Cardiometabolic Effects of Semaglutide in People With HIV: The SLIM LIVER Study

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BACKGROUND

The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide reduces weight and inflammation in the general population.

We previously reported reductions in weight (mean -7.8 kg, 95% confidence interval, [CI, -9.5, -6.1]), insulin resistance (IR), serum triglycerides and liver fat in people with HIV (PWH) receiving semaglutide in ACTG A5371, the SLIM LIVER study.

Here we report additional metabolic, fat imaging and inflammatory marker endpoints, including follow-up after semaglutide discontinuation.

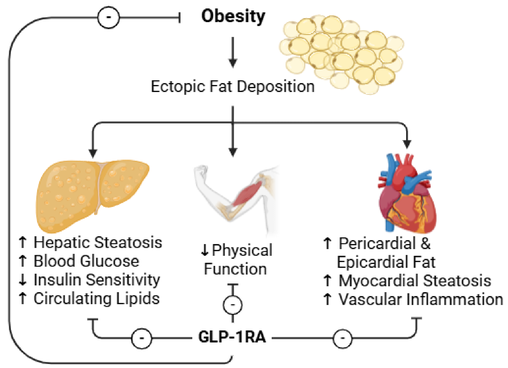


Fig. 1. Therapeutic actions of GLP-1RA

METHODS

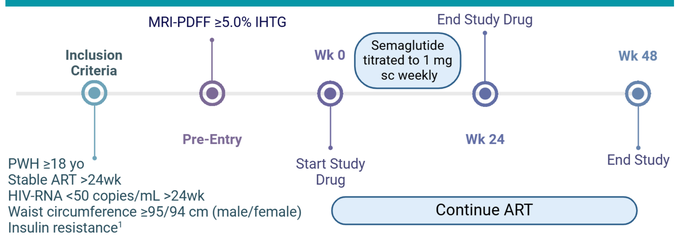


Fig. 2. A5371 The SLIM LIVER study schema. [1]Fasting plasma glucose 100-125 mg/dL, HbA1c between 5.7 and <6.5%, or HOMA-IR >3.0. ART=antiretroviral therapy; IHTG=intrahepatic triglyceride content; MRI-PDFF=Magnetic Resonance Imaging Proton Density Fat Fraction; Wk=week; sc=subcutaneously

ACTG A5371 enrolled PWH ≥18 years old on suppressive antiretroviral therapy with metabolic dysfunction-associated steatotic liver disease.

All participants received low-dose, subcutaneous semaglutide titrated to 1mg weekly for 24 weeks (W) followed by 24 W off semaglutide.

Biomarker/immune profiles and MRI-PDFF were available at W 0 and 24, and other measures at W 0, 24 and 48. Metabolic syndrome was defined according to NCEP ATPIII criteria.

Mean (95% CI) changes were estimated using linear regression and risk estimates by a log link generalized estimating equation model (α=0.05).

RESULTS

Table 1. Clinical and Demographic Characteristics	N=51
Age, years	52 (42, 58)
Gender	
Cisgender woman	18 (37%)
Transgender woman	3 (6%)
Cisgender man	28 (57%)
Race/ethnicity	
Non-Hispanic White	13 (27%)
Black or African American*	16 (33%)
Hispanic	19 (39%)
American Indian or Alaska 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)
Antiretroviral therapy regimen**	
Protease inhibitor	2 (4%)
Non-nucleoside reverse transcriptase inhibitor	10 (22%)
Integrase strand transfer inhibitor	40 (82%)
History of hepatitis C virus infection	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)

Table 1. Per-protocol population. Median (IQR) or frequency presented. ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; HDL=high-density lipoprotein; HOMA-IR=homeostatic model assessment of insulin resistance; LDL=low-density lipoprotein. *Includes one participant who reported Hispanic ethnicity and Black race. **Some participants may be in more than 1 category. ***Defined as >19 IU/L (female sex at birth) and >30 IU/L (male sex at birth).

Table 2. W 0-24 Biomarker Changes*	Estimated mean change	P-value
Adiponectin (log_{10} mg/L)	0.05 (0.02, 0.08)	<0.001
Beta-Hydroxybutyrate (log_{10} mmol/L)	0.12 (0.01, 0.23)	0.03
CD40 Ligand (pg/mL)	-23.67 (-126.6, 79.3)	0.6
EN-RAGE (pg/mL)	1157 (-7079, 9393)	0.8
FABP-4 (pg/mL)	-13.9 (-80, 52)	0.7
GDF-15 (pg/mL)	38 (-30, 106)	0.3
hsCRP (log_{10} mg/L)	-0.13 (-0.24, -0.02)	0.02
IL-4 (log_{10} pg/mL)	0.07 (0.01, 0.13)	0.02
IL-6 (pg/mL)	0.03 (-0.26, 0.33)	0.8
IL-10 (log_{10} pg/mL)	0.04 (-0.03, 0.11)	0.2
IL-13 (pg/mL)	0.12 (-0.64, 0.88)	0.8
IP-10 (pg/mL)	102 (25, 179)	0.01
Leptin (ng/mL)	-7.48 (-10.47, -4.49)	<0.001
MCP-1 (pg/mL)	-25.9 (-57.9, 5.9)	0.1
sCD14 (ng/mL)	-29.9 (-148.4, 88.7)	0.6
sCD163 (ng/mL)	28.3 (-66.6, 123.3)	0.6

