More Studies Explore Weight Gain Linked to HIV Treatment

Disruption of fat metabolism and altered gut microbiome may help explain weight changes associated with antiretroviral therapy.

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Studies presented at the recent 30th Conference on Retroviruses and Opportunistic Infections (CROI) shed more light on factors that affect weight changes after starting or switching antiretroviral treatment.

In recent years, there has been growing concern about weight gain associated with antiretroviral therapy. Unwanted weight gain is not just a cosmetic or self-esteem issue. Excess weight—especially the accumulation of visceral abdominal fat deep within the belly—raises the risk of cardiovascular disease, diabetes, fatty liver disease, several types of cancer and other health problems.

Some prior studies have found that people who start or switch to a regimen containing certain integrase inhibitors or tenofovir alafenamide (TAF), especially in combination, are more likely to gain weight. A recent analysis of participants in the ongoing REPRIEVE cardiovascular trial, published in Clinical Infectious Diseases, found that integrase inhibitor use was associated with modest weight gain during the first two years but not after that point. Conversely, switching from TAF to the older tenofovir disoproxil fumarate (TDF) may help people lose weight. But study results are inconsistent, and weight changes related to HIV and its treatment remain poorly understood.

Factors Linked to Weight Gain and Loss

In another recent study, published in the Journal of Antimicrobial Chemotherapy, Sophie Grabar, MD, MPH, of Hôpital St Antoine in Paris, and colleagues looked at weight gain among nearly 13,000 people starting HIV treatment in the French Hospital Database HIV cohort, comparing outcomes among people with early disease (primary infection or a CD4 count above 350 and a viral load below 100,000) and advanced disease (a CD4 count below 200 or a diagnosis of AIDS). Those with early disease were more likely to have obesity while those with advanced disease were more likely to be underweight at the time of treatment initiation.

After 30 months, people with advanced HIV were three times more likely to experience substantial weight gain than those who started treatment early (63% versus 21%, respectively). What's more,

those with advanced disease gained more weight (about 21 pounds versus about 6 pounds). The integrase inhibitors raltegravir (Isentress) and dolutegravir (sold alone as Tivicay and a component of the Triumeq, Dovato and Juluca coformulations), as well as TAF, were associated with more weight gain than other drugs. In part, the greater weight gain among people with advanced disease could reflect a return to health, but the likelihood of increased weight was higher among both underweight people and those with obesity compared with those of normal weight.

Turning to weight loss, researchers with the Dutch ATHENA cohort looked at weight changes among more than 6,000 individuals with viral suppression who had switched to TAF, an integrase inhibitor or both. Of these, about one quarter had gained at least 7% of body weight within two years after switching.

The 21 participants who later switched away from TAF had gained a median of about 7 pounds after the initial switch and lost about 3 pounds after the second switch. The 37 people who later discontinued an integrase inhibitor had gained a median of about 13 pounds after the first switch and then lost nearly 6 pounds after the second switch. The 11 people who discontinued both drugs had gained about 12 pounds and later lost about 4 pounds. People who stayed on the same regimen lost about 2 pounds. The only factor that predicted greater weight loss was having obesity (a body mass index [BMI] of 30 or higher) at the time of the second switch. The researchers concluded that weight gain associated with TAF or integrase inhibitors "appears to be only partially reversible" after discontinuing these drugs, but weight remained "relatively unchanged" among those who stayed on them.

Cabenuva Does Not Cause Weight Gain

While some modern integrase inhibitors have been linked to weight gain in several studies, this does not appear to be the case for cabotegravir, a component (with rilpivirine) of the long-acting injectable regimen Cabenuva.

The Phase IIIb SOLAR study is the first head-to-head trial comparing Cabenuva versus Biktarvy, a once-daily single-tablet regimen containing the integrase inhibitor bictegravir, TAF and emtricitabine. People who had started Biktarvy as their first treatment, took it for at least six months and had an undetectable viral load either switched to Cabenuva (447 participants) or stayed on the same regimen (233 participants). In both groups, more than 80% of participants were men, about 70% were white and about 20% were Black.

After one year, people taking either regimen were equally likely to maintain viral suppression (90% with Cabenuva and 93% with Biktarvy). Virological failure was rare—1% or less—in both groups.

