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Authors

Nguyen, Quynh

Wooten, Darcy

Lee, Daniel

et al.

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Glucagon-like Peptide 1 Receptor Agonists Promote Weight Loss Among People With Human Immunodeficiency Virus

Quynh Nguyen,[1] Darcy Wooten,[2] Daniel Lee,[2] Manuel Moreno,[2] Katherine Promer,[2] Amutha Rajagopal,[2] Matthew Tan,[3] Michael Tang,[2] Kye Duren,[1] Jeffrey Yin,[4] and Lucas Hill[4]

[1]School of Medicine, University of California San Diego, California, USA; [2]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, California, USA; [3]Department of Medicine, University of California San Diego, California, USA; and [4]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, California, USA

Background. Weight gain and associated metabolic complications are increasingly prevalent among people with human immunodeficiency virus (PWH). Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are incretin-based therapies for diabetes and weight management that have been shown to result in substantial weight loss; however, studies of their effects in PWH are limited.

Methods. A retrospective single-center cohort study was conducted among PWH who were taking GLP-1RAs at the University of California, San Diego Owen Clinic between 1 February 2021 and 1 February 2023. Baseline clinical data were collected and changes in weight, body mass index (BMI), and hemoglobin A1C (A1C) before starting GLP-1RAs compared to the most recent clinic visit were calculated (with a minimum of 3 months follow-up time required). Logistic regression was performed to identify variables associated with >5% of total body weight loss.

Results. A total of 225 patients received on average 13 months of GLP-1RA therapy, with 85 (37.8%) achieving the maximum GLP-1RA dose. GLP-1RA therapy resulted, on average, in a weight loss of 5.4 kg, decrease in BMI by 1.8 kg/m^2, and decrease in A1C by 0.6%. In the multivariable analysis, higher baseline BMI (odds ratio [OR], 1.10 [95% confidence interval {CI}, 1.03–1.16]), treatment duration of GLP-1RA therapy >6 months (OR, 3.12 [95% CI, 1.49–6.49]), and use of tirzepatide (OR, 5.46 [95% CI, 1.44–20.76]) were significantly more likely to be associated with >5% weight loss.

Conclusions. Use of GLP-1RAs led to declines in weight, BMI, and A1C among PWH and offers an additional strategy to address weight gain and diabetes.

Keywords. HIV; GLP-1 receptor agonist.

Weight gain and associated metabolic complications such as hypertension, type 2 diabetes (T2D), hyperlipidemia, and cardiovascular disease have become more prevalent among people with human immunodeficiency virus (PWH) [1]. Advances in modern antiretroviral therapy (ART) have minimized the immunosuppressive impact and associated opportunistic infections seen with uncontrolled HIV [2–4]. A consequence of improved lifespan is that PWH are developing similar comorbidities as people aging without HIV [5, 6]. Newer ART regimens are also associated with weight gain, particularly regimens with second-generation integrase strand transfer inhibitors (INSTIs) such as dolutegravir and bictegravir [7–10]. Additionally, regimens containing the nucleoside reverse transcriptase inhibitor tenofovir alafenamide have also been associated with overall more weight gain compared to regimens containing tenofovir disoproxil fumarate [11], which has been reported to cause weight suppression.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs), initially used as treatment for T2D, have become an exciting new option for weight loss treatment [12–14]. GLP-1 is an incretin hormone secreted by the intestine after food ingestion [12, 15]. It binds to receptors present on the pancreas, stomach, and peripheral and central nervous systems to increase satiety, decrease appetite, slow gastrointestinal motility, and mediate glucose-dependent insulin release [15]. GLP-1RAs are analogs to GLP-1 with a longer half-life than endogenous hormones, and longer-acting forms are associated with greater weight loss [14]. Most GLP-1RAs are administered as daily or weekly injections; semaglutide is also formulated for daily oral administration. Tirzepatide, a newer agent, is a glucose-dependent

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Correspondence: Q. Nguyen, School of Medicine, University of California, San Diego 9500 Gilman Drive, San Diego, CA 92093 (q9nguyen@health.ucsd.edu).

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insulinotropic polypeptide (GIP) analogy which activates both GLP-1 and GIP receptors to further enhance weight loss effects [16, 17]. Thus far, only 3 GLP-1RA agents, liraglutide, the higher-dose semaglutide injection [18], and the dual GLP-1/GIP agonist tirzepatide have been approved in the United States for weight loss.

