Weight Gain and HIV

Some HIV meds are linked to weight gain, but we don't yet know why.

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In recent years, there's been a growing recognition that weight gain is common among people with HIV who are on modern antiretroviral therapy. Much remains to be learned about the causes of HIV-associated weight changes, but in the meantime, you can take steps to manage weight gain and minimize its health consequences.

Overweight and obesity are growing problems in the United States and worldwide due to the increased availability of high-calorie food and decreased physical activity. Experts estimate that as many as 70% of Americans are overweight. And people living with HIV have not been spared.

"Weight gain certainly has been a very big issue in the HIV research world for the last two years," says Monica Gandhi, MD, MPH, the medical director of Ward 86, the HIV clinic at Zuckerberg San Francisco General Hospital. "It's a very consistent finding that's been reported at conference after conference."

In the early years of the epidemic, wasting syndrome, or overall loss of both fat and lean muscle mass, was a hallmark of AIDS. After the advent of effective antiretroviral treatment, weight gain was often a sign of a return to health. But today, excessive weight gain is a more common problem. One study found that more than half of HIV-positive people on long-term treatment struggle with overweight or obesity.

People with HIV may experience different types of weight gain. One type, known as lipohypertrophy (part of lipodystrophy syndrome), involves the buildup of visceral fat deep within the abdomen, resulting in a hard belly. Today, lipodystrophy is most often seen among people who have lived with HIV for a long time and used older antiretrovirals.

The more common generalized weight gain—seen in HIV-positive and HIV-negative people alike—involves an increase in both internal abdominal fat and subcutaneous fat beneath the skin, often around the belly, hips and thighs. Some people gain lean muscle mass as well.

In part, generalized weight gain among people with well-controlled HIV reflects the fact that HIV-positive people have the same lifestyle risk factors as the HIV-negative population, including an unhealthy diet and inadequate physical activity. But unexpected weight gain among people starting antiretrovirals—often several pounds in a short period—appears to be a different problem,

and it may have little connection to how much people eat or exercise.

Excess body weight, and especially visceral fat gain, are linked to a host of health problems, ranging from cardiovascular disease to cognitive impairment. (Click here for “Health Risks of Weight Gain.”) What’s more, weight gain can have a negative effect on self-esteem, contribute to depression and leave people less willing to start or stay on antiretroviral treatment. Thus, managing weight gain has become a key focus in the HIV field.

What Do We Know?

After the advent of effective HIV treatment in the mid-1990s, lipohypertrophy was initially blamed on early protease inhibitors, some of which can cause metabolic abnormalities that contribute to fat gain. But it soon became clear that this was not the whole story.

A study by John Koethe, MD, of Vanderbilt University Medical Center in Nashville, and colleagues analyzed weight gain among more than 14,000 people in the North American NA-ACCORD cohorts who started treatment between 1998 and 2010. They found that 22% of people progressed from a normal body mass index (BMI) to overweight, and 18% went from overweight to obesity, within three years after starting treatment.

A more recent analysis of over 8,000 HIV-positive Kaiser Permanente members who began treatment after 2006 found that while people with HIV were less likely than their HIV-negative counterparts to be overweight or obese at the start of the study, they gained weight faster—0.5 pounds versus 0.2 pounds per year, on average, over 12 years of follow-up.

More rapid weight gain among people with HIV is a concern because it will likely worsen health conditions, such as cardiovascular disease, that are already more common among those living with the virus, according to Michael Silverberg, PhD, MPH, of Kaiser Permanente Northern California.

Weight gain can occur after starting any class of antiretroviral drugs, but some of the newest highly potent and easily tolerated meds are the most common culprits.

The late-stage clinical trials that led to the approval of modern antiretrovirals did not report weight gain as a side effect. However, many of these studies did not systematically record weight, BMI or the presence of overweight or obesity at baseline and after treatment initiation.

