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Open-Label Semaglutide Reduces Metabolic-Associated Steatotic Liver Disease in People With HIV: SLIM LIVER

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Conflicts of Interest

JEL receives research support from Gilead Sciences and serves as a consultant to Theratechnologies and CytoDyn, Inc.

DWK has no conflicts of interest to report.

AK has no conflicts of interest to report.

RM is the founder and Chief Technology Officer for ForeSpect, PLLC, which served as the imaging core-lab for this study.

KK has no conflicts of interest to report.

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BACKGROUND

Metabolic-Associated Steatotic Liver Disease (MASLD), defined as ≥ 1 major cardiovascular disease (CVD) risk factor and steatotic (fatty) liver disease (SLD), is a growing epidemic. Among people with human immunodeficiency virus (PWH), MASLD prevalence frequently exceeds and CVD risk is substantially greater than persons without HIV. As SLD is an independent CVD risk factor, reducing intra-hepatic triglycerides (IHTG, or liver fat) and associated insulin resistance/inflammation reduces CVD risk while preventing progressive liver disease. Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) that is FDA-approved for diabetes and weight loss; semaglutide improves CVD risk and SLD in people with diabetes without HIV.^(1, 2)

OBJECTIVE

We designed a pilot study of the impact of semaglutide on magnetic resonance imaging-proton density fat fraction (MRI-PDFF)-quantified IHTG in PWH and MASLD. We hypothesized that semaglutide would reduce IHTG and improve cardiometabolic parameters.

METHODS

ACTG A5371 ([NCT04216589](#)), the SLIM LIVER study, was a phase IIb, single-arm, open-label trial of semaglutide 1 mg weekly in PWH with central adiposity, insulin resistance/pre-diabetes and SLD (defined as ≥ 5% of liver volume as IHTG). The primary endpoint was the 24-week change in MRI-PDFF-quantified IHTG.

Enrolled participants (02/2021–09/2022) had age ≥ 18 years, suppressed HIV-1 RNA on antiretroviral therapy, ≥ 5% IHTG by MRI-PDFF but no other SLD cause or significant alcohol consumption, no GLP-1RA use within 24 weeks, minimum waist circumference (WC) ≥ 95/94 cm if assigned male/female at birth, respectively, and no diabetes diagnosis but ≥ 1 of: fasting glucose 100–125 mg/dL, hemoglobin A1c (HbA1c) 5.7–6.4% or homeostatic model of insulin resistance (HOMA-IR) >3.0.

MRI performance was standardized, with central reading by Dr. Raja Muthupillai (ForeSpect, PLLC, Houston, TX, USA). Clinical labs were performed at local laboratories and insulin (for HOMA-IR) in batch at end of study (UTHealth, Houston, TX). Elevated alanine aminotransferase (ALT) was defined as >19/30 IU/L for persons assigned female/male at birth, respectively.

Fifty participants provided >90% power to detect an absolute 5% IHTG change (assuming standard deviation [SD]=9%, type 1 error=5%, 25% participants excluded). Per-protocol analyses included participants on semaglutide within 4 weeks of their week 24 MRI and without prohibited medication use. Mean changes and 95% confidence intervals (CI) were estimated using linear regression.

FINDINGS

Forty-nine of 51 participants were included in the per-protocol analysis (Table 1). Clinically significant IHTG reductions were observed over 24 weeks (Table 2). Twenty-nine percent of participants had complete MASLD resolution; 58% had 30% relative IHTG reduction. Significant improvements in anthropometric measurements, glucose regulation markers and triglyceride concentrations were also observed. All participants tolerated semaglutide 1 mg weekly. Most adverse events were Grade 1 gastrointestinal symptoms.

DISCUSSION

In this seminal pilot study, we demonstrate that semaglutide is a highly effective MASLD therapy for PWH, with clinically significant improvements observed in IHTG and traditional CVD risk factors. Given the high cardiometabolic disease burden and growing obesity epidemic among PWH, semaglutide may reduce CVD risk while preventing progressive liver disease. Notably, we observed IHTG reductions and weight loss with semaglutide 1mg weekly similar to those observed with 0.4 mg daily (approximately 2.8 mg/week) for 72 weeks in persons without HIV,(3) supporting shorter duration and lower doses for IHTG reduction in PWH.

A 30% reduction in IHTG on MRI correlates with improvements in steatohepatitis and fibrosis. With 58% of our participants achieving this target, a significant benefit on hepatic histology in PWH and MASLD is likely. MASLD is also associated with glucose dysregulation, lipid disturbances and chronic inflammation, risk factors for CVD. A 1 unit (log)HOMA-IR increase is associated with CVD prevalence/incidence odds ratios of 1.3/1.6(4) and a 40 mg/dL triglyceride reduction with a 4–5% CVD risk reduction.(5) Thus, our observed declines of 1.5 HOMA-IR units and ≈27 mg/dL in triglycerides should translate to improved CVD risk for PWH and MASLD.

Our study has several limitations, including small sample size, lack of randomization and no control arm. While we cannot rule out contributions of external factors, our primary effect size was large, supporting a true benefit of semaglutide. Strengths include SLIM LIVER being the first clinical trial of GLP-1RA for MASLD in PWH and the only agent to show benefit on IHTG in PWH with MASLD. In summary, semaglutide 1 mg weekly is an effective therapy for MASLD in PWH and shows evidence of broader cardiometabolic benefit.

