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## Weight Loss Associated with Semaglutide Treatment Among People with HIV

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### Abstract

**Objective**—There is limited real-world evidence about the effectiveness of semaglutide for weight loss among people with HIV (PWH). We aimed to investigate weight change in a US cohort of PWH who initiated semaglutide treatment.

**Design**—Observational study using the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.

**Methods**—We identified adult PWH who initiated semaglutide between 2018 and 2022 and with 2 weight measurements. The primary outcome was within-person bodyweight change in kg at 1 year. The secondary outcome was within-person Hemoglobin A1c percent (HbA1c) change. Both outcomes were estimated using multivariable linear mixed model.

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**Results**—In total, 222 new users of semaglutide met inclusion criteria. Mean follow up was 1.1 years. Approximately 75% of new semaglutide users were male, and at baseline, mean age was 53 years (standard deviation [SD]: 10), average weight was 108 kg (SD: 23), mean body mass index was 35.5 kg/m<sup>2</sup>, mean HbA1c was 7.7% and 77% had clinically recognized diabetes. At baseline, 97% were on ART and 89% were virally suppressed (VL < 50 copies/mL). In the adjusted mixed model analysis, treatment with semaglutide was associated with an average weight loss of 6.47 kg at 1 year (95% CI -7.67 to -5.18) and with a reduction in HbA1c of 1.07% at 1 year (95% CI -1.64 to -0.50) among the 157 PWH with a post-index HbA1c value.

**Conclusions**—Semaglutide was associated with significant weight loss and HbA1c reduction among PWH, comparable to results of previous studies from the general population.

### Keywords

People with HIV; Semaglutide; Obesity; Weight loss; GLP-1 receptor agonist

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### Introduction

Advancements in and early initiation of antiretroviral therapy (ART) have resulted in the reduction of HIV-associated wasting among people with HIV (PWH). In contrast, there has been an increase in weight gain and obesity, mirroring the obesity epidemic seen in the general population(1,2). This weight gain has been attributed to dietary and other lifestyle factors, living to older ages due to advances in ART, and direct and indirect effects of ART(2). The indirect effect of ART on weight is through suppression of the viral load and return to a normal metabolic state. Direct effects are due to impact of some classes of ART which are more likely to cause weight gain and metabolic side effects(3). Integrase strand transfer inhibitors (INSTIs), especially dolutegravir and bictegravir, are associated with the most weight gain(4). If untreated, obesity can ultimately lead to multiple metabolic and cardiovascular complications, including Type 2 Diabetes (T2D). PWH are already at a higher risk of these complications(5), and obesity further increases their risk. Therefore, it is imperative to treat weight gain in this population.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for the treatment of T2D, and more recently for obesity at higher doses for patients with a BMI 30 kg/m<sup>2</sup> or a BMI 27 kg/m<sup>2</sup> and at least one comorbidity(6). It is available as either an injectable administered subcutaneously (SQ) once weekly or oral tablets administered once daily. Randomized controlled trials (RCTs) in the general population have reported significant and sustained weight loss with semaglutide among both those with and without diabetes(7-13). However, among PWH there is limited real-world evidence about the effectiveness of semaglutide for weight loss. We aimed to investigate weight change in a US cohort of PWH who initiated semaglutide treatment.

### Methods

We conducted an observational within-person longitudinal study in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort. The CNICS cohort is a dynamic, prospective, clinical cohort of PWH aged 18 and older in care at

ten academic sites across the United States. This study included data from eight CNICS sites: University of Alabama at Birmingham, Case Western Reserve University, University of Washington, University of California San Diego, Fenway Health/Harvard University, University of North Carolina Chapel Hill, Johns Hopkins University, and Vanderbilt University. All participants completed informed consent prior to entry into CNICS.

We identified adult PWH who initiated injectable or oral semaglutide in HIV care between 2018 and 2022. Date of first prescription of semaglutide was considered the index date or baseline. PWH were included if they had no previous record of semaglutide use, and at least 2 weight measurements: bodyweight at index date, defined as the most recent bodyweight measurement within one year prior to the index date, and at least one post-index weight measurement occurring at any time after initial prescription date. For those with more than one post-index weight, the last recorded measurement while on semaglutide treatment was used to calculate bodyweight change. Bodyweight change was calculated as post-index bodyweight minus bodyweight at the index date. Follow up ended at the last recorded weight before semaglutide discontinuation.

