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Liver inflammation is common and linked to metabolic derangements in treated HIV

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The A5322 (HAILO) Study

ACTG AIDS CLINICAL TRIALS GROUP

Background and Objectives

- Abnormal serum liver enzymes in people with HIV (PWH) are common and frequently unexplained
- Nonalcoholic fatty liver disease (NAFLD) and drug toxicity are possible etiologies
- Previous studies suggest the prevalence of NAFLD is 13-67% in HIV cohorts and up to >70% amongst PWH who have unexplained transaminase elevation

Objectives:

- **To determine the prevalence of and reasons for hepatic transaminase elevation in a cohort of adults with treated HIV without hepatitis B or C virus infection or heavy alcohol use**

Study Design and Statistical Analysis

Study Design: Analysis of the longitudinal, observational AIDS Clinical Trials Group (ACTG) HAILO cohort (A5322)

- Prospectively, clinical outcomes, medications, plasma HIV-1 RNA, collected every 24 weeks; CD4 cell count, CBC, chemistries, LFTs, fasting blood glucose and lipids every 48 wks; HBV and HCV serologies every 96 weeks
- Self-administered survey of past 30 days of alcohol use every 48 weeks. Alcohol use defined as:
  - Binge = Men: 5+ drinks/2 hours; Women 4+/2 hours
  - Heavy = Men: >14 drinks/week; Women: >7; or binging
  - Moderate = Men: 7-14 drinks/week; Women: 3-7; no binging
  - Light = Men: <7 drinks/week; Women: <3/week; no binging
  - Abstainer = 0 drinks/week

Exclusion Criteria: Heavy alcohol use, anti-HCV Ab+, HBsAg+

Transaminase elevation defined as:
- Alanine aminotransferase (ALT) >30 U/L for men, >19 for women
- Aspartate aminotransferase (AST) >36 for men, >30 for women

Outcomes:
1) ≥1 elevated AST or ALT during follow-up (PRIMARY)
2) ≥2 consecutive elevated AST or ALT during follow-up
3) No ALT or AST elevation

Hepatic Steatosis Index (HIS) = 8 x (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus)

Metabolic Syndrome (MetS) = 3 or more of the following:
- Waist circumference >102cm for men or >88cm for women
- Blood pressure >130/85 or drug treatment for hypertension
- Fasting triglyceride level ≥150 mg/dL
- Fasting HDL <40 mg/dL (men) or <50 mg/dL (women)
- Fasting blood glucose ≥100 mg/dL or diabetes

NAFLD Fibrosis Score = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

ASCVD risk score: Defined as in Goff et al, Circulation 2014

Statistical Analysis: Chi-square and Wilcoxon tests to compare characteristics between persons with and without elevated AST or ALT. Multiple logistic regression models included covariates with p<0.10 in univariate analysis.

