

DURABILITY OF SEMAGLUTIDE EFFECTS AFTER DRUG DISCONTINUATION IN HIV-ASSOCIATED LIPOHYPERTROPHY

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BACKGROUND

- Primarily characterized by abnormal accumulation of abdominal VAT, HIV-associated lipohypertrophy remains a common problem in antiretroviral-treated people with HIV and contributes to co-morbidities.
- We previously showed that the GLP1RA, semaglutide, significantly reduced weight, total body fat and central fat, especially abdominal VAT, after 32 weeks of use (Eckard AR, et al. *Lancet Diabetes Endocrinol* 2024; 12: 523–34).
- In other populations, majority regain weight and/or outcome measures revert to pre-treatment values following drug discontinuation.
- GLP1RA treatment withdrawal effects have not been evaluated in people with HIV.

METHODS

STUDY DESIGN

- Randomized, double-blind, placebo-controlled phase IIb clinical trial
- Participants with HIV-associated lipohypertrophy enrolled at a single site (Cleveland) and randomized 1:1 to receive 32 weeks of once-weekly subcutaneous semaglutide or matching placebo

KEY INCLUSION/EXCLUSION CRITERIA

- Inclusion:** Age ≥18 years, HIV RNA <400 copies/mL ≥6 months, stable ART ≥12 weeks, BMI ≥25 kg/m², WC >95 cm (men) and >94 cm (women), WHR >0.94 (men) and >0.88 (women), subjective abdominal girth increase after ART initiation
- Exclusion:** Diabetes, known cardiovascular disease, pregnancy, history of pancreatitis, thyroid cancer, multiple endocrine neoplasia syndrome type 2, or severe HIV-associated lipohypertrophy

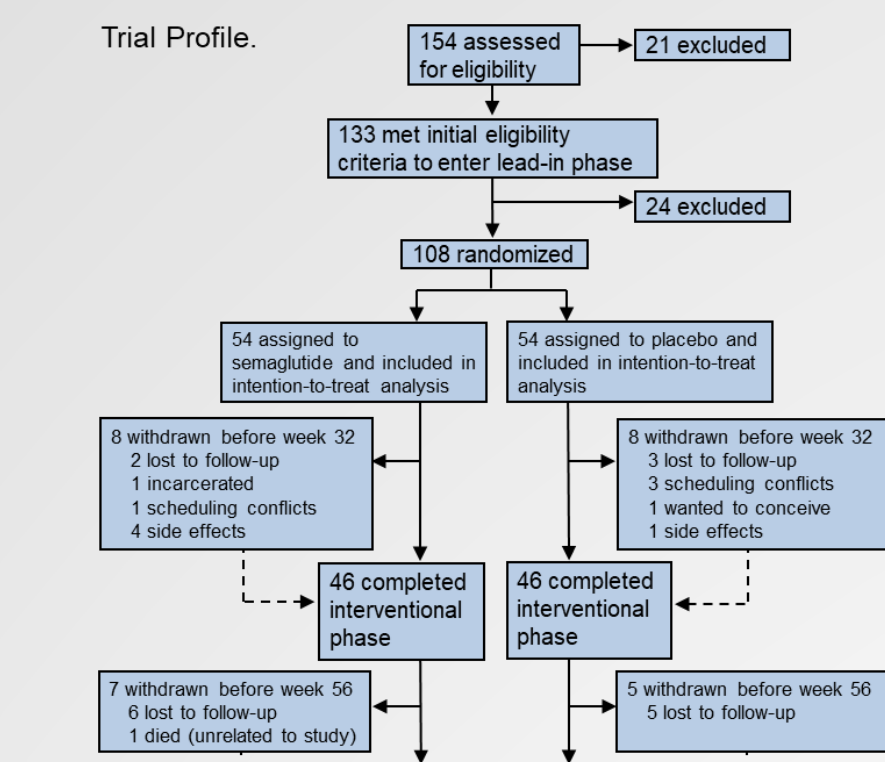
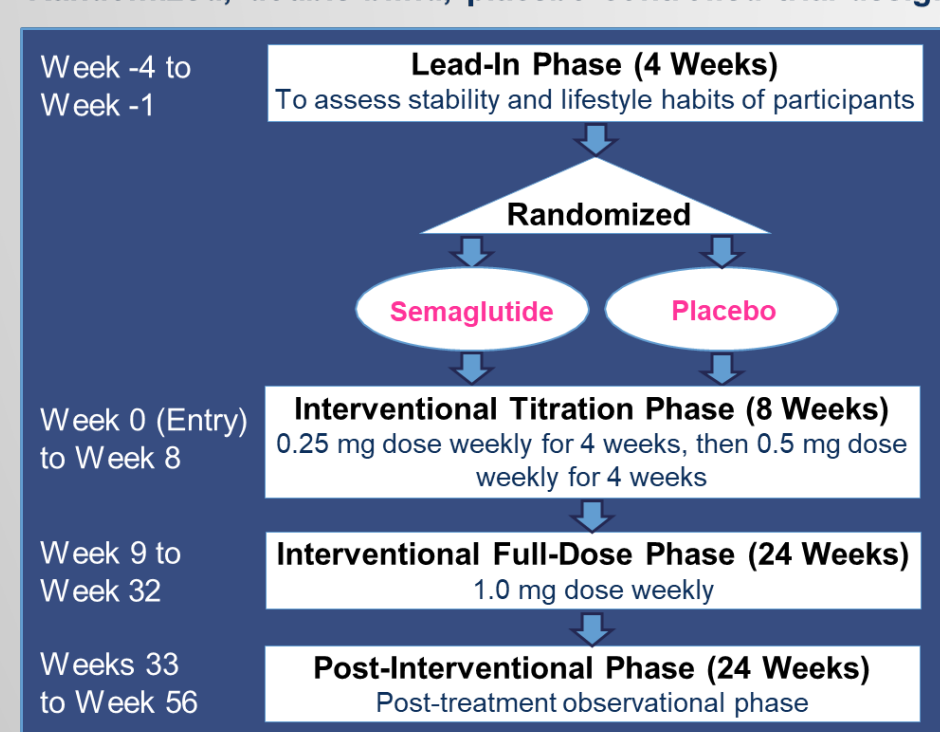
MAIN STUDY ASSESSMENTS

