EASL Biomarkers Differ in Predicting NAFLD, NASH, & Fibrosis in HIV(+)/(–) Individuals

Ricky Hsu[1,2], Laurence Brunet[3], Jennifer Fusco[3], Gregory Fusco[3]

[1]NYU Langone Medical Center, New York, NY, USA; [2]AIDS Healthcare Foundation, New York, NY, USA; [3]Epividian, Durham, NC, USA

Contact Information:
Ricky Hsu, MD
AIDS Healthcare Foundation - Northern US Medical Director
352 7th Ave., Suite 1205, New York, NY 10001
p: 212-627-7560
@: ricky.hsu@aidshealth.org

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Background

- Non-alcoholic fatty liver disease (NAFLD): Steatosis in >5% of hepatocytes[1]
  - 20-73% of HIV(+) individuals[2,3]
  - 20-38% of the U.S. population[4,5]
- Non-alcoholic steatohepatitis (NASH): Wide spectrum of disease severity (inflammation, fibrosis, cirrhosis, hepatocellular carcinoma)[1]
  - 20-40% of HIV(+) individuals with NAFLD[3]
  - 15-30% of the U.S. population with NAFLD[4,5]
- NAFLD progressing to NASH is a leading cause of both cirrhosis and liver transplantation[1,6]

OBJECTIVE

To compare biomarker-based risk scores composed of commonly run laboratory markers with high sensitivity and specificity for identifying NAFLD, NASH, and fat-induced liver fibrosis over 3 calendar periods in a large U.S. cohort of HIV(+) and HIV(–) individuals

Methods

Study population

- OPERA cohort: Prospectively captured, routine clinical data from electronic health records in the US (84 clinics, 17 states, 1 US territory, ~7% of HIV(+) people in care in the US)
- HIV(+) and HIV(–) individuals in the OPERA Database for whom all 6 scores [Table 1] could be calculated during at least one of the 3-year calendar periods of interest (2006-2008, 2011-2013, 2016-2018)
- No diagnoses of viral hepatitis, celiac disease, sclerosing cholangitis, or alcohol abuse

Table 1. Fatty liver disease scores used to identify NAFLD, NASH, and liver fibrosis[1]

Dx	Score	Cut-off	Equation
NAFLD	HSI NAFLD	> 36	(8 x ALT/AST) + BMI [kg/m²] + T2DM[†] [yes=2, no=0] + sex [female=2, male=0]
	NAFLD Liver Fibrosis	> –1.455	–1.675 + (0.037 × Age) + (0.094 × BMI [kg/m²]) + (1.13 × IFG or diabetes[‡] [yes=1, no=0]) + (0.99 × AST/ALT) – (0.013 × platelets [10⁹/L]) – (0.66 × albumin [g/dL])
NASH	Modified* HAIR	≥2	HTN[§] [yes=1, no=0] + ALT [≥27 IU/L=1, <27 IU/L=0] + HbA1c [>5.7=1, ≤5.7=0]
	Campos NASH	≥5	HTN[§] [yes=1, no=0] + T2DM[†] [yes=1, no=0] + AST [≥27 IU/L=1, <27 IU/L=0] + ALT [≥27 IU/L=1, <27 IU/L=0] + sleep apnea [yes=1, no=0] + race [black=0, non-black=2]
Liver Fibrosis	Fib-4 Index	> 2.67	(Age × AST [U/L]) / (platelets [10⁹/L] × (ALT [U/L])[½])
	NAFLD Liver Fibrosis	> 0.675	–1.675 + (0.037 × Age) + (0.094 × BMI [kg/m²]) + (1.13 × IFG or diabetes[‡] [yes=1, no=0]) + (0.99 × AST/ALT) – (0.013 × platelet [10⁹/L]) – (0.66 × albumin [g/dL])

*Lower ALT threshold[7] and HbA1c instead of insulin resistance index due to data availability
[†]T2DM is defined a HbA1c > 6.5 or a diagnosis of type-2 diabetes mellitus (T2DM) or anti-diabetic medications
[‡]Impaired fasting glucose (IFG)/diabetes is defined as a HbA1C > 5.7 or a diagnosis of T2DM or anti-diabetic medications
[§]Hypertension (HTN) defined as blood pressure of 140/90 or greater or a diagnosis of HTN