Figure 1: Cohort Selection and AST/ALT Characterization

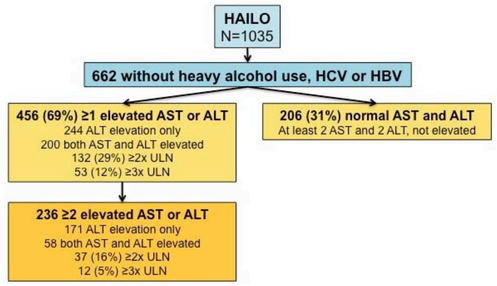


Table 1: Baseline Characteristics by AST/ALT Elevation

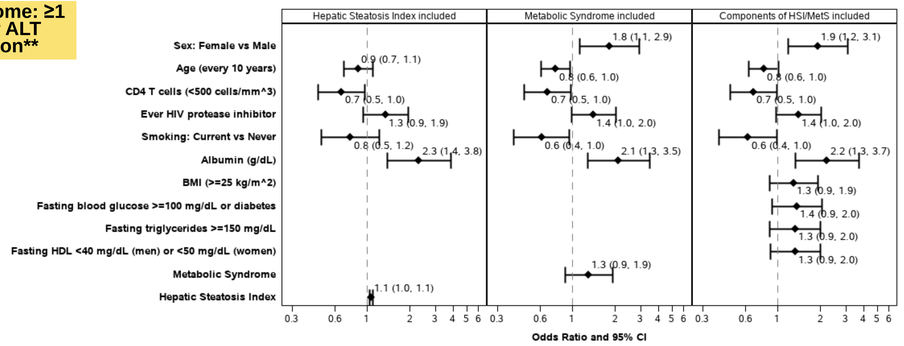
Characteristic (at entry)	No elevation (N=206)	≥1 elevation (N=456)	P-value
Age (years)	**52 (47, 58)**	**50 (45, 56)**	**0.04***
Sex: Male	**173 (84%)**	**351 (77%)**	**0.04****
Race/Ethnicity: White	**114 (55%)**	**226 (50%)**	**0.03****
Black	**62 (30%)**	**122 (27%)**	
Hispanic	**24 (12%)**	**92 (21%)**	
Other	**6 (3%)**	**10 (2%)**	
Body mass index (kg/m²)	**26.9 (23.3, 30.9)**	**27.8 (24.7, 31.5)**	**0.01***
Waist circumference (cm)	96.3 (86.8, 104.9)	96.1 (89.6, 105.0)	0.15*
On lipid lowering meds: Yes	**74 (36%)**	**208 (46%)**	**0.02****
Statins	49 (24%)	149 (33%)	--
Diabetes	**15 (7%)**	**63 (14%)**	**0.02***
Hypertension treatment or BP >130/85	118 (57%)	273 (60%)	0.53**
Drinking Category: Abstainer	98 (48%)	208 (46%)	0.88**
Light Drinker	92 (45%)	213 (47%)	
Moderate Drinker	16 (8%)	35 (8%)	
Ever cocaine	164/205 (80%)	360/454 (79%)	0.71**
Smoking: Current	52 (25%)	81 (18%)	0.08**
Prior	61(30%)	154 (34%)	
Never	93 (45%)	221 (48%)	
CD4 nadir (cells/mm³)	191 (62, 287)	197 (67, 300)	0.70*
CD4 at entry (cells/mm³)	**589 (448, 803)**	**634 (470, 858)**	**0.04***
HIV RNA <200 copies/mL	196 (95%)	431 (95%)	0.74**
Current ARV regimen (yes/no)			
PI	70 (34%)	176 (39%)	0.26**
r/LPV	2	12	--
r/ATV	44	89	--
r/DRV	22	57	--
INSTI	48 (23%)	92 (20%)	0.36**
NNRTI	93 (45%)	209 (46%)	0.87**
Efavirenz	79	176	--
Ever d4T, AZT or ddI	78 (38%)	192 (42%)	0.30**
Ever PI	124 (60%)	307 (67%)	0.08**
Cumulative d4T or ddI exposure (years)	0 (0, 0)	0 (0,0)	NS
Cumulative AZT (years)	0 (0, 2.2)	0 (0, 3.5)	0.17*
Years since ART initiation	7.80 (4.50, 11.90)	8.15 (4.60, 12.35)	0.48*
AST (U/L)	20 (17, 24)	26 (22, 33)	<0.001*
ALT (U/L)	19 (14, 23)	31 (22, 41)	<0.001*
Alkaline phosphatase (U/L)	**77 (63, 99)**	**83 (67, 102)**	**0.03***
Platelets (x10⁹)	224 (196, 226)	227 (192, 266)	0.65*
Albumin (g/dL)	**4.4 (4.2, 4.6)**	**4.5 (4.2, 4.7)**	**0.01****
Hemoglobin A1c (%)	5.5 (5.2, 5.8)	5.5 (5.3, 6.0)	0.09*
Estimated GFR by CKD-EPI	**89 (74, 101)**	**92 (79, 104)**	**0.02***
Fasting cholesterol (mg/dL)	182 (163, 202)	190 (162, 216)	0.06*
Fasting triglycerides ≥150 mg/dL	**62 (30%)**	**196 (43%)**	**<0.01****
Fasting HDL <40 (men) or <50 mg/dL (women)	**57 (28%)**	**165 (36%)**	**0.03****
Fasting glucose ≥100 mg/dL or pre-diabetes	**49 (24%)**	**146 (32%)**	**0.03****
Fasting LDL (mg/dL)	107 (89, 127)	109 (89, 130)	0.34*
Metabolic Syndrome	**58 (28%)**	**164 (36%)**	**<0.05****
Hepatic Steatosis Index	**34.72 (30.36, 39.04)**	**38.34 (34.36, 42.56)**	**<0.001***
<30	**42 (20%)**	**37 (8%)**	**<0.001***
≥36	**82 (40%)**	**300 (66%)**	**<0.001***
NAFLD Fibrosis Score	**-1.646 (-2.454, -1.090)**	**-1.979 (-2.646, -1.199)**	**0.02***
<-1.455	**121 (59%)**	**313 (69%)**	**0.01****
>0.675	7 (3%)	10 (2%)	0.36**
ASCVD Risk Score (%)	5.6 (3.1, 10.4)	4.7 (2.4, 8.9)	0.09*

