NAFLD IS COMMON AND ASSOCIATED WITH CARDIOVASCULAR RISK IN REPRIEVE PARTICIPANTS

Carl J. Fichtenbaum, MD[1] Heather J. Ribaudo, PhD[2], Jana Taron, MD[3], Jorge Leon-Cruz, MS[2], Netanya S. Utay, MD[4] Ken S. Ho, MD, MSc[5], Anne F. Luetkemeyer, MD[6], Shobha Swaminathan, MD[7], Carrie D. Johnston, MD, MSc[8], Evelynne S. Fulda, BA[9], Emma Kileel, MPH[9], Michael T. Lu, MD, MPH[10], Steven K. Grinspoon, MD[9], Jordan E. Lake, MD[11], and REPRIEVE Trial Investigators. [1]University of Cincinnati, [2]Harvard T.H. Chan School of Public Health, [3]University Medical Center Freiburg, [4]University of Texas Southwestern Medical Center, [5]University of Pittsburgh School of Medicine, [6]University of California, San Francisco, [7]Rutgers New Jersey Medical School, [8]Weil Cornell School of Medicine, [9]Massachusetts General Hospital, [10]Harvard Medical School, [11]University of Texas Health Science Center.

Background

- REPRIEVE (NCT02344290) is a prospective, double-blind, randomized, placebo-controlled, multi-center, phase III efficacy study of major adverse cardiovascular events with two arms (4 mg daily pitavastatin calcium vs. placebo) among persons with HIV (PWH) currently on antiretroviral therapy (ART).

- Non-alcoholic fatty liver disease (NAFLD) is a common problem in persons with HIV (PWH).

- NAFLD is associated elevated cardiovascular disease (CVD) risk.

Objective

The objective of this analysis was to estimate the prevalence and cardiometabolic characteristics of NAFLD among REPRIEVE participants who underwent computed tomography (CT).

Methods

- The REPRIEVE Mechanistic substudy is embedded within an international primary CVD prevention RCT of pitavastatin calcium vs. placebo among 7,770 PWH ages 40-75 years on antiretroviral therapy (ART).

- A subset of 655 U.S. participants had non-contrast CT with measurement of hepatic steatosis defined as a mean hepatic attenuation <40 HU or liver/spleen ratio <1.0.

- NAFLD was defined as steatosis in the absence of self-reported frequent alcohol use (usually/often/sometimes drinking more than 1-2 alcoholic drinks per day).

- Elevated waist circumference was defined as >88 cm for women and >102 cm for men.

- The prevalence of NAFLD was compared by demographic, cardiometabolic and HIV-specific parameters.

- Distributions of immune activation / inflammatory indices data were compared among those with or without NAFLD.

- Differences in prevalence across subgroups used chi-square tests. Participant characteristics were compared with chi-square of Wilcoxon tests. Modelling used log binomial regression and Wilcoxon tests.

