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Pitavastatin Does Not Improve Hepatic Steatosis in REPRIEVE Mechanistic Substudy

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BACKGROUND

- Hepatic steatosis (HS) and metabolic dysfunction-associated steatotic liver disease (MASLD) are common among persons with HIV (PWH).
- We present longitudinal HS and MASLD prevalence, cardiometabolic characteristics and cardiovascular outcomes among REPRIEVE mechanistic substudy (MS) participants.
- The primary objective was to determine the effect of pitavastatin therapy on HS among people with HIV on suppressive antiretroviral therapy (ART) who do not have an indication for statin therapy.

METHODS

- REPRIEVE was a double-blind randomized trial evaluating pitavastatin for primary prevention of major adverse cardiovascular events (MACE) in PWH.
- Participants in the REPRIEVE MS underwent coronary CT at entry and 2 years (Figure 1).
- Quantification of Fat: HS (mean hepatic attenuation <40 Hounsfield units [HU] or liver/spleen ratio <1.0) was assessed on non-contrast CT images.
- MASLD is defined by presence of HS along with 1-5 clinical traits of metabolic syndrome.
- Participants with viral hepatitis or frequent alcohol use (usually/often drinking more than 1-2 alcoholic drinks per day) were excluded.

Figure 1 – Analysis Population

804 enrolled in REPRIEVE MS
402 Pitavastatin; 402 Placebo

Excluded: 194 with frequent alcohol use, HBV, HCV, or unevaluable for HS at entry

610 included in analysis
302 Pitavastatin; 308 Placebo

	Median (IQR) or N (%)
Age (years)	50 (46, 55)
Female	108 (18%)
White	336 (55%)
Black or African American	207 (34%)
Hispanic or Latino	156 (26%)
ASCVD risk score (%)	4.40 (2.59, 6.80)

Despite low-to-moderate cardiovascular risk, hepatic steatosis was common and did not improve with pitavastatin. Hepatic steatosis was associated with new onset diabetes, but not MACE.

RESULTS

Prevalence of Hepatic Steatosis

- HS prevalence at baseline was 22%
  - Pitavastatin arm – 24%
  - Placebo arm – 20%
- At 24 months, HS prevalence was 26% - Pitavastatin / 20% - Placebo
- Resolution (or progression) by CT was not different between those assigned to pitavastatin versus placebo at 24 months (P=0.76, J-T Test). (Figure 2)

MASLD

- MASLD was present in 17% of participants at baseline (104 of 610).
- Resolution (or progression) of MASLD was not different between those assigned to pitavastatin versus placebo at 24 months (data not shown).

Major Adverse Cardiovascular Events

- 29 participants (4%) experienced MACE with no difference by baseline HS status (P=0.9, Grays Test) (Fig. 3a)

Incident Diabetes Events

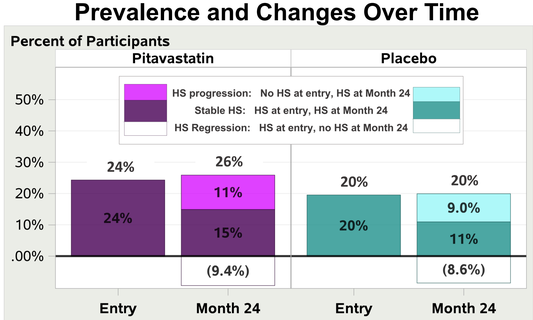
- New onset diabetes occurred more frequently among those with HS
  - Cumulative incidence 16.5% vs. 5.5% (P<0.001, Gray's Test). (Fig. 3b)
- Adjusting for HS, an increased risk of diabetes mellitus with pitavastatin was not apparent. (Figure 4)

Table 1 – Participant Cardiometabolic Parameters

		All Participants (N=610)	With HS (N=133)
Hepatic Steatosis		**133 (22%)**	
BMI (kg/m²)		27.1 (24.3, 30.3)	29.2 (26.3, 31.8
	Overweight	242 (40%)	55 (41%)
	Obese	167 (27%)	56 (42%)
Pre-diabetes		121 (20%)	37 (28%)
Elevated blood pressure		284 (47%)	75 (56%)
Elev. waist circumference*		209 (37%)	144 (32%)
Elev. triglycerides		205 (34%)	149 (31%)
Reduced HDL-C		205 (34%)	56 (42%)
HOMA-IR >2.5*		166 (29%)	59 (46%)
hsCRP >2 mg/dL*		274 (46%)	75 (58%)
Number of metabolic disorders	1	123 (20%)	15 (11%)
	2	133 (22%)	26 (20%)
	3+	278 (46%)	85 (64%)
MASLD		**104 (17%)**	**104 (78%)**

** Missing data: Fasting glucose, n=9; waist circumference, n=39; HOMA-IR, n=33; hsCRP, N=8.*

Figure 2 – Longitudinal Hepatic Steatosis Prevalence and Changes Over Time



21 participants (11 pitavastatin, 10 placebo) unevaluable for HS at week 24 are excluded

Figure 3 – Cumulative incidence of MACE and New Onset Diabetes by Hepatic Steatosis Status at REPRIEVE Entry

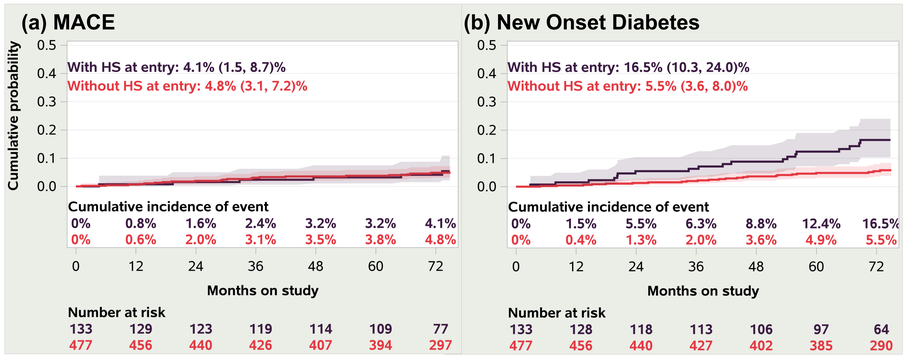


Figure 4 – Pitavastatin effect on Diabetes, Stratified by Hepatic Steatosis Status at REPRIEVE Entry

CONCLUSIONS

- In this cohort with controlled HIV and low-to-moderate cardiovascular risk, HS and MASLD were common and did not improve with pitavastatin over 24 months.
- Hepatic steatosis at baseline was not associated with more MACE events but was associated with incident diabetes.
- Persons without hepatic steatosis at baseline assigned to pitavastatin did not have a higher cumulative incidence of diabetes.
- In addition to statins, additional risk factors should be addressed to lower risk of MACE.

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