The primary outcomes of interest were the trajectory of within-person bodyweight change in kg and percentage of bodyweight change at 1 year. The secondary outcome was the trajectory of within-person Hemoglobin A1c (HbA1c) percent change at 1 year. We excluded participants from the secondary outcome who did not have HbA1c values prior to and after treatment initiation. The primary and secondary outcomes were estimated using a linear mixed model with a random intercept and a random slope using exchangeable covariance matrix to account for repeated measures on participants. Models were adjusted for age, sex, race/ethnicity, CNICS site, diabetes status as a binary variable, CD4 cell count, HIV viral load (VL), and a non-linear time term (time<sup>2</sup>). Covariate definitions have been previously defined(4). We assumed that all PWH who received a semaglutide prescription took the medication, as it was not possible to directly evaluate medication adherence. We also investigated whether the effect of semaglutide on weight change differed based on the administration of INSTI. Analyses were conducted using Stata version 17 (StataCorp, College Station, TX).

## Results

In total, 222 new users of semaglutide were identified in the CNICS cohort in the relevant time period. Mean follow up was 1.1 years. Approximately 75% of new semaglutide users were male, mean age at baseline was 53 years (standard deviation [SD]: 10), average baseline weight was 108 kg (SD: 23), and mean body mass index (BMI) was 35.5 kg/m<sup>2</sup>. Mean hemoglobin A1c (HbA1c) was 7.7% and 77% had clinically recognized diabetes at baseline. At semaglutide initiation, 54% were on metformin, 39% were on insulin, and 15% were on a Sodium-glucose Cotransporter-2 (SGLT2) Inhibitor. At baseline, 89% were virally suppressed (VL < 50 copies/mL) and 97% were on ART, with 82% receiving an INSTI based regimen. In addition, 18% were on a concomitant antipsychotic medication at baseline (Table 1).

Of the 125 patients who had available data on the maximum dose reached, 87 (69.6%) received low doses of subcutaneously injected semaglutide (0.25, 0.5, and 1 mg), while 24 (19.2%) received high doses of subcutaneously injected semaglutide (1.7, 2, and 2.4 mg). The remaining 14 (11.2%) were on oral doses of 3, 7, or 14 mg.

In fully adjusted mixed models, treatment with semaglutide was associated with significant bodyweight loss: 6.47 kg at 1 year (95% CI: -7.71 to -5.23) (Figure 1) and percent bodyweight loss: 5.72% (-6.86 to -4.58) at 1 year among 222 PWH. Reductions in body weight were -6.49 (-7.77, -5.21) kg ( $p < 0.001$ ) in people receiving INSTI and -6.38 (-8.10, -4.66) kg ( $p < 0.001$ ) in people not receiving INSTI. There was no significant difference between the two groups ( $p$  for interaction = 0.883), verifying that PWH receiving an INSTI lost weight. In addition, treatment with semaglutide was also associated with a significant reduction in HbA1c: 1.07% at 1 year (95% CI -1.64 to -0.50) among the 157 PWH with a post-index HbA1c value.

## Discussion

Among PWH in our cohort who were new users of semaglutide, a significant weight loss of 6.47 kg was observed at 1 year. Despite the metabolic effects of ART, our results provide evidence that semaglutide, even at lower doses, is an effective treatment option for weight loss and diabetes management among PWH. Our results are consistent with the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) and Semaglutide Treatment Effect in People with Obesity (STEP) randomized controlled trials, which included people without HIV with diabetes and/or obesity. The average weight loss achieved in STEP-2 in patients with T2D and obesity (mean BMI 35.7 kg/m<sup>2</sup>) after 68 weeks of treatment using the 1 mg semaglutide SQ once weekly dose was -6.90 kg, which was comparable to our study (-6.47 kg)(14). A 1.5% reduction in HbA1c was observed in STEP-2 with 1 mg semaglutide. The weight loss achieved by the 0.5 and 1 mg SQ doses in the SUSTAIN 1 through 11 trials ranged from -3.5 to -6.5 kg (7-13); the higher end of this range being similar to the weight loss achieved in our study.