Given the potential benefits of GLP-1RAs in PWH who are overweight or obese, we performed a retrospective cohort study to examine whether PWH who started on GLP-1RAs demonstrate weight loss and body mass index (BMI) changes. We also compared weight and hemoglobin A1C (A1C) changes in patients with T2D versus those without T2D, and evaluated for factors associated with >5% weight loss.

METHODS

A single-center, retrospective cohort study was conducted among PWH receiving care at the University of California, San Diego (UCSD) Owen Clinic, a Ryan White HIV/AIDS Program–funded primary care HIV clinic. All patients with HIV aged 18 years or older who were prescribed a GLP-1RA agent for at least 3 months between 1 February 2021 and 1 February 2023 were included in the study. Patients were prescribed GLP-1RAs for diabetes only, for obesity only, or for the combination of diabetes and obesity. Patients who were prescribed but never initiated GLP-1RAs and those for whom weight data were not available after GLP-1RA initiation were excluded.

Data Collection

The following baseline data were collected at the time of GLP-1RA initiation: age, sex assigned at birth, race and ethnicity, cardiometabolic comorbidities as documented in the medical record, CD4 cell count, HIV-1 RNA level, A1C, weight, BMI, and ART regimen prior to GLP-1RA initiation. The primary outcome was change in weight calculated as the difference between baseline weight and the most recent clinic measurement while the patient was still on GLP-1RA therapy. Secondary outcomes included changes in BMI and A1C from baseline as well as the frequency of attaining ≥5% weight loss. For patients who were prescribed >1 GLP-1RA during the study period, only data related to the GLP-1RA that they were using for the longest duration were included. If a patient switched or stopped agents, the reason for stopping the agent was documented.

Additionally, patients' ART regimen while receiving GLP-1RA therapy was collected and regimens were categorized as follows:

- Second-generation INSTI with 2 nucleoside reverse transcriptase inhibitors (NRTIs);
- First-generation INSTI with 2 NRTIs;
- Nonnucleoside reverse transcriptase inhibitor with 2 NRTIs;
- Protease inhibitor with 2 NRTIs;
- 2-drug regimen (including dolutegravir-containing 2-drug regimens); or
- Multidrug regimen not listed above.

Statistical Analyses

Absolute change in weight, BMI, and A1C was calculated for the time period from GLP-1RA initiation to the most recent clinic visit where weight and/or A1C was captured. The duration of therapy (in months) was defined as the first date of the initial GLP-1RA prescription through the most recent date that weight and BMI data for changes in weight, or A1C data for A1C changes, were recorded in the electronic health record while the patient was still prescribed the GLP-1RA. Changes in weight, BMI, and A1C were calculated for the total population, as well as subgroups that include those with a baseline BMI >30 kg/m^2,those with and without a diagnosis of diabetes, and those with differing amounts of follow-up time. Variables were compared in those with or without >5% weight loss during the study period in a univariate analysis using Pearson χ^2 test for categorical variables and Student *t* test or Mann-Whitney *U* test for continuous variables. Statistical tests were 2-tailed with statistical significance set at an α level of .05. Duration of follow-up was included as a categorical variable of 3–6 months, 6–12 months, or >12 months. Stepwise multivariable logistic regression was conducted to identify variables associated with >5% weight loss, with age, sex assigned at birth, race, ethnicity, type of GLP-1RA (reference group defined as patients receiving semaglutide), maximum dose reached (yes/no), antiretroviral regimen, CD4 count, suppressed viral load (VL <50 copies/mL), initial A1C, initial BMI, presence of diabetes, and duration of follow-up as described above being included in the models. As a supplementary analysis, multivariable linear regression was conducted using percentage weight change as the dependent variable with the same variables included in the model as listed above. Statistical analysis was conducted using MedCalc version 20.218.

The study was reviewed by the UCSD institutional review board and was deemed exempt (project number 07322).