Analyses

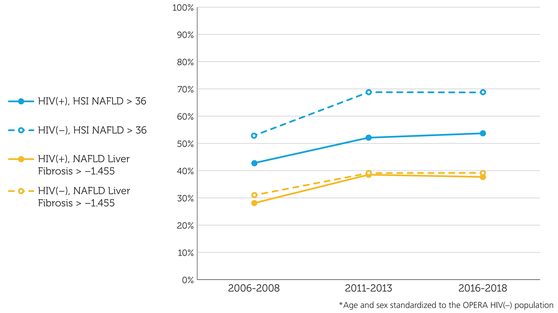
- Scores calculated for every available ALT measurement
  - Albumin, AST, platelet, HbA1c: closest to and up to 365 days prior to the ALT measurement
  - T2DM, HTN, Sleep apnea: if diagnosed at any time prior to the ALT measurement
- Average scores over each calendar period to mitigate outliers
- Period prevalence of NAFLD, NASH, and liver fibrosis estimated with each score
  - Age and sex standardized to the OPERA HIV(–) population
  - Difference in prevalence between HIV(+) and HIV(–) populations

Results

Table 2. Sex and age distribution by calendar period in the HIV(+) and HIV(–) populations

Period	Sex	Age	HIV(+), n (%)	HIV(–), n (%)
2006-2008	Overall	Overall	7,583 (100)	1,645 (100)
	Male	≤25	532 (7.0)	108 (6.6)
		26-49	4,925 (64.9)	687 (41.8)
		≥50	837 (11.0)	289 (17.6)
	Female	≤25	97 (1.3)	51 (3.1)
		26-49	950 (12.5)	237 (14.4)
		≥50	242 (3.2)	273 (16.6)
2011-2013	Overall	Overall	25,347 (100)	65,903 (100)
	Male	≤25	2,662 (10.5)	3,072 (4.7)
		26-49	13,496 (53.2)	13,973 (21.2)
		≥50	4,412 (17.4)	10,000 (15.2)
	Female	≤25	395 (1.6)	5,243 (8.0)
		26-49	3,068 (12.1)	18,851 (28.6)
		≥50	1,314 (5.2)	14,764 (22.4)
2016-2018	Overall	Overall	46,229 (100)	100,699 (100)
	Male	≤25	6,165 (13.3)	5,083 (5.0)
		26-49	21,761 (47.1)	19,727 (19.6)
		≥50	9,571 (20.7)	17,587 (17.5)
	Female	≤25	718 (1.6)	8,418 (8.4)
		26-49	5,211 (11.3)	25,895 (25.7)
		≥50	2,803 (6.1)	23,989 (23.8)

Figure 1. Standardized* NAFLD period prevalence



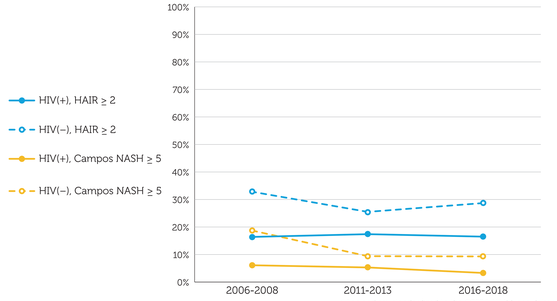
*Age and sex standardized to the OPERA HIV(–) population

Table 3. Standardized* NAFLD period prevalence and prevalence difference (%, 95% CI)

Measure	Period	Prevalence, HIV(+)	Prevalence, HIV(–)	Difference
HSI NAFLD score > 36	2006-2008	42.8 (41.4, 44.3)	52.9 (50.6, 55.3)	**–10.1 (–12.9, –7.4)**
	2011-2013	52.1 (51.2, 52.9)	68.8 (68.5, 69.2)	**–16.8 (–17.7, –15.8)**
	2016-2018	53.7 (53.1, 54.3)	68.7 (68.4, 69.0)	**–15.0 (–15.7, –14.3)**
NAFLD Liver Fibrosis score > -1.455	2006-2008	28.1 (26.7, 29.4)	31.0 (29.2, 32.8)	**–2.9 (–5.2, –0.7)**
	2011-2013	38.5 (37.6, 39.4)	39.1 (38.8, 39.4)	–0.6 (–1.5, 0.3)
	2016-2018	37.7 (37.1, 38.3)	39.2 (39.0, 39.5)	**–1.5 (–2.2, –0.8)**

*Age and sex standardized to the OPERA HIV(–) population

Figure 2. Standardized* NASH period prevalence



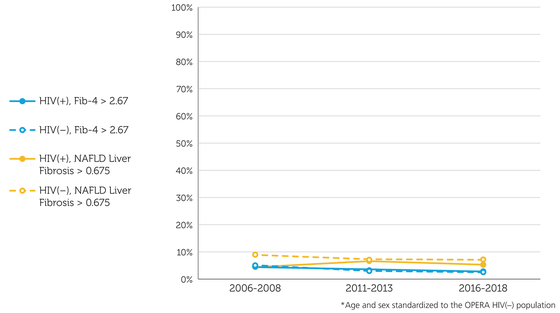
*Age and sex standardized to the OPERA HIV(–) population