This started to change after the new drugs came into widespread use. In 2017, a short research letter in the journal AIDS described weight gain as an “unexpected bothering side effect” of the integrase inhibitor dolutegravir. Soon thereafter, reports of excess weight among people starting integrase inhibitors began to snowball, and today, weight gain is a major topic at HIV conferences.

Along with integrase inhibitors, the newer tenofovir alafenamide (TAF) is more often associated with weight gain than the older tenofovir disoproxil fumarate (TDF). TDF protects against weight gain and blood lipid abnormalities, while TAF does not have this effect. Combining drugs that

promote weight gain can have an additive effect: Dolutegravir plus TAF has been linked to the biggest gains.

Another study by Koethe and colleagues pooled data from more than 5,600 people who started treatment in eight large clinical trials sponsored by Gilead Sciences between 2003 and 2015. They found that weight gain was greater in more recent studies and in those that tested newer regimens. Nearly half of the participants experienced at least a 3% gain in body weight, more than a third had at least a 5% gain and nearly one in five had at least a 10% gain during the two years after starting treatment.

Overall, the average gain was just over 4 pounds. But when broken down by specific drug class, those who started on integrase inhibitors gained about 7 pounds compared with about 4 pounds for those who used either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors. Among the integrase inhibitors, the average gain was about 9 pounds with dolutegravir or bictegravir versus 6 pounds with elvitegravir. Among those who started NNRTIs, the average gain was nearly 7 pounds with rilpivirine (continued on page 7) versus 4 pounds with efavirenz. And among the nucleoside/nucleotide reverse transcriptase inhibitors, the average gain was about 9 pounds with TAF, nearly 5 pounds with TDF and nearly 7 pounds with abacavir.

A larger NA-ACCORD analysis of nearly 23,000 people starting first-line treatment found that those who used integrase inhibitors or protease inhibitors gained an average of about 12 pounds after five years on treatment, compared with about 8 pounds for those who started NNRTIs. Here, too, those who started dolutegravir saw the greatest gains: nearly 16 pounds on average.

“Our findings raise the possibility that modern antiretroviral therapy regimens with improved tolerability and potency may lead to weight gain in some people living with HIV, necessitating increased clinical attention to the maintenance of healthy body weight, lifestyle modification and exercise at [treatment] initiation,” Koethe and colleagues concluded.

Like people starting treatment for the first time, those who switch regimens may also gain weight. Another NA-ACCORD analysis found that among 870 people who switched treatment and maintained a low viral load, switching from an NNRTI to an integrase inhibitor was linked to more weight gain, driven primarily by dolutegravir.

A study of the OPERA cohort included more than 115,000 people in 65 U.S. cities who were taking a three-drug regimen containing TDF. Those who switched from TDF to TAF without changing their other meds gained an average of about 5 pounds during the ensuing nine months, regardless of the other drugs in their regimen. But those who also switched to an integrase inhibitor gained up to twice as much.

There is not much data yet about weight gain associated with the experimental long-acting integrase inhibitor cabotegravir, which is given by injection every month or two instead of taken as a daily pill. But so far, studies have not reported major weight changes.

Who Is at Risk?

Not everyone is equally prone to weight gain after starting or switching antiretrovirals. People who start treatment with a lower CD4 T-cell count or higher viral load are more likely to gain weight. In fact, in the eight-trial analysis, a lower pretreatment CD4 count was the strongest risk factor.

Older people are more likely to develop lipodystrophy, and some research suggests they are at greater risk for generalized weight gain as well, although study results have been mixed. But even adolescents starting treatment with dolutegravir have experienced unusual weight gain.

Perhaps most strikingly, women tend to put on more pounds than men, as do Black people compared with white people—meaning Black women with HIV are particularly susceptible to weight gain.

Women and people of color have been underrepresented in HIV research in the United States and Europe. Studies of mostly white men appear to have underestimated the problem of treatment-associated weight gain, highlighting the importance of greater diversity in clinical trials.