Previous real-world evidence from the general population is also consistent with our findings. A post hoc analysis of four Semaglutide Real-world Evidence (SURE) studies (SURE Canada, Denmark/Sweden, Switzerland and UK) including 1,212 patients with T2D and a mean BMI of 35 kg/m<sup>2</sup> treated with lower doses of SQ semaglutide for approximately 30 weeks (52 weeks permissible in UK study), showed a significant decrease of body weight of 4.7 kg, slightly less weight loss compared with our study likely due to shorter follow-up time in the SURE studies(15). HbA1c reductions observed in our study were also consistent with the SURE studies. Reductions in weight were less pronounced in our study compared to a retrospective study including 175 patients assessing weight loss among people who were overweight or obese, where patients lost an average weight of 12.3 (6.6) kg after 6 months; this could be due to 44% of patients taking higher doses of semaglutide (1.7 or 2.4 mg)(6). Furthermore, only 16% of patients had diabetes and generally patients with T2D experience less dramatic weight loss compared to those without diabetes.

This study expands on findings from general population studies with respect to semaglutide as a weight loss agent by focusing on PWH. Despite the metabolic effects of ART, our results provide evidence that semaglutide, even at lower doses, is an effective treatment option for weight loss and diabetes control among PWH. Semaglutide has also been shown to reduce the risk of cardiovascular disease and chronic kidney disease among people with T2D(7). Semaglutide might be especially beneficial for PWH with other comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and early-stage chronic kidney disease, however future studies among PWH are warranted to confirm these benefits given the complex dynamics of HIV- disease and other comorbidities.

There are a number of important strengths and limitations to this study. The CNICS cohort is a prospective, longitudinal, and dynamic cohort, enabling the capture of PWH in routine clinical care. Unlike RCTs, it does not have eligibility restrictions, making its findings generalizable to geographically and demographically diverse PWH in care. Our cohort of new semaglutide users among PWH offers a heterogeneous, real-world assessment that demonstrates clinically relevant levels of weight loss after one year of treatment. While we do not emulate a clinical trial specifically, we used a quasi-experimental approach, which eliminates the impact of potential within-person confounding factors. Limitations include the inability to account for adherence, the risk of time-varying confounding from an unknown factor given the observational nature of this study, some participants may have been censored before their first post-index weight measurement, missing HbA1c values, and missing prescribed semaglutide doses in some patients. Furthermore, due to the small sample size and missing dose data in certain sites, the study was underpowered for conducting subgroup analyses by dose and route of administration. Moreover, the COVID-19 pandemic resulted in a decrease in recorded weight measurements in the clinic, which could have introduced a bias towards the null. Although the average follow-up time was around 1 year, studies with longer follow-up time are warranted to assess the durability of semaglutide in achieving weight loss and improving HbA1c among PWH.

## Conclusion

This study is an important step forward, showing that semaglutide significantly decreases bodyweight and HbA1c among PWH and thus, may play a key role in the obesity and diabetes epidemics in this population. Despite the lower range of semaglutide doses used, semaglutide demonstrated significant benefit in PWH both in terms of weight loss and diabetic control. Future work is needed to find optimal treatment and dosing recommendations for this important high-risk population.

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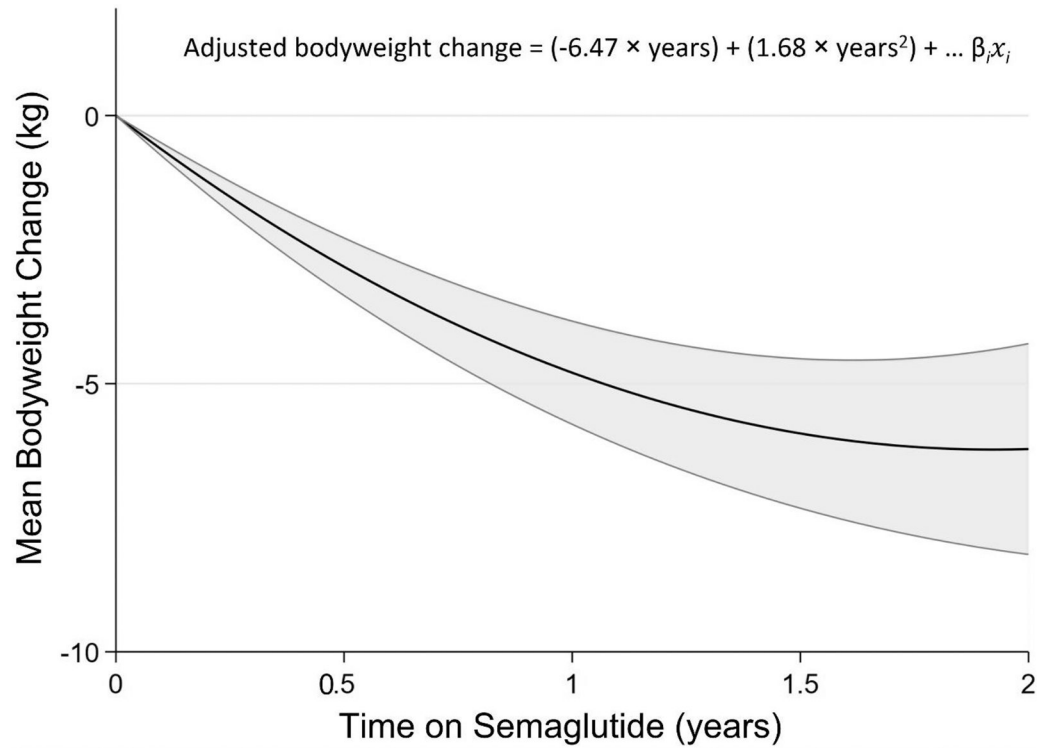
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## Data availability statement:

The datasets generated during and analyzed during the current study are not available.

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**Figure 1.** Adjusted bodyweight change (and 95% CI) over time among people with HIV who are new users of semaglutide

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**Table 1.**

Baseline characteristics for people with HIV initiating treatment with semaglutide

Variable	Mean (SD) or n(%)
<b>N</b>	222
<b>Age (years)</b>	52.8 (10.2)
<b>Males</b>	166 (74.8)
<b>Race/ethnicity</b>	
White	107 (48.2)
Black	78 (35.1)
Hispanic	33 (14.9)
Other/missing	4 (1.8)
<b>HbA1c % (n=219)</b>	7.7 (2.2)
<b>Diabetes</b>	170 (76.6)
<b>Treated Hypertension</b>	167 (75.22)
<b>Weight (kg)</b>	107.6 (23.0)
<b>BMI<sup>a</sup>(kg/m<sup>2</sup>)</b>	35.5 (7.0)
<b>BMI categories</b>	
Normal (18.5 – 24.9 kg/m <sup>2</sup> )	11 (4.9)
Overweight (25.0 – 29.9 kg/m <sup>2</sup> )	36 (16.2)
Obesity Class I (30.0 – 34.9 kg/m <sup>2</sup> )	65 (29.3)
Obesity Class II (35.0 – 39.9 kg/m <sup>2</sup> )	60 (27.0)
Obesity Class III (≥ 40.0 kg/m <sup>2</sup> )	50 (22.5)
<b>CD4 cell count (n=220)</b>	796 (392)
<b>HIV VL &lt;50 copies/mL</b>	198 (89.2)
<b>ART</b>	216 (97.3)
<b>Integrase inhibitor</b>	183 (82.4)
<b>TAF</b>	154 (69.37)
<b>Metformin</b>	121 (54.5)
<b>Insulin</b>	86 (38.7)
<b>Antipsychotic</b>	40 (18.0)
<b>SGLT-2 inhibitor</b>	34 (15.3)
<b>Lipoatrophy score (n=125)</b>	
None (0)	94 (75.2)
Mild (1-12)	31 (24.8)
Moderate-Severe (>12)	0 (0.0)
<b>Lipohypertrophy score (n=125)</b>	
None (0)	38 (30.4)
Mild (1-12)	72 (57.6)
Moderate-Severe (>12)	15 (12.0)
<b>ASCVD<sup>b</sup>risk score (n=219)</b>	

Variable	Mean (SD) or n(%)
Low risk <5%	47 (21.46)
Borderline 5-<7.5%	19 (8.68)
Intermediate 7.5- <20%	73 (33.33)
High risk 20	80 (36.53)

*Abbreviations:* BMI, Body Mass Index; VL, Viral Load; ART, Antiretroviral Therapy; TAF, Tenofovir Alafenamide; SGLT-2, Sodium-Glucose Transport Protein 2 Inhibitor; ASCVD, Atherosclerotic Cardiovascular Disease

<sup>a</sup>BMI is calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>ASCVD risk score is a 10-Year risk calculator to predict the risk of a first atherosclerotic cardiovascular event.