Table 2. Estimated mean change (95% CI) presented. *Includes per protocol analysis population (n=49). EN-RAGE=extracellular newly identified receptor for advanced glycation end-products binding protein; FABP-4=Fatty Acid Binding Protein 4; GDF-15=Growth differentiation factor 15; hsCRP=High-Sensitivity C-Reactive Protein; IL=Interleukin; IP=Interferon-gamma-inducible protein; MCP-1=Monocyte chemoattractant protein; sCD=soluble cluster of differentiation.

Figure 3. Cardiometabolic Changes During (W 0-24) and After (W24-48) Semaglutide Therapy

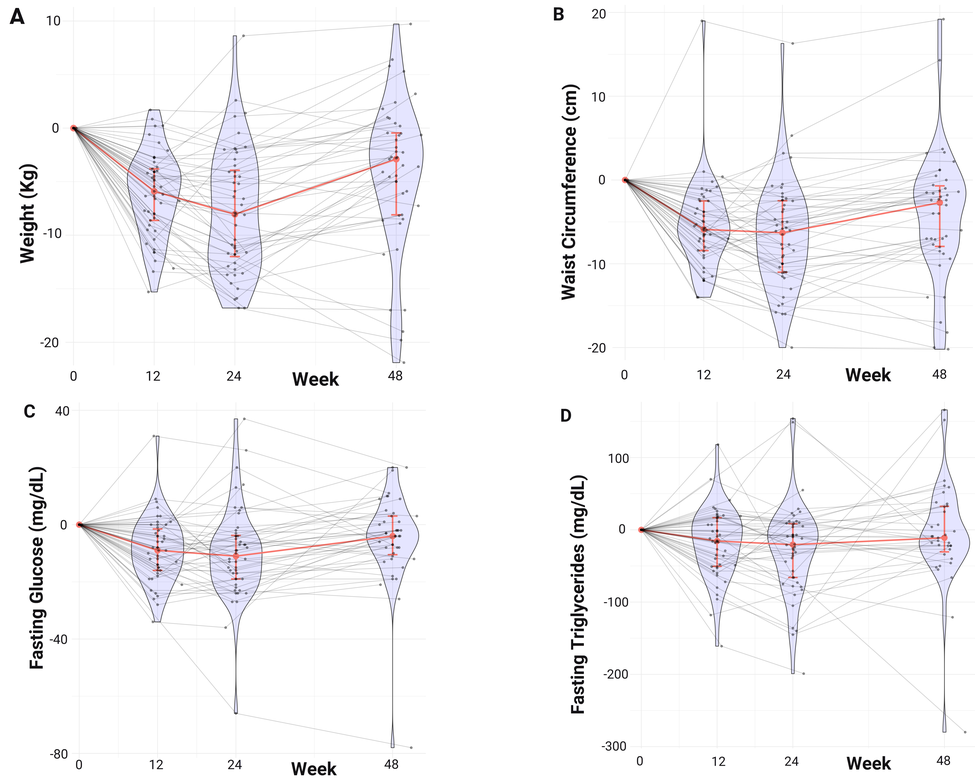


Fig. 3. Absolute change in mean weight (A), waist circumference (B) and glucose (C) and triglyceride (D) plasma concentrations.

Additionally,

- 24 weeks of semaglutide was associated with a relative risk (RR) reduction of 25% *(RR=0.75 [0.58, 0.98]* in metabolic syndrome (estimated risk [95% CI]=0.77 [0.67, 0.90] at W 0 and 0.58 [0.46, 0.74] at W 24) and reduced visceral (-13%) and abdominal subcutaneous (-12%) fat by MRI (all p<0.05).
- After 24 weeks off semaglutide, absolute weight regain mean (95% CI) change was +2.9 kg (1.5, 4.3), with women, White non-Hispanics and PWH <40 years of age regaining more.
- Among those who lost and regained weight (n=31), 75% of lost weight was regained. Weight regain was accompanied by significant increases in waist circumference (2.0 cm [0.9, 3.1]) and fasting glucose (5.1 mg/dL [0.9, 9.3]) without significant short-term changes in blood pressure, total or LDL cholesterol, triglycerides or metabolic syndrome estimated risk.

CONCLUSIONS

- **Short-term, low-dose semaglutide was associated with cardiometabolic benefit in PWH.**
- **Rapid weight regain and some loss of cardiometabolic benefit occurred off semaglutide, similar to the general population.**
- **Further study of higher-dose semaglutide and strategies to maintain benefits of semaglutide following initial therapy are needed in PWH.**

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