RESULTS

Baseline Characteristics

A total of 275 PWH were prescribed a GLP-1RA agent during the study period. Of those, 50 were excluded due to lack of follow-up data (follow-up time frame <3 months, no follow-up visit, or never started agent) with 225 patients included in the final analysis. Baseline demographics prior to GLP-1RA initiation are shown in Table 1. Of note, median weight was 100.4 kg (interquartile range [IQR], 89.3–115.0 kg), median BMI was 34.0 kg/m^2 (IQR, 30.4–36.8 kg/m^2), and median A1C was 6.4% (IQR, 5.6%–8.0%). Average follow-up time on GLP-1RA to evaluate weight and A1C changes was 13 months,

Table 1. Comparison of Participants Who Did and Did Not Experience >5% Weight Loss

Characteristic	Total (N = 225)	≥5% Weight Loss (n = 99)	<5% Weight Loss (n = 126)	*P* Value
Median age, y (IQR)	56 (47–62)	57 (49–63)	55 (47–62)	.20
Race				.06
White	110 (48.9)	55 (55.6)	55 (43.7)	
Black	33 (14.7)	15 (15.2)	18 (14.3)	
Asian	7 (3.1)	0 (0.0)	7 (5.6)	
Other/mixed	71 (31.6)	29 (29.3)	42 (33.3)	
Unknown	4 (1.8)	0 (0.0)	4 (3.2)	
Ethnicity				.66
Hispanic	87 (38.7)	37 (37.4)	50 (39.7)	
Non-Hispanic	134 (59.6)	61 (61.6)	73 (57.9)	
Unknown	4 (1.8)	1 (1.0)	3 (2.4)	
Sex assigned at birth				.06
Female	40 (17.8)	23 (23.2)	17 (13.5)	
ART regimen				.65
2nd-gen INSTI + 2 NRTIs	121 (53.8)	55 (55.6)	66 (52.4)	
1st-gen INSTI + 2 NRTIs	8 (3.6)	2 (2.0)	6 (4.8)	
NNRTI + 2 NRTIs	17 (7.6)	9 (9.1)	8 (6.3)	
PI + 2 NRTIs	11 (4.9)	4 (4.0)	7 (5.6)	
2-drug regimen	38 (16.9)	14 (14.1)	24 (19.0)	
Multiclass	30 (13.3)	15 (15.2)	15 (11.9)	
Median CD4 count, cells/μL (IQR)	706 (494–938)	747 (481–971)	687 (501–922)	.43
VL <50 copies/mL	199 (88.4)	88 (88.9)	111 (88.1)	.85
Median initial weight, kg (IQR)	100.4 (89.3–115)	104.1 (91.8–116.8)	99.1 (88.1–113.2)	.04
Median initial BMI, kg/m^2 (IQR)	34.0 (30.4–36.8)	34.6 (31.5–38.3)	33.0 (29.7–36.0)	.01
Median initial A1C, % (IQR)	6.4 (5.6–8.0)	6.1 (5.5–7.9)	6.5 (5.6–8.1)	.15
Diabetes	128 (56.9)	50 (50.5)	78 (61.9)	.09
Type of GLP-1RA				.01
Dulaglutide	69 (30.7)	20 (20.2)	49 (38.9)	
Liraglutide	7 (3.1)	2 (2.0)	5 (4.0)	
Semaglutide (injectible)	116 (51.6)	60 (60.6)	56 (44.4)	
Semaglutice (oral)	17 (7.6)	6 (6.1)	11 (8.7)	
Tirzepatide	14 (6.2)	10 (10.1)	4 (3.2)	
Exenatide	2 (0.9)	1 (1.0)	1 (0.8)	
Max dose of GLP-1RA reached	85 (37.8)	40 (40.4)	45 (35.7)	.47
Follow-up time				.06
3–6 mo	62 (27.6)	20 (20.2)	42 (33.3)	
7–12 mo	66 (29.3)	29 (29.2)	37 (29.4)	
>12 mo	97 (43.1)	50 (50.5)	47 (37.3)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: A1C, hemoglobin A1C; ART, antiretroviral therapy; BMI, body mass index; GLP-1RA, glucagon-like peptide 1 receptor agonist; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

with 43.1% on therapy for >12 months. The majority of patients had at least 1 metabolic comorbidity including 56.9% with T2D, 65.3% with hypertension, 63.1% with hyperlipidemia, 4.0% with history of stroke, 24.0% with nonalcoholic fatty liver disease, and 8.0% with coronary artery disease. A total of 70.7% of patients had a regimen containing either dolutegravir or bictegravir (Table 1). For all 38 patients receiving a 2-drug regimen, 1 of the agents was dolutegravir.

Patients in our study population were prescribed a variety of GLP-1RA agents with the largest proportion receiving semaglutide injections (51.6%) and a small number (6.2%) receiving tirzepatide, the dual GLP-1 and GIP agonist (Table 1). Over the 2-year study period, 48 patients (21.3%) had changed to a different GLP-1RA agent or had stopped GLP-1RA therapy. Of these patients, 10 (20.8%) had intolerance due to side effects, 2 (4.2%) had issues with insurance coverage, 4 (8.3%) had achieved their weight loss goal, and 14 (29.2%) reported a lack of efficacy with the GLP-1RA.