- Body composition by whole-body dual-energy X-ray absorptiometry; non-contrast helical computed tomography at L4-L5 level

STATISTICAL ANALYSIS

- Regressions:** Generalized estimating equations were used to model effects of semaglutide on outcome variables, examining the interaction between time and treatment while controlling for covariates. Appropriate linear combination of regression coefficients were then assembled to extract the true effect size of semaglutide.

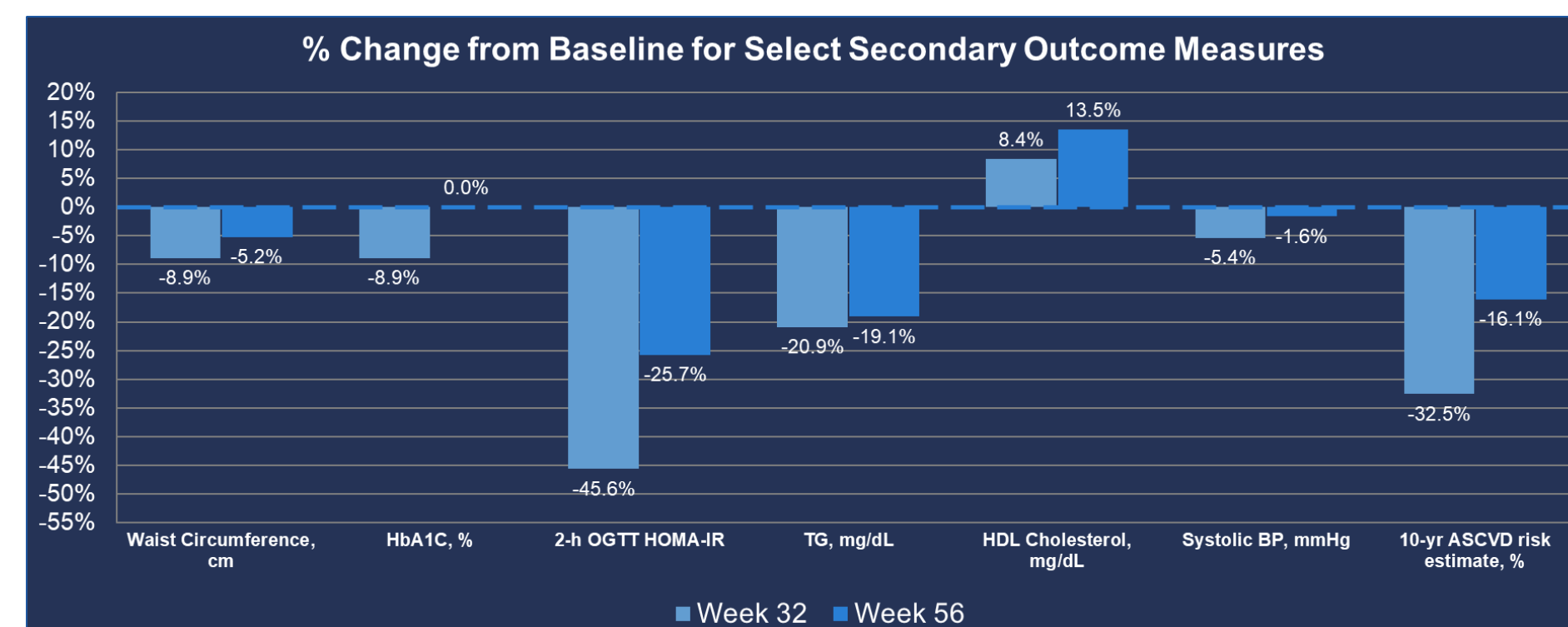
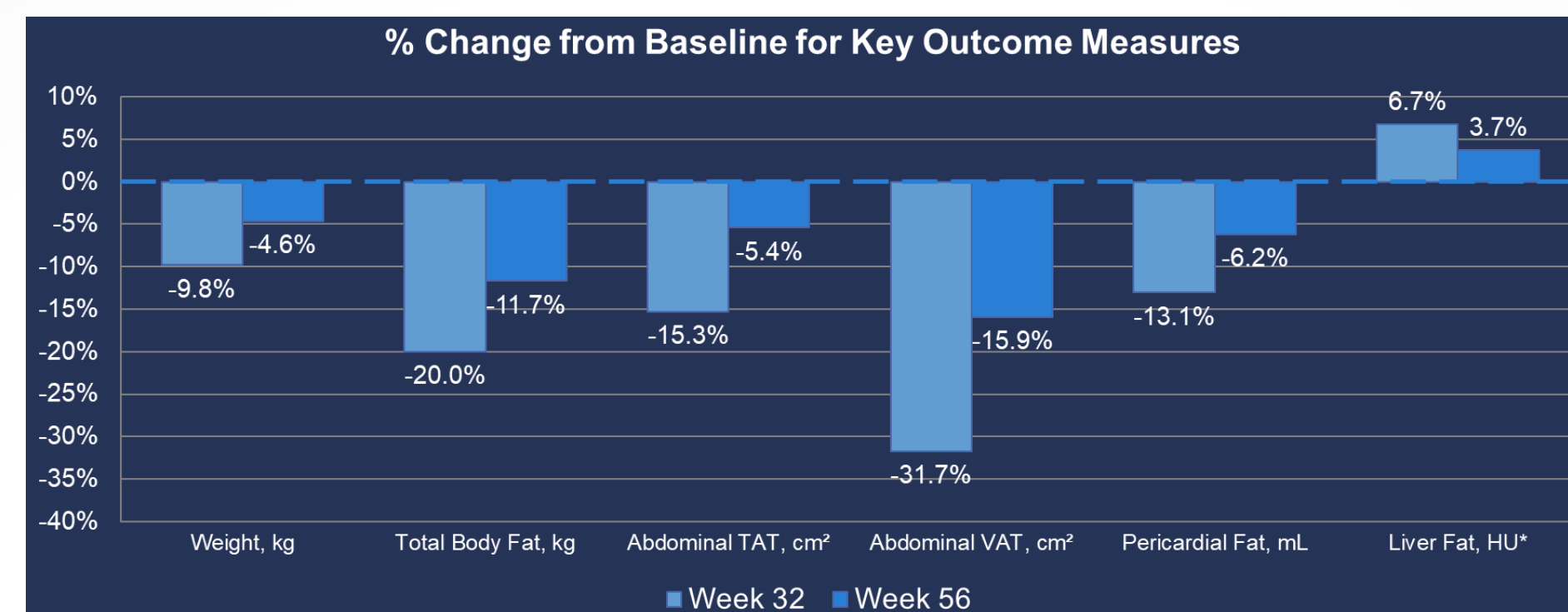
Randomized, double-blind, placebo-controlled trial design