Results

Table 1 – Prevalence of Hepatic Steatosis, NAFLD

	Presence of Hepatic steatosis			Presence of NAFLD		
	n / N	Percent [95% CI]	P-value	n / N	Percent [95% CI]	P-value
All Participants						
	139 / 655	21% [18, 24] %	-	97 / 477	20% [17, 24] %	-
Age (years)						
40-49	52 / 284	18% [14, 23] %	0.055	35 / 206	17% [12, 22] %	0.051
50-59	72 / 320	23% [18, 27] %		50 / 231	22% [16, 27] %	
60+	15 / 51	29% [17, 42] %		12 / 40	30% [16, 44] %	
Natal sex						
Male	125 / 544	23% [19, 27] %	0.015	88 / 392	22% [18, 27] %	0.014
Female	14 / 111	13% [6, 19] %		9 / 85	11% [4, 17] %	
Race						
White	90 / 354	25% [21, 30] %	0.009	61 / 252	24% [19, 29] %	0.011
Black or African American	32 / 229	14% [9, 18] %		20 / 166	12% [7, 17] %	
Asian	1 / 7	14% [0, 40] %		1 / 4	0% [0, 67] %	
Other	16 / 65	25% [14, 35] %		15 / 55	27% [16, 39] %	
Ethnicity						
Not Hispanic or Latino	98 / 488	20% [17, 24] %	0.20	63 / 346	18% [14, 22] %	0.046
Hispanic or Latino	39 / 157	25% [18, 32] %		33 / 124	27% [19, 34] %	
BMI (kg/m²)						
<18.5	- / 6	0% [0, 0] %	<0.0001	- / 5	0% [0, 0] %	<0.0001
18.5-24.9	26 / 219	12% [8, 16] %		12 / 154	8% [4, 12] %	
25-29.9	56 / 255	22% [17, 27] %		41 / 185	22% [16, 28] %	
30+	57 / 175	33% [26, 40] %		44 / 133	33% [25, 41] %	
Elevated waist circumference						
No	65 / 395	16% [13, 20] %	<0.0001	44 / 280	16% [11, 20] %	0.0009
Yes	67 / 220	30% [24, 37] %		49 / 170	29% [22, 36] %	

Figure 1 – Steatosis and NAFLD Classification

Table 3 – Metabolic Parameters

	Hepatic Steatosis			NAFLD		
	Total (N=655)	No (N=516)	Yes (N=139)	Total (N=477)	No (N=380)	Yes (N=97)
Metabolic syndrome	158 (25%)	103 (20%)	55 (41%)	121 (26%)	79 (21%)	42 (44%)
P-value			<0.001			<0.001
Elevated waist circumference	220 (36%)	153 (32%)	67 (51%)	170 (38%)	121 (34%)	49 (53%)
P-value			<0.001			<0.001
Elevated triglycerides	215 (33%)	157 (31%)	58 (42%)	156 (33%)	113 (30%)	43 (45%)
P-value			0.010			0.005
Reduced HDL-C	213 (33%)	155 (30%)	58 (42%)	172 (36%)	125 (33%)	47 (49%)
P-value			0.007			0.004
Elevated blood pressure	312 (48%)	235 (46%)	77 (55%)	215 (45%)	163 (43%)	52 (54%)
P-value			0.039			0.06
Elevated fasting glucose	128 (20%)	90 (18%)	38 (28%)	91 (19%)	65 (17%)	26 (27%)
P-value			0.010			0.027
Number of criteria met 0	131 (20%)	115 (22%)	16 (12%)	99 (21%)	88 (23%)	11 (11%)
1	175 (27%)	149 (29%)	26 (19%)	119 (25%)	103 (27%)	16 (16%)
2	191 (29%)	149 (29%)	42 (30%)	138 (29%)	110 (29%)	28 (29%)
3	110 (17%)	74 (14%)	36 (26%)	81 (17%)	55 (14%)	26 (27%)
4	39 (6%)	24 (5%)	15 (11%)	34 (7%)	21 (6%)	13 (13%)
5	9 (1%)	5 (1%)	4 (3%)	6 (1%)	3 (1%)	3 (3%)
P-value			<0.001			<0.001
HOMA-IR	1.5 (1.0, 2.7)	1.4 (1.0, 2.4)	2.1 (1.2, 3.8)	1.7 (1.0, 2.9)	1.6 (1.0, 2.6)	2.5 (1.3, 3.9)
P-value			<0.001			<0.001
>=2	232 (36%)	159 (32%)	73 (53%)	185 (39%)	129 (34%)	56 (58%)
P-value			<0.001			<0.001
TRIG:HDL Elevated	393 (60%)	295 (57%)	98 (71%)	295 (62%)	219 (58%)	76 (78%)
P-value			0.004			<0.001