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Table 1.

Clinical and Demographic Characteristics, Per-Protocol Population

	N (%) or median (interquartile range)
Age (years)	52 (42, 58)
Gender	
Cis woman	18 (37%)
Trans woman	3 (6%)
Cis man	28 (57%)
Race/ethnicity	
White non-Hispanic	13 (27%)
Black or African American*	16 (33%)
Hispanic	19 (39%)
American Indian or Alaskan Native	1 (2%)
BMI (kg/m ²)	35 (31, 39)
Waist circumference (cm)	114 (107, 124)
CD4 ⁺ T lymphocyte count (cells/mm ³)	701 (586, 869)
HIV-1 RNA (<50 copies/mL)	49 (100%)
ART regimen**	
PI	2 (4%)
NNRTI	10 (22%)
INSTI	40 (82%)
History of hepatitis C virus	4 (8%)
Glucose (mg/dL)	98 (93, 107)
Total Cholesterol (mg/dL)	170 (145, 200)
HDL cholesterol (mg/dL)	45 (38, 53)
LDL cholesterol (mg/dL)	98 (77, 129)
Triglycerides (mg/dL)	116 (95, 183)
AST (IU/L)	22 (18, 28)
ALT (IU/L)	28 (22, 40)
Elevated ALT***	26 (53%)
HOMA-IR	3.8 (2.8, 6.1)

* Includes one participant who reported Hispanic ethnicity and Black race

**
Some participants may be in more than 1 category.

Defined as >19 IU/L if female sex at birth and >30 IU/L if male sex at birth.

Cis=cisgender, Trans=transgender BMI=body mass index, CD=cluster of differentiation, ART=antiretroviral therapy, PI=protease inhibitor, NNRTI= non-nucleoside reverse transcriptase inhibitor, INSTI=integrase strand transfer inhibitor, HDL=high-density lipoprotein, LDL=low-density lipoprotein, AST=aspartate aminotransferase, ALT=alanine aminotransferase, HOMA-IR=homeostatic model assessment of insulin resistance

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Table 2.

Changes in IHTG, Cardiometabolic and HIV-Associated Parameters

Outcome	Baseline*	Week 24*	Absolute (95% CI)	Percent (95% CI)
<i>Primary</i>				
IHTG (%)**	12.7 (6.1)	8.5 (4.7)	-4.2 (-5.4, -3.1)	-31.3 (-39, -23.6)
<i>Secondary</i>				
Weight (kg)	103 (20.8)	95.1 (22.8)	-7.8 (-9.5, -6.1)	-8.1 (-9.8, -6.4)
BMI (kg/m ²)	35.5 (5.6)	32.7 (6.3)	-2.8 (-3.4, -2.2)	-8.1 (-9.8, -6.4)
Waist circumference (cm)	115 (11.8)	108 (12.9)	-6.7 (-8.5, -4.8)	-5.8 (-7.5, -4.2)
HOMA-IR	5.4 (5.1)	3.9 (3.9)	-1.5 (-3.2, 0.3)	-
Fasting glucose (mg/dL)	100 (13.1)	90.5 (12.3)	-9.9 (-14.7, -5.1)	-8.7 (-13.2, -4.2)
HbA1c (%)	5.69 (0.37)	5.45 (0.36)	-0.25 (-0.32, -0.17)	-4.2 (-5.5, -2.9)
Fasting total cholesterol (mg/dL)	175 (43.3)	174 (34.8)	-4.0 (-10.8, 2.9)	-0.23 (-4.2, 3.7)
Fasting triglycerides (mg/dL)	150 (87.9)	131 (75.8)	-26.8 (-46.0, -7.5)	-10.5 (-20.8, -0.2)
Fasting HDL cholesterol (mg/dL)	46 (10.5)	47.6 (11.4)	2.0 (-0.02, 4.1)	5.3 (0.6, 10.0)
Fasting LDL cholesterol (mg/dL)	101 (35.1)	102 (30.7)	-1.0 (-7.1, 5.1)	3.0 (-4.5, 10.4)
<i>Other</i>				
ALT (IU/L)	30.7 (13.4)	24.8 (11.9)	-6.1 (-9.5, -2.6)	-15.3 (-23.8, -6.7)
Elevated ALT***	26 (53%)	20 (41.7%)		
CD4 ⁺ T lymphocyte count (cells/mm ³)	762 (340)	730 (302)	-14.0 (-81.1, 53.1)	8.2 (-14.3, 30.7)
HIV-1 RNA (<50 copies/mL)	49 (100%)	46 (97.9%)		

* Mean and standard deviation or frequency (%) presented.

** No difference in effect size when excluding the 4 participants with history of cured hepatitis C virus infection.

*** Defined as >19 IU/L if female sex at birth and >30 IU/L if male sex at birth.

IHTG=intra-hepatic triglyceride, BMI=body mass index, HOMA-IR=homeostatic model assessment of insulin resistance, HbA1c=hemoglobin A1c, ALT=alanine aminotransferase, CD=cluster of differentiation, HIV=human immunodeficiency virus, RNA=ribonucleic acid