Do Weight-Loss Drugs Work for People With HIV?

In limited studies to date, semaglutide and other weight-loss drugs appear to be safe and effective for people living with HIV.

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Popular weight-loss medications such as semaglutide (Wegovy) and tirzepatide (Zepbound) look like a promising option for people with HIV who gain weight while taking antiretroviral therapy, according to studies presented at recent conferences.

“GLP-1 agonists are revolutionizing the treatment of obesity in the general population, and I have no doubt they will do the same in people with HIV,” Rajesh Gandhi, MD, of Harvard Medical School, commented in a New England Journal of Medicine conference update.

Weight gain is a growing concern for people living with HIV and their health care providers. Not only do many people find weight gain and body shape changes distressing, but they also raise the risk for cardiovascular disease, fatty liver disease and other health problems.

Research continues to yield conflicting findings about weight changes after starting or switching antiretrovirals, especially integrase inhibitors. Numerous studies have found that people who start a new regimen can gain weight, sometimes as much as 10 or even 20 pounds. This appears to be more likely when people switch away from tenofovir disoproxil fumarate (Viread) or efavirenz (Sustiva), which have a weight-suppressing effect. Weight gain among HIV-positive people may also be attributable to a return to health after starting treatment or normal changes that occur with age.

People with HIV are often urged to take steps to manage their weight, but this is easier said than done. In general, changing antiretrovirals in an effort to lose weight does not seem to have much effect. Maintaining a healthy diet and getting more exercise is sound advice, but for many people, lifestyle changes are not enough to shed excess pounds.

The use of weight-loss medications has recently skyrocketed, so much that they are in short supply. In June 2021, the Food and Drug Administration approved semaglutide (brand name Wegovy; previously approved for type 2 diabetes as Ozempic) for people with obesity and those with overweight who have additional comorbidities, such as hypertension or abnormal blood fat levels. In November 2023, the agency approved tirzepatide (brand name Zepbound; previously

approved for diabetes as Mounjaro) for the same indication. Both drugs are self-injected once weekly. An oral formulation of semaglutide (Rybelsus) is not approved for weight loss.

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that mimics a natural hormone that suppresses appetite, regulates insulin and blood sugar levels and slows emptying of the stomach. Tirzepatide mimics the action of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Other related drugs, including orforglipron and retatrutide (which mimics three hormones), are currently in the pipeline.

Semaglutide and tirzepatide are generally safe, but they can cause side effects, including nausea, vomiting, diarrhea, constipation and abdominal pain and bloating. More serious adverse events may include gastroparesis (stomach paralysis) and pancreatitis. They can lead to loss of lean muscle mass as well as fat, which may be a concern for older people. Weight typically rebounds after the medications are discontinued. What's more, at over $1,000 per month, the drugs are expensive, and they may not be covered by health insurance.

In clinical trials of HIV-negative people, nondiabetic adults with obesity who used semaglutide reduced their weight by around 15% on average (about 34 pounds), while those who used higher doses of tirzepatide lost around 20% (about 50 pounds). In addition, semaglutide may improve fatty liver disease, and a recent study showed that it reduced the risk of heart attacks and strokes in nondiabetic people with obesity and cardiovascular disease. These would be important benefits for HIV-positive people, who are at greater risk for liver and heart disease compared with their HIV-negative peers.

But how well do weight-loss drugs work for people living with HIV?

Weight Gain on Antiretroviral Therapy

As reported at the International AIDS Society Conference on HIV Science (IAS 2023) this summer, Marisa Brizzi, PharmD, of the University of Cincinnati, and colleagues evaluated the effect of GLP-1 receptor agonists on metabolic outcomes in HIV-positive and HIV-negative people with type 2 diabetes. They hypothesized that GLP-1 might be depleted during HIV infection and that integrase inhibitors might disrupt fat cells, affect hormones that regulate glucose and lipid metabolism, stimulate appetite or reduce insulin sensitivity.

This retrospective cohort study included 15 adults with HIV matched with 30 HIV-negative people. Nearly 90% were men, and the mean age was 57 years. Most of the HIV-positive people were on integrase inhibitors. A majority (73%) used dulaglutide (Trulicity) and 13% used liraglutide (Victoza for diabetes or Saxenda for weight loss), two older and less effective drugs; only 13% used semaglutide, and none used tirzepatide.