Table 2 – Cardiovascular and HIV parameters

		Hepatic Steatosis			NAFLD		
		Total (N=655)	No (N=516)	Yes (N=139)	Total (N=477)	No (N=380)	Yes (N=97)
ASCVD risk score (%)		4.6 (2.6, 7.0)	4.3 (2.5, 6.7)	5.3 (3.0, 7.5)	4.7 (2.5, 7.0)	4.3 (2.4, 6.7)	5.8 (3.3, 7.7)
P-value				0.007			0.002
	0-<2.5	154 (24%)	129 (25%)	25 (18%)	114 (24%)	99 (26%)	15 (15%)
	2.5-<5	202 (31%)	164 (32%)	38 (27%)	139 (29%)	115 (30%)	24 (25%)
	5-10	256 (39%)	190 (37%)	66 (47%)	195 (41%)	144 (38%)	51 (53%)
	>10	43 (7%)	33 (6%)	10 (7%)	29 (6%)	22 (6%)	7 (7%)
P-value				0.020			0.005
Smoking status	Current	163 (25%)	131 (25%)	32 (23%)	107 (22%)	86 (23%)	21 (22%)
	Former	209 (32%)	156 (30%)	53 (38%)	147 (31%)	114 (30%)	33 (34%)
	Never	281 (43%)	227 (44%)	54 (39%)	222 (47%)	179 (47%)	43 (44%)
P-value				0.22			0.75
Elevated ALT (>30 U/L men; >19 U/L women)		190 (29%)	132 (26%)	58 (42%)	140 (29%)	96 (25%)	44 (45%)
P-value				<0.001			<0.001
Duration of HIV (years)	<5	52 (8%)	41 (8%)	11 (8%)	37 (8%)	29 (8%)	8 (8%)
	5-10	140 (21%)	110 (21%)	30 (22%)	97 (20%)	76 (20%)	21 (22%)
	>10	463 (71%)	365 (71%)	98 (71%)	343 (72%)	275 (72%)	68 (70%)
P-value				0.96			0.66
History of AIDS-defining event		123 (19%)	89 (17%)	34 (24%)	86 (18%)	60 (16%)	26 (27%)
P-value				0.05			0.012
Nadir CD4 count (cells/mm³)	<50	136 (21%)	105 (20%)	31 (22%)	104 (22%)	79 (21%)	25 (26%)
	50-199	192 (29%)	150 (29%)	42 (30%)	139 (29%)	112 (29%)	27 (28%)
	200-349	175 (27%)	138 (27%)	37 (27%)	128 (27%)	103 (27%)	25 (26%)
	350+	129 (20%)	105 (20%)	24 (17%)	91 (19%)	75 (20%)	16 (16%)
P-value				0.45			0.43
CD4 count (cells/mm³)		606 (425, 774)	596 (426, 770)	609 (425, 799)	584 (426, 769)	584 (425, 769)	597 (429, 786)
P-value				0.53			0.63
HIV-1 RNA (copies/mL)	<LLQ	566 (88%)	446 (88%)	120 (89%)	410 (88%)	327 (87%)	83 (88%)
	LLQ -< 400	66 (10%)	54 (11%)	12 (9%)	49 (10%)	40 (11%)	9 (10%)
	400+	12 (2%)	9 (2%)	3 (2%)	9 (2%)	7 (2%)	2 (2%)
P-value				0.80			0.94

Additional Results and Summary of Findings

- Hepatic steatosis was noted in 21%.
- NAFLD prevalence was 20%
  - 97/477 without ↑ alcohol use.
- NAFLD was more prevalent with male sex, older age, non-black race (Table 1).
- ASCVD risk score was higher in those with NAFLD (median 5.8% vs. 4.3%, P=0.002, Table 2).
- ALT was ↑ in those with NAFLD (45% vs. 25%, P<0.001, Table 2).
- NAFLD was associated with higher levels of LpPLA-2 (144 vs. 130 ng/ml, P=0.013) and hsCRP (2.2 vs. 1.6 mg/L, P=0.013). (Table 4)
- Obesity, metabolic syndrome, elevated waist circ., ↓ HDL and ↑ triglycerides, all associated with NAFLD in unadjusted analyses (P<0.005, Data not shown).
  - Effects were explained by obesity, metabolic syndrome & ↑ HOMA-IR (Figure 2).
- HIV-specific characteristics, ART and other circulating markers of immune activation/inflammation (IL-6, sCD163, MCP-1, sCD14 and D-dimer) not associated with NAFLD.