Table 4. Standardized* NASH period prevalence and prevalence difference (%, 95% CI)

Measure	Period	Prevalence, HIV(+)	Prevalence, HIV(–)	Difference
HAIR score ≥ 2	2006-2008	16.4 (15.5, 18.0)	32.8 (30.7, 34.9)	**–16.0 (–18.5, –13.6)**
	2011-2013	17.4 (16.7, 18.2)	25.5 (25.2, 25.8)	**–8.0 (–8.8, –7.3)**
	2016-2018	16.5 (16.0, 17.0)	28.7 (28.4, 28.9)	**–12.2 (–12.7, –11.6)**
Campos NASH score ≥ 5	2006-2008	6.1 (5.3, 6.8)	18.7 (16.9, 20.6)	**–12.7 (–14.7, –10.7)**
	2011-2013	5.3 (4.9, 5.6)	9.4 (9.2, 9.6)	**–4.1 (–4.6, –3.7)**
	2016-2018	3.3 (3.1, 3.6)	9.3 (9.1, 9.5)	**–6.0 (–6.2, –5.7)**

*Age and sex standardized to the OPERA HIV(–) population

Figure 3. Standardized* liver fibrosis period prevalence



*Age and sex standardized to the OPERA HIV(–) population

Table 5. Standardized* liver fibrosis period prevalence and prevalence difference (%, 95% CI)

Measure	Period	Prevalence, HIV(+)	Prevalence, HIV(–)	Difference
FIB-4 index > 2.67	2006-2008	4.4 (3.7, 5.2)	5.1 (4.1, 6.1)	–0.7 (–2.0, 0.6)
	2011-2013	3.6 (3.3, 4.0)	3.0 (2.9, 3.2)	**0.6 (0.2, 1.0)**
	2016-2018	2.8 (2.6, 3.1)	2.5 (2.5, 2.6)	**0.3 (0.0, 0.6)**
NAFLD Liver Fibrosis score > 0.675	2006-2008	4.4 (3.7, 5.4)	8.9 (7.6, 10.2)	**–4.4 (–5.9, –2.8)**
	2011-2013	6.6 (6.0, 7.1)	7.3 (7.1, 7.5)	**–0.7 (–1.3, –0.2)**
	2016-2018	5.3 (5.00, 5.7)	7.1 (6.9, 7.2)	**–1.7 (–2.1, –1.4)**

*Age and sex standardized to the OPERA HIV(–) population

Discussion

- Age and sex distribution differed greatly between HIV(+) and HIV(–)
- After age/sex standardization in HIV(+) persons
  - NAFLD prevalence increased over calendar periods (HSI NAFLD score: 43% to 54%; NAFLD Liver Fibrosis score: 28% to 38%)
  - NASH prevalence remained stable over calendar periods (Modified HAIR score: 16% to 17%; Campos NASH score: 3% to 6%)
  - Fibrosis prevalence remained stable over calendar periods (FIB-4: 3% to 4%; NAFLD Liver Fibrosis score 4% to 7%)
- HIV(+) persons had a lower standardized prevalence of NAFLD and NASH than HIV(–) persons at most time points with either score
- Study population restricted to those with all 6 scores calculated within a calendar period
  - Likely disproportionally included individuals at higher risk of fatty liver disease
  - HIV(+) persons were much more likely to have all biomarkers required for the 6 tests (>80%) than the HIV(–) persons (<25%)
  - Likely overestimated the true prevalence especially among those without HIV
- Despite similar published predictive values among biomarker-based risk scores, calculated prevalence of NAFLD, NASH and liver fibrosis differed markedly across scores in a large, clinic-based population, particularly with NAFLD risk prediction estimates
- Further clinical validation of these scores is required before broad utilization in the staging of fatty liver disease

KEY FINDINGS

- After age/sex standardization in HIV(+) persons, NAFLD prevalence increased from 2006 to 2018 while NASH and fibrosis prevalence remained stable
- HIV(+) persons had a lower standardized prevalence of NAFLD and NASH than HIV(–) persons at most time points with either score; this could be an artifact of testing frequency required to calculate scores that were more readily performed on the HIV(+) population (>80%) and only performed on HIV(–) individuals with comorbidities requiring testing (<25%)
- Further clinical validation of these liver biomarker scores, perhaps by liver biopsy or MRI elastography, is required before broad utilization in the staging of fatty liver disease

References

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