HIV-positive people with diabetes lost about 23 pounds, on average, compared with about 4 pounds for HIV-negative people, or 8.0% versus 1.5% of their baseline body weight. What's more, 60% of people with HIV achieved at least 5% weight loss, compared with 33% of HIV-negative

participants.

In this cohort, people with HIV and diabetes “had significantly greater weight loss” compared to people with diabetes alone, the researchers concluded. “The greater weight loss observed in people with HIV may be related to differences in the mechanistic pathways leading to weight gain.”

While these results appear to suggest that people with HIV might benefit more from weight-loss drugs, most participants used older medications, and the amount of weight lost in the HIV-negative group was substantially lower than that seen in pivotal trials of semaglutide and tirzepatide for people without diabetes.

In a related study, presented at IDWeek in October, Quynh Nguyen, a medical student at the University of California San Diego, and colleagues looked at prescribing practices and clinical outcomes among people with HIV who used weight-loss drugs. This retrospective cohort study included 225 adults with overweight or obesity who were prescribed GLP-1 receptor agonists between February 2021 and February 2023. A majority were men, and the average age was 54. Most were on integrase inhibitors, 90% had an undetectable viral load and CD4 counts were high.

In this study, 53% received injectable semaglutide, 31% used dulaglutide, 8% used oral semaglutide, 6% used tirzepatide and 3% used liraglutide. Ninety-nine people (43%) received the drugs for weight management alone, while the rest also had type 2 diabetes. Participants used the medications for about 15 months, on average.

People who received GLP-1 drugs lost about 12 pounds, on average. Nearly a quarter achieved greater than 5% weight loss, body mass index (BMI) fell by 1.8 and 18% went from obesity to overweight classification; blood glucose (hemoglobin A1C) also decreased. Those without diabetes tended to lose more weight. People with a higher baseline BMI and longer duration of treatment were more likely to experience greater than 5% weight loss, while those who used dulaglutide were less likely to do so. Age, sex, race/ethnicity, HIV viral load, CD4 count and antiretroviral regimen were not predictive of weight change.

“Use of GLP-1 receptor agonists led to improvements in weight, BMI and hemoglobin A1C among people with HIV and offers an additional strategy to address weight gain and related metabolic complications,” the researchers concluded.

Lipohypertrophy

In another study presented at IDWeek, Grace McComsey, MD, of Case Western Reserve University in Cleveland, and colleagues assessed the effects of semaglutide on lipohypertrophy, or abnormal fat accumulation, in people with HIV. McComsey noted that it’s not just weight that matters but also where fat is located. Visceral fat deep within the abdomen is more strongly associated with cardiovascular disease and other health problems than subcutaneous fat under the skin.

This trial enrolled 108 nondiabetic adults on stable antiretroviral therapy with viral suppression. A

majority (60%) were men, and the median age was 52. More than 80% were on integrase inhibitors, and CD4 counts were high. They had a BMI of 25 or higher (indicating overweight or obesity), a large waist circumference or waist-to-hip ratio and reported that they developed increased abdominal girth after starting antiretrovirals. They were randomly assigned to receive semaglutide or a placebo once weekly for 32 weeks. CT and DEXA scans were done to measure total, visceral, subcutaneous, trunk and limb fat, lean body mass and body composition.

Body weight fell by 8.3% in the semaglutide group while rising by 0.2% in the placebo group. A majority (65%) of people taking semaglutide, but only 4% of those taking the placebo, achieved at least 5% weight loss. BMI also decreased significantly in the semaglutide group.

Total fat fell by 15% in the semaglutide group but rose by 0.2% in the placebo group. Visceral and trunk fat fell by 13% and 17% in the semaglutide group but increased by 5% and 0.4%, respectively, in the placebo group. Subcutaneous and limb fat both fell by 13% in the semaglutide group; in the placebo group, subcutaneous fat rose by 1.5% and limb fat was unchanged. Lean body mass fell by 5.4% in the semaglutide group compared with just 0.6% in the placebo group. Fat accumulation in the liver and around the heart did not change much in either group.

Semaglutide was safe and well tolerated, McComsey reported. Side effects were common, but severe or serious adverse events were rare. Adherence was good despite the COVID-19 pandemic and the need for weekly injection visits. (Outside of clinical trials, most people use self-injection pens.)

“Semaglutide significantly decreased central fat in people with HIV with lipohypertrophy, primarily driven by reductions in visceral adipose tissue,” the researchers concluded. “Semaglutide may offer an effective treatment to decrease visceral adiposity and reduce comorbidity risk.”