Corresponding author:
Carl J. Fichtenbaum
Cincinnati, Ohio
E-mail: carl.fichtenbaum@uc.edu

Table 4 – Immune / Inflammatory Indices

	Hepatic Steatosis			NAFLD		
	Total (N=655)	No (N=516)	Yes (N=139)	Total (N=477)	No (N=380)	Yes (N=97)
LpPLA-2 (ng/mL)	131 (92.2, 169)	129 (90.1, 165)	140 (99.4, 176)	132 (95.9, 171)	130 (91.1, 168)	144 (107, 187)
P-value			0.025			0.013
sCD163 (ng/mL)	846 (626, 1096)	846 (616, 1078)	845 (666, 1204)	852 (649, 1120)	851 (634, 1113)	860 (674, 1215)
P-value			0.34			0.50
sCD14 (ng/mL)	1818 (1527, 2174)	1827 (1537, 2176)	1721 (1483, 2120)	1818 (1506, 2173)	1831 (1536, 2194)	1699 (1440, 2085)
P-value			0.34			0.18
MCP-1 (pg/mL)	186 (147, 242)	185 (145, 236)	193 (157, 256)	186 (146, 245)	185 (144, 239)	199 (155, 267)
P-value			0.11			0.11
IL-6 (pg/mL)	1.63 (1.02, 2.89)	1.63 (1.00, 2.85)	1.68 (1.18, 3.33)	1.62 (1.01, 2.93)	1.58 (0.99, 2.80)	1.66 (1.15, 3.73)
P-value			0.24			0.20
D-Dimer (ng/mL)	243 (146, 397)	242 (144, 397)	249 (147, 391)	251 (153, 431)	249 (153, 431)	257 (149, 420)
P-value			0.98			0.84
Hs Crp (mg/L)	1.70 (0.90, 3.60)	1.60 (0.80, 3.50)	2.30 (1.20, 4.00)	1.80 (0.90, 3.90)	1.60 (0.80, 3.60)	2.20 (1.20, 5.30)
P-value			0.003			0.013

Figure 2 – Risk Factors of NAFLD

		Relative Risk	P-value
Natal sex			
Female	71	0.47 (0.26, 0.86)	0.015
Age (per 10 years)	444	1.27 (0.98, 1.64)	0.07
Race/ethnicity			
Black Non-Hispanic	137	0.60 (0.36, 1.00)	0.17
Hispanic (Regardless of Race)	120	1.07 (0.75, 1.54)	0.17
	21	0.88 (0.35, 2.22)	0.17
BMI (kg/m²)			
30+	122	1.76 (1.21, 2.57)	0.003
HOMA-IR			
>=2	175	1.38 (0.93, 2.07)	0.11
Metabolic syndrome			
Yes	116	1.56 (1.06, 2.30)	0.023

Conclusions

- In this cohort with controlled HIV, high CD4 counts, and low to moderate cardiovascular risk, NAFLD (20%) was common including 45% with higher ALT values.
- NAFLD was more prevalent with older age, and those self-identified as males and non-black race; it was also associated with higher BMI and metabolic syndrome.
- NAFLD was associated with selected indices of inflammation and metabolic disturbances but not HIV specific indices or ART.
- Elevated LpPLA-2 and hsCRP levels suggest a correlation between NAFLD and cardiovascular risk in PWH.

Limitations

- Cross-sectional analysis of relatively healthier group of PWH (non-diabetics with lower ASCVD risk scores)
- Hepatic steatosis by CT scan detects those with 30% or higher fat content.

Acknowledgements