BASELINE CHARACTERISTICS	Semaglutide (N=54)	Placebo (N=54)
Demographics		
Age, years	53 (40, 57)	53 (41, 57)
Sex		
Male	38 (70.0%)	27 (50.0%)
Female	16 (30.0%)	27 (50.0%)
Race		
Black	33 (61.1%)	34 (60.0%)
White	20 (37.0%)	18 (33.3%)
Bi-racial	0 (0.0%)	2 (3.7%)
Native American	1 (1.9%)	0 (0.0%)
Hispanic ethnicity	4 (7.0%)	5 (9.0%)
HIV variables		
CD4+ T-cell count, cells/μL	826 (407, 1058)	793 (579, 994)
HIV duration, months	203 (116, 305)	226 (155, 282)
Abdominal therapy duration, mo.	168 (88, 230)	148 (88, 198)
Current INSTI use	45 (83.0%)	43 (80.0%)
Current protease inhibitor use	10 (19.0%)	8 (15.0%)
Current tenofovir alafenamide use	43 (80.0%)	37 (68.5%)
Anthropometric measurements		
Weight, kg	97.5 (87.3, 110.6)	97.9 (83.6, 115.5)
Body mass index, kg/m ²	32.9 (28.4, 36.0)	33.8 (29.9, 39.7)
Waist circumference, cm	107.0 (98.5, 113.0)	106.4 (101.8, 124.8)
Waist-to-hip ratio	0.95 (0.93, 1.02)	0.97 (0.94, 1.03)
Whole-body dual-energy absorptiometry measurements		
Total body fat, kg	34.4 (27.4, 40.2)	35.5 (28.3, 49.7)
Total trunk fat, kg	18.6 (14.6, 23.0)	20.0 (15.3, 25.9)
Total limb fat, kg	15.6 (12.6, 19.2)	17.9 (11.6, 22.3)
Total lean body mass, kg	60.1 (50.7, 66.8)	56.9 (47.6, 65.6)
Computed tomography area and volume measurements		
Abdominal TAT, cm ²	416.1 (350.3, 475.7)	445.7 (384.8, 502.9)
Abdominal SAT, cm ²	301.6 (225.8, 382.0)	332.6 (230.5, 389.4)
Abdominal VAT, cm ²	101.2 (78.0, 143.2)	118.0 (83.5, 151.5)
VAT:TAT ratio	0.3 (0.2, 0.4)	0.2 (0.2, 0.4)
Pericardial fat, mL	78.6 (55.1, 115.6)	72.35 (47.5, 102.9)
Total right psoas muscle, cm ²	14.7 (12.0, 18.6)	13.78 (10.4, 17.8)
Computed tomography density measurements		
Liver, HU	58.7 (53.3, 63.6)	56.0 (51.6, 60.8)
Abdominal TAT, HU	-92.8 (-95.0, -90.1)	-91.1 (-94.1, -87.8)
Abdominal SAT, HU	-94.7 (-97.1, -91.5)	-92.7 (-96.8, -88.2)
Abdominal VAT, HU	-96.8 (-99.1, -94.8)	-97.5 (-99.6, -95.1)
Pericardial fat, HU	-109.5 (-110.9, -107.9)	-109.7 (-110.6, -108.6)
Total right psoas muscle, HU	47.1 (43.4, 51.0)	47.3 (43.2, 51.9)
Glucose metabolism and insulin resistance		
HbA _{1c} , %	5.5 (5.1, 5.8)	5.6 (5.3, 5.8)
Fasting glucose, mg/dL	101.0 (93.0, 105.0)	108.0 (98.0, 117.0)
Fasting insulin, uIU/ml	11.0 (6.0, 18.0)	15.00 (9.0-23.0)
Fasting HOMA-IR	2.5 (1.5, 4.7)	3.8 (2.5, 6.8)
2-hour OGTT glucose, mg/dL	105.0 (83.0, 129.0)	115.5 (92.0, 138.0)
2-hour OGTT insulin, uIU/ml	35.0 (21.0, 62.0)	38.0 (23.0, 60.0)
2-hour OGTT HOMA-IR	10.7 (4.9, 19.0)	11.1 (5.1, 36.3)
Lipoprotein profiles		
Total cholesterol, mg/dL	181.50 (154.0, 203.0)	189.5 (154.0, 211.0)
HDL cholesterol, mg/dL	46.8 (38.5, 56.3)	43.3 (36.7, 52.1)
LDL cholesterol, mg/dL	103.5 (82.0, 129.0)	108.5 (80.0, 133.0)
VLDL cholesterol, mg/dL	21.0 (16.0, 32.0)	26.0 (20.0, 36.0)
Triglycerides, mg/dL	103.5 (79.0, 159.0)	133.0 (104.0, 168.0)
Vital signs		
Heart rate, beats/minute	76 (64, 82)	76 (71, 84)
Systolic blood pressure, mmHg	126 (120, 136)	126 (115, 137)
Diastolic blood pressure, mmHg	80 (76, 86)	80 (75, 84)
Baseline variables		
Smoking status		
Current	15 (27.8%)	23 (42.6%)
Past/never	39 (72.2%)	31 (57.4%)
Estimated daily dietary intake		
Total calories, kcal	1604 (1170, 2083)	1905 (1192, 2113)
Estimated weekly physical activity		
Low intensity, minutes	2520.0 (1260.0, 4200.0)	2130.0 (1260.0, 3360.0)
Moderate intensity, minutes	2100.0 (1260.0, 3360.0)	2730.0 (1680.0, 3480.0)
High intensity, minutes	1950.0 (0.0, 720.0)	0.0 (0.0, 420.0)
Cardiovascular disease risk		
10-year ASCVD risk estimate, %	5.0 (2.6, 8.0)	5.4 (2.5, 8.8)