*Wilcoxon test; **Chi-square test; Significant differences bolded.

No differences between groups in history of cocaine use or use of glucocorticoids, diabetes medications, antifungal therapy, NSAIDs, testosterone/anabolic steroids, progesterone/progestin, estrogen, acetaminophen. **Similar findings restricting comparison to ≥2 consecutive elevated AST or ALT vs no elevation, with additional findings of lower frequency of r/PI use (p=0.030) and hypertension treatment or BP>130/85 (p=0.046), and greater cumulative AZT exposure (p=0.040) in the AST/ALT elevation group; metabolic differences were strengthened.**

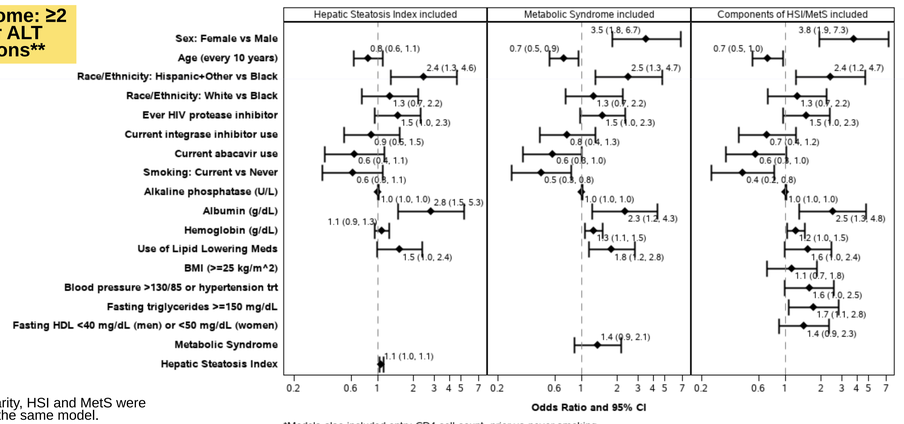
Figures 2A and 2B: Independent Predictors of Transaminase Elevation

2A. Outcome: ≥1 AST or ALT elevation**



*Models also included race/ethnicity, prior vs never smoking, lipid lowering meds, hyperlipidemia, and alkaline phosphatase.

2B. Outcome: ≥2 AST or ALT elevations**



*Models also included entry CD4 cell count, prior vs never smoking.

**Given collinearity, HSI and MetS were not included in the same model.

Conclusions

- **Liver enzyme elevation in the absence of HCV infection, chronic HBV infection, or heavy alcohol use is very common (two-thirds by single elevation, one-third by two consecutive elevations) in this PWH cohort, suggesting a high rate of untreated liver injury/inflammation**
- **Transaminase elevation is associated with female sex, Hispanic ethnicity, higher CD4 and albumin levels, elevated triglycerides, and elevated blood pressure, consistent with findings from other studies of demographic and metabolic associations with NAFLD**
- **The CD4 association was lost with a stricter definition of AST/ALT elevation (2+ elevations), suggesting metabolic abnormalities are a stronger driver of liver disease development than HIV-related factors, but it is unknown if HIV-related variables (e.g. ART effects) may mediate metabolic dysregulation**
- **Higher Hepatic Steatosis Index was consistently associated with transaminase elevation, suggesting NAFLD may be a common cause of liver inflammation in PWH receiving suppressive ART**
- **The diagnosis of NAFLD in our cohort is limited given the absence of imaging or biopsy**
- **Future research is needed to understand the contribution of NAFLD and other mechanisms of liver injury in PWH on suppressive ART, and design interventions to reduce liver injury and liver-associated complications**

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