The ADVANCE trial in South Africa looked at more than 1,000 people starting first-line HIV regimens; most were Black, and 60% were women. Two years after they started treatment, men gained an average of about 3 pounds on a regimen containing efavirenz plus TDF, 8 pounds on dolutegravir plus TDF and 11 pounds on dolutegravir plus TAF. Among women, the corresponding gains were about 7, 10 and 18 pounds. A smaller subset of participants followed for nearly three years saw continued weight gain, reaching 16 pounds for men and 27 pounds for women taking dolutegravir plus TAF. One in four men and over half of the women taking this combo saw a weight gain of 10% or more, and 8% of the men and 23% of the women met the criteria for obesity.

These findings are “a call to arms,” Sara Bares, MD, of the University of Nebraska Medical Center in Omaha, wrote in a recent editorial. “As we continue to investigate the causes, consequences and management of weight gain following [antiretroviral therapy] initiation (and switch), we must strive to enroll sufficient numbers of women from diverse racial and ethnic backgrounds to allow for sex- and race-stratified analyses.”

What Causes Weight Gain?

The causes of weight gain among people living with HIV are still not fully understood, but they appear to involve a complex interplay of the effects of the virus and its treatment on immune function, inflammation and metabolism.

People with advanced immune suppression and opportunistic illnesses often gain weight as they return to health after starting treatment. HIV infection increases metabolic demands, and stopping viral replication reduces energy expenditure—leading to weight gain if food intake stays the same. Some experts think the seesaw effect as HIV depletes the immune system and antiretrovirals restore immune function may trigger fat gain. Treatment also limits the detrimental effects of HIV on fat cells and prevents opportunistic infections that cause diarrhea, a major cause of weight loss. Plus, people who feel better tend to eat more.

But this return-to-health effect does not fully explain treatment-associated weight gain, which occurs even among people who start treatment early and those who switch to newer antiretrovirals with a fully suppressed viral load and a normal CD4 count. One small study found that people starting treatment gained weight despite no changes in appetite, eating habits, calorie consumption or metabolic rate. Newer meds are less likely to cause side effects that lead to weight loss, such as nausea, diarrhea and reduced appetite, but this is also not an adequate explanation.

Even with effective treatment, chronic HIV infection triggers ongoing immune activation and inflammation, which promotes fat accumulation. What's more, the virus damages the gut, leading to changes in the microbiome and leakage of bacteria that spurs inflammation; antiretrovirals may not fully reverse this damage.

In a study of people who gained weight after starting treatment, those who had biomarkers indicating a high level of immune activation were more likely to gain weight—an effect that was most pronounced among women.

Studying HIV-negative people who take antiretrovirals for pre-exposure prophylaxis (PrEP) can help tease out the return-to-health effect. In the DISCOVER trial, people who switched from TDF/emtricitabine to TAF/emtricitabine for PrEP gained more than 2 pounds on average over a year, while those who stayed on the TDF combo saw no change in weight.

Several mechanisms have been proposed to explain why integrase inhibitors, in particular, lead to weight gain. Some studies suggest this class of drugs may damage fat cells, interfere with hormones produced by fat tissue and promote insulin resistance. What's more, dolutegravir appears to block a receptor for melanocyte-stimulating hormone, which plays a role in regulating appetite.

In summary, much remains to be learned, and weight gain will continue to be an active area of HIV research.

"I'm concerned that we don't understand why weight gain is happening," says Steven Grinspoon, MD, a professor of medicine at Harvard Medical School and director of the Nutrition Obesity Research Center at Harvard. "Are there genetic predispositions? What is the mechanism of it? Will the weight gain reverse over time? There are many unanswered questions. We also don't have good data as to whether the fat [linked to] integrase inhibitors is associated with the same types of morbidities as weight gain in general."

"There may be an element of return to health involved, but for some people, it's much more than that—you can't tell me that someone who gains 20 or 30 pounds is returning to health," he adds. "That's a small minority of patients, but for that minority, it's important. I think we should study those people that have the most severe weight gain to see if there's anything special about them."