Weight Loss and BMI Changes

For the overall study population, on average, patients had a 5.4 kg weight loss and a 1.8 kg/m^2 reduction in BMI, and 44% (99/225) had a >5% weight loss (Table 2). For patients with a baseline BMI ≥30 kg/m^2 before starting GLP-1RA therapy, average weight loss was 6.2 kg with 49.4% (89/180) having ≥5% weight loss (Table 2). For patients with T2D regardless of initial BMI,

Table 2. Changes in Weight, Body Mass Index, and Hemoglobin A1C Before and After Glucagon-like Peptide 1 Receptor Agonist in Subpopulations

Factor Assessed	All Patients (N = 225)	BMI ≥30 kg/m^2 (n = 180)	With T2D (n = 128)	Without T2D (n = 97)
Mean change in weight, kg	−5.4	−6.2	−3.8	−7.3
Mean change in BMI, kg/m^2	−1.8	−2.1	−1.5	−2.3
Mean change in A1C, %	−0.6	−0.5	−0.9	−0.1
>5% weight loss, No. (%)	99 (44.0)	89 (49.4)	50 (39.1)	49 (50.5)

Abbreviations: A1C, hemoglobin A1C; BMI, body mass index; T2D, type 2 diabetes.

Table 3. Changes in Weight, Body Mass Index, and Hemoglobin A1C Before and After Glucagon-like Peptide 1 Receptor Agonist Therapy, by Follow-up Time

Factor Assessed	All Patients (N = 225)	3–6 m (n = 62)	7–12 m (n = 66)	>12 m (n = 97)
Δ in mean weight, kg	−5.4	−3.6	−6.4	−5.9
Δ in mean BMI, kg/m^2	−1.8	−1.2	−2.2	−2.0
Δ in A1C, %	−0.6	−0.3	−0.5	−0.8
>5% weight loss, No. (%)	99 (44.0)	20 (32.3)	29 (43.9)	50 (51.5)

Abbreviations: A1C, hemoglobin A1C; BMI, body mass index.

average weight loss was 3.8 kg with 39.1% (50/128) having ≥5% weight loss; among these patients with T2D, the average baseline A1C was 8.1% with a mean reduction of 0.9%. For patients without T2D regardless of initial BMI, average weight loss was 7.3 kg and 50.5% (49/97) of patients without T2D had ≥5% weight loss (Table 2).

We also analyzed weight and BMI changes in our population based on length of time on GLP-1 RA therapy. The average weight loss and BMI change was 3.6 kg and 1.2 kg/m^2, respectively, for patients taking GLP-1 RA <6 months compared to 5.9 kg and 2.0 kg/m^2 for patients on >12 months of therapy. More than 51% of patients on >12 months of therapy had >5% weight loss, while only 32% of those on <6 months of therapy had achieved this degree of weight loss (Table 3).

Comparing those that did (n = 99 [44%]) and did not (n = 126 [56%]) achieve at least 5% weight loss, in the univariate analysis those that achieved ≥5% weight loss had a higher BMI at baseline, were less likely to be taking dulaglutide, and were more likely to be taking semaglutide or tirzepatide (Table 1). In the multivariable analysis, higher baseline BMI (odds ratio [OR], 1.10 [95% confidence interval {CI}, 1.03–1.16]) and use of tirzepatide (OR, 5.46 [95% CI, 1.44–20.76]) were significantly associated with ≥5% weight loss, whereas receipt of dulaglutide (OR, 0.44 [95% CI, .22–.85]) as compared to other agents and follow-up time of ≤6 months (OR, 0.32 [95% CI, .15–.67]) were significantly associated with decreased likelihood of ≥5% weight loss. Similarly, in the multivariable linear regression model in which percentage weight change was the dependent variable, follow-up time >6 months and the type of GLP-1 RA agent used were significantly associated with a greater percentage of weight loss. In addition, the absence of diabetes was also significantly associated with a greater percentage of weight loss.

