Weight Gain and HIV Antiretrovirals: Lipodystrophy for the Integrase Era

#1 in TheBodyPro's Top 10 HIV Clinical Developments of 2019

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As 2019 draws to a close, TheBodyPro takes stock of the year's most noteworthy developments in HIV. And not just any developments: We're looking specifically at those with the largest impact for people who provide HIV care and services in the U.S. In this series, veteran clinician-researcher David Alain Wohl, M.D., guides us through the new research and other important moments of 2019 that have the greatest potential to alter the HIV clinical landscape in the months and years to come.

"Can this stuff make you gain weight?" Meg, a 48-year-old woman, asked as she plopped down into a seat after being checked in by the nurse.

A few months before, in late 2018, I had finally convinced Meg to switch from the lopinavir/ritonavir (Kaletra) she had been on for over a decade in favor of the integrase inhibitor dolutegravir (Tivicay) plus emtricitabine/tenofovir alafenamide (F/TAF, Descovy). It was not an easy sell to a long-term survivor who credited her regimen with saving her life, but my warnings of potential drug interactions and my "It will only be two tiny pills!" pitch wore down her reluctance. A supervisor at a nursing home and

mother to two teens, Meg at first appreciated the convenience of her new meds. I smiled and did the "told you so" thing at our first post-switch follow-up.

But then the scales tipped -- literally. She wanted to know if I was responsible for the 23 lb. weight gain that ruined her waistline. And I had to admit: I was.

Reports of integrase strand transfer inhibitor (INSTI)-associated excessive weight gain started circulating as early as 2017 (this "signal" was included in our 2018 Top Ten at position No. 3). But the data at that time were from observational cohorts and antiretroviral switch studies where confounding factors were hard to either measure or avoid.

At the International AIDS Society conference in July 2019, any doubts that newer INSTI can cause weight gain faded further with each slide Michelle Moorhouse clicked through, as she showed the changes in weight experienced by participants in the NAMSAL and ADVANCE trials -- both of which were comparative studies of first-line antiretroviral regimens in men and women in sub-Saharan Africa (Cameron and South Africa, respectively). In each of these trials, a regimen of emtricitabine/tenofovir disoproxil fumarate (TDF/FTC, Truvada) plus dolutegravir was compared to efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF, Atripla). In the ADVANCE study, there was a third arm of F/TAF plus dolutegravir.

The mean increase in weight among those assigned the INSTI in the trials was remarkable -- and was particularly pronounced in women. In updated data from the ADVANCE trial subsequently presented at the European AIDS Conference in November, the mean change in weight for women was:

- 9 kg among those assigned F/TAF plus dolutegravir
- 5 kg among those on TDF/FTC plus dolutegravir
- 3 kg among those receiving EFV/FTC/TDF

In each of these study treatment arms, the gains experienced by women were 2 kg to 3 kg greater than those observed in the male participants.

Importantly, almost everyone in the ADVANCE trial gained 10% or more of their baseline weight, and the proportion that gained even more than that has increased over time. Whole body DEXA scan data from a subset of participants show that while much of this weight gain was trunk fat (especially for women), limb fat and lean tissue also increased.

Beyond the dissatisfaction some may experience from packing on the pounds, there is the additional concern of the adverse health consequences that accompany being overweight or obese. In one report, INSTI treatment in a longitudinal German cohort was associated with weight gain and hepatic steatosis. In addition, an analysis from the NA-ACCORD study linked INSTIs (as well as protease inhibitors) with incident diabetes mellitus, thought it has yet to examine whether weight gain mediated this association.

While the spotlight has been mostly on dolutegravir, there is evidence that its antiretroviral classmate bictegravir (BIC) -- as well as the NRTI TAF, with which it is often paired -- also boost weight more than alternative agents. An analysis of eight

Gilead Sciences-sponsored trials conducted by the company comparing a variety of initial regimens found nearly identical trends in weight gain for bictegravir and dolutegravir. TAF also produced greater increases than TDF (or abacavir, for that matter), as was observed in ADVANCE.

The Bottom Line on HIV Integrase Inhibitors and Weight Gain

In a busy year buzzing with the flight of potentially revolutionary new HIV medications, evidence of large weight increases accompanying dolutegravir and bictegravir has been a bombshell. These antiretrovirals had been hailed as the end product of decades of therapeutics evolution; are potent; have a high barrier to viral resistance; and play well with other meds. But, as their market share grew, so did the waist circumference of our patients -- although, initially, we may not have noticed. I certainly didn't.

But with the clinical trial data presented this year, we now know without a doubt that some of our favorite new meds may cause weight gain, especially when taken by women -- and particularly by women who are black. The pathogenesis of this (apparently generalized) increase in fat and lean tissue is not clear.

Unfortunately, there is not yet any information on the effects of switching antiretrovirals when excessive weight does occur. That said, clinical trials show that reported changes in weight following the initiation of newer non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been significantly less than those seen with INSTIs. In particular, in an analysis of changes in weight experienced by participants in clinical trials of doravirine (Pifeltro), the differences at 96 weeks between three drugs -- this NNRTI, efavirenz (Sustiva) and ritonavir-boosted darunavir (Prezista) were fairly modest. (Note that these participants were mostly men and white; but the same can be said for the Gilead studies.)

Given these data, it is tempting to switch the INSTI for an NNRTI such as doravirine or rilpivirine (Edurant). This is what I did for Meg, and it worked. An N=1 forced experiment! Of course, real studies need to help guide such switches on a larger scale.

Right now, I believe that the sum of the benefits of dolutegravir, bictegravir, and TAF are greater than the risks vis-a-vis weight gain. However, now that I am sensitized to the problem, I am tracking my patients' weight closely, looking for an antiretroviral smoking gun through the haze of soft drinks, fast food, and Little Debbies.

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