In a related analysis, Darrel Tan, MD, of St. Michael's Hospital in Toronto, and colleagues looked at weight and metabolic changes among SOLAR participants. At study entry, more than one third were classified as overweight and just over 20% had obesity; altogether, 59% were above normal weight. Insulin resistance was common in both groups, at just over 40%, but only 4% had diabetes; 17% had metabolic syndrome, and 9% were taking lipid-lowering medications.

After a year, weight remained stable in both groups, even though Cabenuva recipients switched away from TAF. People who switched to Cabenuva saw a median loss of less than 1 pound while those who stayed on Biktarvy gained about 1 pound; 3% and 4%, respectively, experienced a weight increase of 10% or more. Most people stayed within the same BMI category. There were no clinically relevant changes in waist circumference, hip circumference or waist-to-hip ratio in either group. Furthermore, the proportion of people with insulin resistance or metabolic syndrome remained stable in both groups. Tan noted that further analyses would be done to see whether certain people are more likely to experience weight and metabolic changes, as prior research suggests that women—especially Black women—are more prone to treatment-associated weight gain.

What Causes Weight Gain?
Some studies presented at CROI explored mechanisms underlying weight gain associated with HIV treatment

Ikrak Jung, PhD, of Johns Hopkins University School of Medicine, and colleagues hypothesized that integrase inhibitors might disrupt adipose (fat) tissue function via estrogen receptors. “Estrogen is recognized as a master regulator of the energy homeostasis and is a major determinant of sex differences in the control of energy homeostasis,” they noted as background.

In a laboratory study, precursor fat cells were exposed to dolutegravir or the non-nucleoside reverse transcriptase inhibitors efavirenz (Sustiva) or doravirine (Pifeltro and Delstrigo) during differentiation into mature white or brown adipocytes. White adipocytes store fat, while brown adipocytes, which contain more mitochondria, release energy to maintain body heat (a process known as thermogenesis). Dolutegravir—but not the other two drugs—appeared to interfere with mitochondrial activity and thermogenesis in normal brown fat cells but not in engineered cells with deleted estrogen receptors. “These findings suggest a novel mechanism by which [integrase inhibitors] may lead to weight gain potentially in a sex-dependent manner,” the researchers concluded.

Sandra Pinto-Cardoso, PhD, of Instituto Nacional de Enfermedades Respiratorias in Mexico, and colleagues asked whether the gut microbiome—the ecosystem of bacteria and other microorganisms in the intestines—might influence weight gain in people taking integrase inhibitors. They looked at changes in the gut microbiome in people with viral suppression who switched from efavirenz/TDF/emtricitabine (the drugs in the Atripla coformulation) to Biktarvy. They collected stool samples from 63 people, including seven women, one year after the switch.

More than three quarters of the participants (45 men and four women) gained weight, including 19 who gained more than 5% and six who gained more than 10% of body weight. Fourteen of the remaining participants lost weight. Bacteria diversity in the gut increased after the switch—generally a sign of a healthier microbiome. In particular, levels of Faecalibacterium, a type of anti-inflammatory commensal bacteria, increased. Biomarkers of microbial translocation (leakage of bacteria from the gut that can trigger inflammation) improved, but levels of sCD163 (a marker of innate immune activation associated with cardiovascular problems) increased. However,

individual participants' microbiomes varied greatly. "Assessment of complex biological pathways involved in weight gain, obesity, host metabolism and the gut microbiota in the context of treated HIV infection may lead to the identification of novel therapeutic targets," the researchers suggested.

Importantly, it is unclear to what extent specific antiretrovirals actually cause weight gain themselves. In part, weight gain when switching treatment occurs because drugs that suppress weight are discontinued in favor of those that don't. The older TDF is known to suppress weight and lower lipid levels; this has been observed even among HIV-negative people using TDF/emtricitabine (Truvada) for pre-exposure prophylaxis. The newer TAF does not have this effect, so when TAF is substituted for TDF, weight can go up. The same may also be true for efavirenz. In fact, people who metabolize efavirenz slowly and therefore have higher drug levels are most likely to lose weight. Many people who previously used both efavirenz and TDF have switched to regimens containing an integrase inhibitor plus TAF, which could in part explain why they gain weight.

Taken together, these study findings underscore the importance of personally tailored treatment that takes into account comorbidities and other individual factors that could raise the risk of undesired weight changes.

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