RESULTS

Most body composition and cardiometabolic effects observed after 32 weeks of *semaglutide* were no longer evident 24 weeks after drug discontinuation in people with *HIV-associated lipohypertrophy* and without diabetes.

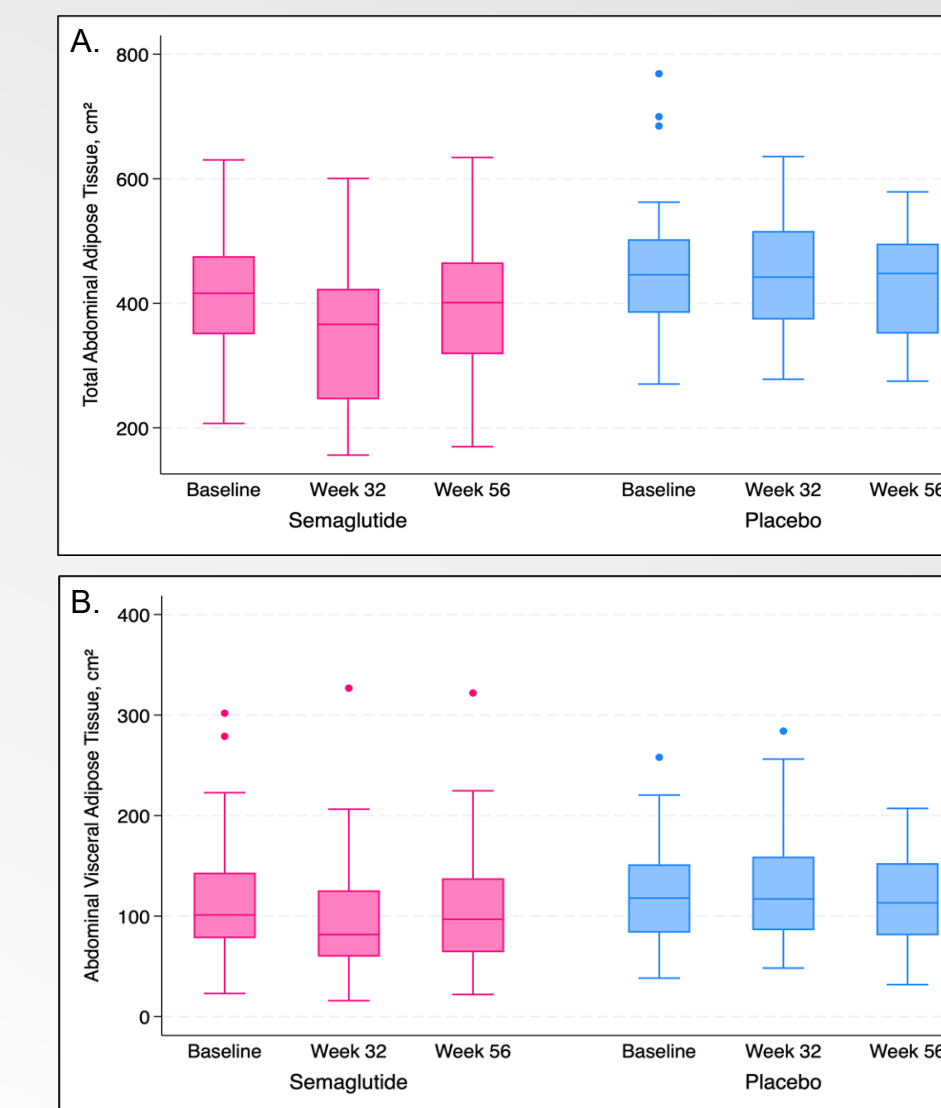


Final fitted linear combination of regression coefficients models estimated effect size at each timepoint on the outcome measure, adjusted for sex and multiplicative effects of treatment and time. Graphs represent estimated % change at weeks 32 and 56 in outcome variables from semaglutide treatment calculated using the formulas $100(e^{\beta}-1)$ and $100(\beta/\text{regression intercept})$ for ln-transformed and non-transformed variables, respectively. All depicted outcomes showed statistically significant semaglutide effects at week 32 except pericardial fat. All depicted outcome measures did not show statistically significant effects at week 56 (p=0.05) except waist circumference (p=0.04), triglycerides (p=0.046), and HDL cholesterol (p=0.01).