McComsey noted that the loss of lean body mass could be a problem for a population prone to losing muscle and bone mass over time, and there is concern that lipoatrophy, or fat wasting in the face and limbs, could worsen.

A study presented at the recent European AIDS Conference (EACS 2023) raised another potential concern. Sebastian Noe, MD, of MVZ München am Goetheplatz, and colleagues assessed the effect of GLP-1 receptor agonists on circulating CD4 cells in HIV-positive people with sustained viral suppression. Based on previous studies of related drugs, they hypothesized that these medications might lead to a decrease in CD4 counts.

This retrospective analysis included 76 people with HIV treated with semaglutide or dulaglutide for type 2 diabetes or obesity at two HIV clinics in Germany. Most were white men in their 50s, and about half had diabetes. The median current CD4 count was high, above 800, but the median nadir (lowest-ever) count was just under 300. The data suggested that GLP-1 receptor agonist use “might be associated with a non-time-dependent decrease in CD4 cells,” with a median decrease of 64 cells, but not everyone was equally affected. “Further research is needed to confirm our findings and to identify people living with HIV at risk of a relevant decrease in CD4 cells,” the

researchers concluded. “The clinical relevance of these findings merits further investigation.”

Finally, another study at IDWeek evaluated the effect of tesamorelin (Egrifta) on visceral fat in people taking integrase inhibitors. Tesamorelin, a synthetic growth hormone-releasing factor analog, works differently from GLP-1 receptor agonists, acting on the pituitary gland in the brain to stimulate growth hormone production. A previous study showed that it reduced visceral adipose tissue by about 15% in HIV-positive people with lipohypertrophy, but the research was done before integrase inhibitors were the preferred treatment for HIV.

Therefore, Taryn McLaughlin, PhD, of Theratechnologies, Steven Grinspoon, MD, of Massachusetts General Hospital, and colleagues asked whether tesamorelin would have a similar effect for people taking integrase inhibitor regimens. They drew on data from a previous trial that enrolled 61 HIV-positive participants with fatty liver disease. Of these, 39 (64%) were on integrase inhibitors, most commonly dolutegravir (41%). They were randomly assigned to take tesamorelin or a placebo for 52 weeks.

At baseline, demographics, HIV-related variables and body composition measurements were similar for integrase inhibitor recipients and those taking other antiretrovirals. Over a year of treatment, BMI did not change significantly in the tesamorelin or placebo groups. Integrase inhibitor recipients assigned to tesamorelin saw an 8.3% reduction in visceral adipose tissue, while placebo recipients had a 10.8% increase. Furthermore, the tesamorelin group experienced a 5% decline in liver fat from baseline while the placebo group saw no change. People taking integrase inhibitors in the placebo group experienced a gain in visceral fat despite no change in BMI, while tesamorelin reduced both visceral and liver fat, the researchers concluded.

The Bottom Line

Taken together, these studies indicate that weight-loss medications hold promise for people with HIV who struggle to lose weight or shed abdominal fat. But research in this population is still limited, and the medications are not without drawbacks, including side effects and cost.

“Because some people with HIV have fat maldistribution, with disproportionate central adipose tissue hypertrophy, the finding that semaglutide reduces visceral adipose tissue is particularly welcome,” Gandhi commented. “We have known for years that excessive visceral fat is associated with an increased risk for cardiac disease, so the impact of GLP-1 agonists on cardiometabolic health in people with HIV could be substantial.”

Speaking at the IAS conference, Francois Venter, MD, of the University of the Witwatersrand in South Africa, put recent studies in context, emphasizing that weight management is key to preventing and treating metabolic problems in people living with HIV.

“In the last few weeks alone, there’s been an explosion of new [weight-loss] agents, but they are eye-wateringly expensive in rich countries and completely unavailable in low- and middle-income countries,” he said. “Lifestyle changes, exercise and diet are incredibly important for your health, but to shift weight downwards in someone with established weight gain is next to impossible. You

really do need pharmaceutical or surgical help.”

Venter urged advocates to push for more trials to test weight-loss medications for people with HIV. One such study, the SWIFT trial (NCT04174755), is currently underway, comparing semaglutide plus a lifestyle intervention versus lifestyle changes alone; results are expected in 2025. Once the drugs are approved, he suggested, further activism will likely be needed to ensure broad access.

Click here for more news about HIV and weight gain.

Click here for more reports from IAS 2023, IDWeek 2023 and EACS 2023.

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