Title:

Do Integrase Inhibitors *Cause* Weight Gain?

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A majority of initial and salvage antiretroviral (ARV) regimens for HIV treatment now contain an integrase strand transfer inhibitors (INSTI). The reason: relatively high tolerability and greater likelihood of sustained treatment success as compared to other classes.[1] The INSTI dolutegravir (DTG), in particular, revolutionized antiretroviral therapy (ART). Due to a remarkably high barrier to resistance and other advantages, it quickly became the go-to ARV anchor drug in the United States (US) following approval in 2013. However, practitioners must now incorporate several post-marketing safety signals into clinical decision making. Reports of central nervous system (CNS) side effects with DTG weren't shocking because we had all seen individuals quit the med due to headache or insomnia. A warning about neural tube defects was startling, but has not been confirmed. Now, another surprising post-approval observation has evolved into an overt clinical conundrum: do INSTI's, especially DTG, lead to excessive weight gain? If so, does this signify toxicity or faster return to health?

A fascinating story has built to this predicament. In 2017, a short research letter described weight gain as an "unexpected bothering side effect" of DTG.[2] Authors observed that 55 of 517 (11%) individuals prescribed the drug at a single center (most of whom had switched from an alternate agent) stopped it due to intolerability; 4 out of those 55 (7%) reported weight gain as the intolerable side effect. Weight increases on DTG ranged from 4 to 12 kg. This report raised eyebrows, but didn't cause much of a stir.

Shortly thereafter, two larger retrospective studies corroborated the association between INSTI's and weight gain. In one, a switch from efavirenz (EFV) to an INSTI led to more weight

gain than continued EFV; weight change was most pronounced with DTG.[3] In the other, initiating an INSTI led to greater body mass index (BMI) gain per year, higher obesity incidence, and reduced time to obesity compared to initiating a boosted protease inhibitor (bPI) or non-nucleoside reverse transcriptase inhibitor (NNRTI).[4] Although the number taking an INSTI in this report was small (and most were taking RAL), INSTI use was the strongest predictor of clinical obesity (increasing the risk seven-fold). These reports turned more heads, but still many wondered, "Is this real?"

Now, a barrage of cohort studies substantiates that the findings are real and shouldn't be ignored. This issue of *Clinical Infectious Diseases* highlights one such study. Bourgi et al. performed a retrospective analysis of treatment-naïve persons with HIV at a single center who started ART between 2007 and 2016.[5] Controlling for sex, baseline BMI, CD4 count, and HIV RNA, adjusted average weight gain was greatest with DTG at 6 and 18 months (significantly greater than NNRTI's and ELV, and higher than RAL and bPIs, though that difference didn't reach statistical significance). There was a trend towards higher obesity incidence with DTG.

While limitations abound (single center, somewhat small numbers taking each INSTI, mostly male cohort, relatively high prevalence of obesity at baseline), the study adds to what seems to have swelled overnight into an indisputable collection of evidence showing that INSTI's, especially DTG, are associated with more weight gain than other ARV's. At CROI 2019, at least six observational studies examined weight changes with INSTI's. In the largest of these (another retrospective analysis led by Dr. Bourgi), investigators examined weight change in over 24,000

treatment-naïve persons in NA-ACCORD cohorts and found that, at five years after ART initiation, INSTI's led to greater change in predicted weight as compared to NNRTI's and bPI's (though the bPI difference was not statistically significant).[6] At two years, DTG led to non-significantly more weight gain than RAL and both led to significantly more weight gain than ELV. The five additional studies (one prospective and four retrospective, including one in women only) examined weight changes in virologically suppressed, treatment-experienced persons switching to or adding an INSTI; four out of five found significantly greater weight gain with INSTI's compared to non-INSTI's.[7-11] Data from randomized clinical trials (RCT's) have been summarized recently.[12] Though not designed to compare weight changes, RCT's that reported comparisons of weight substantiate the cohort study findings.

Turning then to critical questions: do INSTI's lead to weight gain directly or indirectly? Does the exaggerated weight gain with INSTI's increase risk of metabolic disturbances or cardiovascular events? Does it magnify the likelihood of neurocognitive impairment (since obesity and metabolic syndrome are risk factors)? In other words, is the weight gain a bothersome side effect or something more sinister? Answers remain unclear.