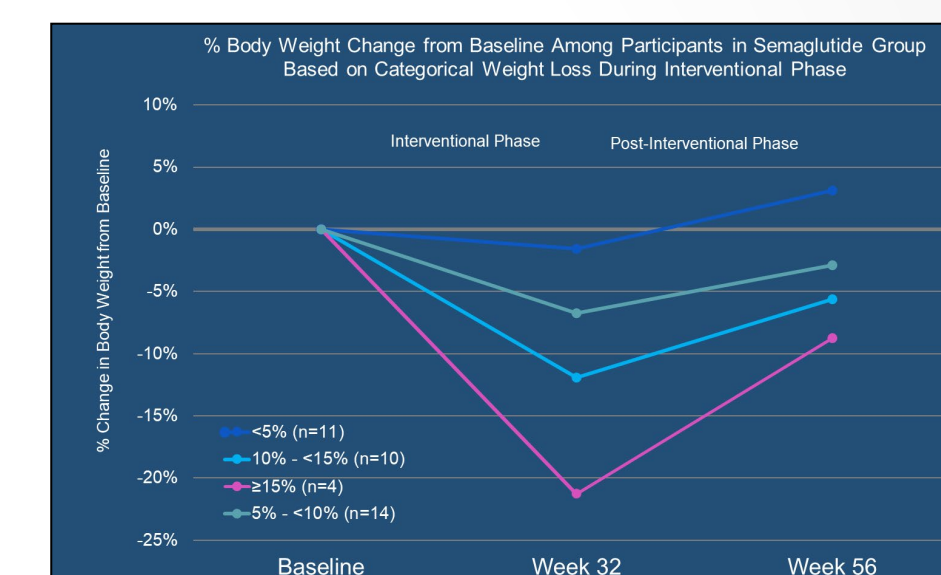
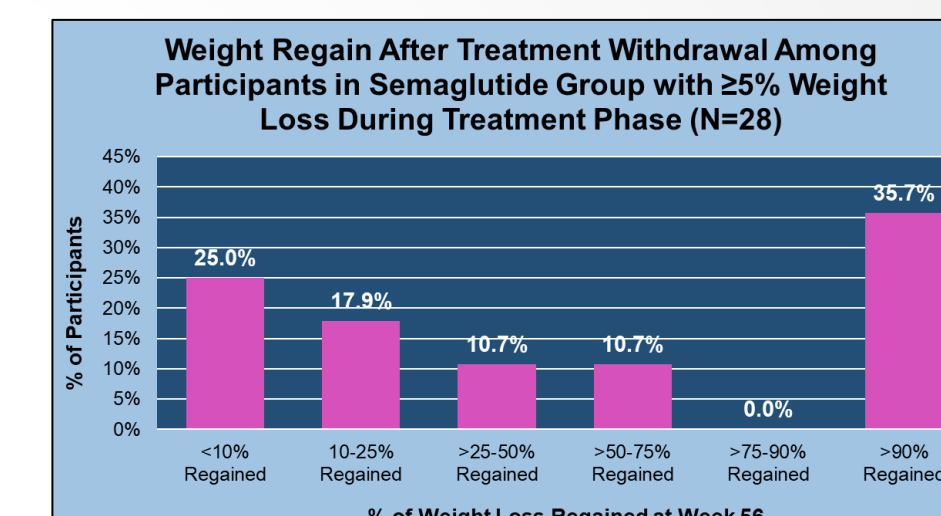
Other outcome measures with significant effects at week 32 but not week 56 include waist-to-hip ratio, total limb fat, abdominal SAT, VAT density, 2-h OGTT glucose, 2-h OGTT insulin, VLDL cholesterol; BMI (p=0.04) and trunk fat (p=0.04) still showed statistically significant effects week 56. All other outcome variables did not show statistically significant effects at either week 32 or 56.

SUMMARY OF RESULTS

- We previously showed that 32 weeks of semaglutide use was effective in producing meaningful improvements in many key body composition and cardiometabolic parameters (e.g., total body fat, abdominal fat, liver fat, glucose metabolism, systolic blood pressure, 10-year ASCVD risk, hsCRP, among others).
- In the current analysis, some residual semaglutide effects were still present, but most outcome measures no longer showed statistically significant effects 24 weeks after drug discontinuation.
- Among participants in the semaglutide group with ≥5% body weight loss at week 32, majority showed weight regain with over a third regaining all the weight 24 weeks after drug discontinuation; however, more than half still had ≥5% net loss.



Box and whisker plots depicting abdominal A. TAT and B. VAT at each time point by group. Statistically significant effects of semaglutide were evident at week 32; however, there were no statistically significant treatment effects at week 56 compared to baseline (24 weeks after drug discontinuation).



Data in bottom graph represent means and include only participants in semaglutide group who completed the study. 15 of 28 (53.6%) participants with ≥5% weight loss at week 32 still had a ≥5% net loss at week 56 compared to baseline.

Abbreviations: GLP1RA, glucagon-like peptide 1 receptor agonist; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; INSTI, integrase strand transfer inhibitor; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; HU, Hounsfield unit, HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; OGTT, oral glucose tolerance test; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides; BP, blood pressure; hsCRP, high-sensitivity C-reactive protein

CONCLUSIONS

- This is the first randomized controlled trial of GLP1RAs in HIV and the first study to investigate the durability of semaglutide treatment after drug discontinuation.
- Semaglutide holds promise as an effective treatment in HIV, HIV-associated lipohypertrophy, and related co-morbidities.
- However, much of the positive semaglutide effects achieved over 32 weeks of treatment were largely reversed after 24 weeks off drug.
- Apparent lack of durability with GLP-1RA treatment in people with HIV raises concern for prolonged treatment requirements.
- Longer and larger studies of GLP-1RAs are needed in HIV.

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