DISCUSSION

Our study showed that GLP-1RAs resulted in weight loss and reduction of BMI among people with HIV and is one of the first studies to evaluate GLP-1RAs in PWH. This is consistent with studies of GLP-1RAs in the general population [19]. We observed that weight loss and decrease in BMI were more prominent in those patients with a baseline BMI ≥30 kg/m^2. Additionally, there was a numerically greater amount of weight loss in those without T2D compared to those with T2D. The decrease in A1C was relatively small; however, the baseline mean A1C was relatively low at 7.0% in the total population and 8.1% in those with diabetes. The muted weight reduction seen with GLP-1RAs in people with T2D in our study cohort is consistent with data from the semaglutide treatment effect in people with obesity clinical trials, which found that mean weight loss was lower in people with T2D than those without [20].

Not surprisingly, length of time on GLP-1RAs was associated with greater weight loss, consistent with published studies in the general population [19]. Published trials that investigated multiple doses of GLP-1RAs also reported that higher doses were associated with greater weight reduction, though it is unclear how fast doses were increased or whether maximum dosage was reached [19, 21]. Approximately 38% of patients in our study cohort achieved maximum GLP-1RA dose; however, achieving maximum GLP-1RA dose was not associated with an increased likelihood of achieving ≥5% weight loss. Other studies have not analyzed results by BMI, though we would expect those with more excess body weight to lose more. Additionally, dulaglutide, an agent originally designed for diabetes management and shown to have less of an impact on weight loss [22], was associated with less weight loss compared to other GLP-1RAs, whereas tirzepatide use was significantly associated with greater odds of achieving at least 5% weight loss.

Our findings are consistent with those of 2 prior studies examining the impact of GLP-1RAs on body weight in PWH. The first study, by Tauhid et al, focused on 35 individuals on GLP-1RAs, of whom 66% lost weight and 31% lost >5% body weight [23]. The second study by Lloyd et al specifically compared weight loss after GLP-1RA therapy in patients with T2D versus patients with T2D and HIV. They found that PWH with T2D had significantly greater weight loss compared to patients with T2D alone [24]. Our study expands upon these findings with a greater sample size, inclusion of more GLP-1RA agents, and further subpopulation analysis.

A recent randomized control study of semaglutide versus placebo in people with HIV showed that semaglutide was significantly associated with not only more weight loss but also more loss of total lean mass (5.4% vs 0.6%, $P < .01$) [25]. Patients receiving semaglutide also lost more subcutaneous adipose tissue. Taken together, there is interest in understanding whether GLP-1RAs might cause or potentiate the development of lipoatrophy. Additional prospective data are needed to better understand the risk of lipoatrophy and other potentially negative weight and metabolic effects associated with GLP-1RA therapy. These risks must be weighed against the benefits of weight loss and the cardioprotective effects that have been demonstrated with this class of medication.

Our study has several limitations. The retrospective design made it challenging to determine whether patients were truly taking their GLP-1RAs since we used GLP-1RA prescription as a proxy for therapeutic administration. However, this would have only underestimated the effect size of these agents. Additionally, the chart review did not allow for assessment of tolerability of different GLP-1RA agents and how changes in agents impacted overall weight loss. Finally, it was not possible to assess the impact of lifestyle modifications due to inconsistent documentation of these interventions in the electronic health record or the impact of other medications on A1C reduction.

CONCLUSIONS

This study has demonstrated that use of GLP-1RAs in people with HIV promotes weight loss, a reduction in BMI, and small improvements in A1C. Patients with a BMI ≥30 kg/m^2, those who were on therapy for longer durations, and those receiving tirzepatide saw the most weight loss benefit. Additional studies assessing risks of GLP-1RA use in PWH (including lipoatrophy) and determining the best implementation strategies for these medications are needed.

Note

Potential conflicts of interest. D. L. holds stock ownership in Gilead Sciences; is an advisor/consultant for EMD Serono, Theratechnologies, Janssen Pharmaceuticals, and Curio Science Workshop; has received honoraria from the American Academy of HIV Medicine and Scripps Mercy Hospital; has received payment for expert testimony from Grant & Eisenhofer, P.A., and Shook, Hardy, & Bacon, LLP.; received support for travel from EMD Serono, Theratechnologies, and Curio Science Workshop; and participated as president of the board of directors for Being Alive San Diego. Q. N. reports support for travel from the Infectious Diseases Society of America. M. T. reports grants from the National Institutes of Health (T32AI007384-29, 2UL1TR001442-06) and has received payment for presentation from DKBmed. K. P. reports grants from Janssen and AstraZeneca and has received honoraria from ViiV through Medscape. D. W. reports support for travel from Vindico; has participated on the ViiV Healthcare advisory board; and has received honoraria from Clinical Care Options and Vindico. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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