Some studies identified specific risk factors for weight gain with INSTI's, including older age, female sex, and black or Hispanic ethnicity.[8.10] The current Bourgi et al. analysis found no difference between sex or race, but numbers of women were small.[5] Pharmacogenetics may predict weight changes with specific ARV's but are not fully understood. Per one retrospective investigation, CYPB26 EFV slow metabolizers gained more weight than others after switching to

an INSTI; however, this finding varied based on racial characteristics and specific INSTI.[13] Why would EFV slow metabolizers gain more weight after changing to an INSTI? It was suggested that slower EFV metabolism pre-switch correlates with feeling better post-switch and thus consumption of more calories, but no study to date has controlled for activity level or caloric intake; plus, generalized weight gain seems to occur after switch to an INSTI from a variety of pre-switch agents, so this explanation seems far from complete.[7,10]

It has also been proposed that perhaps INSTI's lead to exaggerated weight gain due to faster viral load suppression, thus more rapidly reducing HIV-related inflammation and basal energy expenditure?[4] A compelling part of Bourgi et al.'s data addresses this question.[5] Viral load reductions between specific INSTI's were not significantly different over the first 12 months, yet weight change differed. At 18 months, viral loads were the same across ART classes, but weight change varied. Thus, viral kinetics do not explain the weight findings.

What other mechanisms could be contributing? Could direct off-target effects of INSTI's be to blame? Bourgi et al. discuss data that DTG may increase appetite through stimulation of melanocyte stimulating hormone.[5] This is captivating, but far from confirmatory. Some analyses have examined ARV effects on adipocyte differentiation and function (adipose tissue is not passive but part of a complex signaling network). These studies found that ELV affects adipocytes less than EFV and that RAL causes neutral effects on adipocytes, but this wouldn't explain weight gain after switching EFV to an INSTI.[14,15] To complicate matters further, a recent investigation observed improvements in insulin sensitivity after a bPI to DTG or RAL switch,

despite decreases in serum leptin levels and a trend towards increased waist circumference with both INSTI's.[16] This is difficult to juxtapose with other INSTI weight change findings since actions of leptin (a hormone secreted by adipose cells) and mechanisms of leptin sensitivity are complex. Our understanding of effects of ARV's on regulation of energy expenditure and storage remains limited.

Do side effects like CNS intolerability or weight gain differ with newer INSTI's like bictegravir (BIC) or investigational cabotegravir (CAB)? Anecdotally, I have not seen nearly the rates of headache or insomnia with BIC as with DTG, suggesting some difference in CNS properties, though effects of BIC on weight have not been examined thoroughly. One RCT reported weight changes with BIC to be similar to DTG, but this must be confirmed.[17] Curiously, a study of intramuscular CAB for persons without HIV did not detect significant weight gain over time, but whether this is due differences in the drug, drug delivery, or host must be investigated.[18]

Additional outstanding questions beg study. Does the NRTI backbone play a role? A recent single-center study suggested that tenofovir alafenamide (TAF) leads to more weight gain than tenofovir disoproxil fumarate (TDF) in the first year after initiation and that switching TDF to TAF is associated with weight gain, so this question should be addressed.[19] Bourgi et al. lacked adequate numbers taking DTG with TDF or TAF to make an adequate comparison to ABC.[5] Few of the cohort studies have tackled the NRTI question. Additionally, most (not all) studies found less weight gain with ELV as compared to RAL or DTG, but is ELV unique or does the requisite cobicistat booster make the difference?

Returning to the most crucial point of uncertainty: is weight gain with INSTI's altering clinical outcomes? Weight gain affects self-perceptions and may limit a person's willingness to continue ART, but weight changes, especially increases in central adiposity, also raise risks of numerous comorbidities. However, data comparing weight-associated clinical outcomes are starkly limited. In the retrospective analysis of weight and body measurements in women with HIV, hypertension was more frequent after switch to or addition of an INSTI as compared continuing a non-INSTI, but clinical endpoints are overall lacking in the cohort studies.[7]

The analysis by Bourgi et al. adds pieces to the puzzle, but huge gaps remain. For now, clinicians must weigh pros and cons of various INSTI's, but I do not think practice or guidelines should change. Practitioners should incorporate counseling and shared decision making about potential weight change into ARV initiation and switch visits and monitor for metabolic complications, but INSTI's should remain first-line. Notably, in the Bourgi et al. study, no person taking DTG, RAL, or ELV changed ART over 18 months, and HIV RNA levels were more likely to remain suppressed on these compared to non-INSTI options, underscoring the enormous treatment advantage of INSTI's.[5] It is essential that future studies seek a better understanding of the mechanisms and long-term clinical implications of INSTI-associated weight gain and include comparisons of agents that now predominate HIV clinical care, such as BIC and TAF.

Potential Conflicts of Interest: B. R. W. has nothing to disclose.

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