in APRI relative to baseline (Year 0)

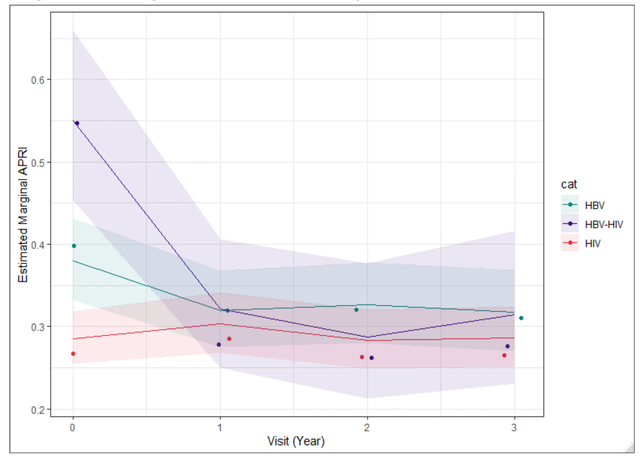
Predictor	OR	95% CI (LL, UL)	P value
Time on ART	1.30	1.10, 1.55	<0.001
HBV-HIV vs. HBV	4.10	1.88, 8.92	<0.001
HIV vs. HBV	1.569881	0.85, 2.89	0.148
Age	0.968507	0.94, 0.99	0.014
Sex (male vs. female)	0.525187	0.31, 0.89	0.017
BMI	1.015316	0.98, 1.05	0.429
Alcohol consumption (any) Yes vs. no	0.593333	0.27, 1.29	0.188

Variables included at univariate level
OR = odds ratio, CI = confidence intervals, LL = lower limit, UL = upper limit

Results

- Significant differences in APRI scores were observed at baseline between the three groups, HIV, HBV, and HIV/HBV co-infected, respectively. Overall APRI scores were low in all three subject groups.
- Declines in APRI were significant from baseline to year 1 in HBV mono-infected and HIV/HBV co-infected subjects; at the end of follow up there were no significant differences between APRI scores in any of the groups.
- Older age and male sex were significantly associated with lower odds of a ≥30% decline in APRI during follow-up while HIV/HBV coinfection was associated with a higher odds of a ≥30% decline in APRI in multivariable analysis

Figure 1. Changes in APRI over time by status



Limitations

- APRI scores are not perfect measures of fibrosis and are only a screening tool. Low scores do not completely rule out the possibility of advanced fibrosis in a subset of patients.
- Falsely elevated AST can occur for other reasons than liver fibrosis such as ART toxicity, immune reconstitution, or muscle damage.
- Similarly low platelets can occur for other reasons in HIV patients such as advanced immune-suppression prior to ART, other infections, and drugs.

Conclusions

- In this cohort, antiviral therapy improved APRI scores similarly across all cohorts. These declines all likely reflect decreases in viral associated inflammation, rather than changes in fibrosis per se.
- HBV-HIV co-infection does not appear to negatively impact initial changes in APRI score in response to treatment in the short term
- In other cohorts, co-infection has been shown to be associated with increased mortality and advanced liver disease even among those on ART. Further follow up is needed to assess changes in APRI long-term and whether the low APRI scores achieved after initial declines on treatment are sustained.

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