Title: **Is modern antiretroviral therapy causing weight gain?**

Author: Sara H. Bares MD, University of Nebraska Medical Center, Division of Infectious Diseases, Omaha, NE

Corresponding author:

Sara H. Bares, MD

985400 Nebraska Medical Center

Omaha, NE 68195-5400

Phone: 402-559-8650

Fax: 402-559-5581

Email: sara.bares@unmc.edu

Weight gain following the initiation of antiretroviral therapy (ART) has been reported across multiple settings and study populations. While this weight gain often represents a return to health among those who are underweight at the time of ART initiation [1], weight gain among those in the normal and overweight categories prior to the initiation of ART has been associated with an increased risk of metabolic and cardiovascular disease [2-4]. The observational nature of many of the studies published to date limits the interpretation of the findings due to potential confounding by HIV-specific, demographic, and environmental factors that contribute to weight gain.

In this issue of *Clinical Infectious Diseases,* Sax et al [5] examined weight data from eight randomized comparative trials of ART in 5680 treatment-naïve participants. This pooled analysis offers a unique opportunity to evaluate the changes in weight in those initiating ART in the context of numerous rigorously conducted randomized trials, which, by design, eliminate the possibility of confounding by indication.

Although Gilead Sciences sponsored all of the parent trials, the transparency in the authors' presentation of the results was welcome and there were several important findings from this work. First, the authors observed strong associations between weight gain and HIV disease characteristics. The correlation between low baseline CD4 cell count and high baseline HIV RNA levels and weight gain has been reported by others [6, 7] and supports the notion that some of the observed weight gain signals a return to health. For providers, this finding raises questions regarding the clinical significance of this weight gain. In this analysis, the authors found that over one third of participants in these trials experienced a greater than 5% increase in weight and nearly one fifth experienced a 10% or greater increase in weight. Although the absolute numbers are marked, the fact that some component of the weight gain noted in this analysis represents a return to health complicates any conclusions regarding the clinical significance.

Similar analyses of weight gain in different study populations will help to shed light on some of the confounding. Weight analysis in switch trials, particularly among participants with virologic suppression at the time of switch, avoid confounding by the return to health phenomenon and such studies have demonstrated similar findings [8-10]. Additionally, evaluations of weight changes in pre-exposure prophylaxis trials may help avoid confounding by HIV disease factors. It is imperative that analysis of weight gain be done in ongoing and future pre-exposure prophylaxis trials.

The second major finding is the association between weight gain with black race and female sex. In this analysis, black women gained twice as much weight as non-black women in the 96 weeks following ART initiation. This finding was statistically significant in spite of the fact that women made up only 11.7% of the study population and black women only 5.5%. While this pooled analysis included contributions from sites in predominantly resource-rich countries, notably without any study sites in the African continent, the findings are corroborated by the recently published ADVANCE and NAMSAL efficacy trials of DTG conducted in Africa. These studies were comprised of over 50% women and DTG was unequivocally associated with excess weight gain as compared to efavirenz, particularly with tenofovir alafenamide-emtricitabine [11, 12].

Why are certain demographic groups more affected by this weight gain than others? These findings are particularly concerning given the disproportionate burden of HIV and obesity in the black and female population in the United States [13, 14]. The mechanism is unclear, but a number of factors including environmental and genetic factors may play a role.

Genome-wide association studies have found multiple genes associated with obesity in the general population [15], and functions of proteins that are pharmacodynamic antiretroviral targets may be affected by genetic variants. Sax et al discuss the potential role of off-target interactions such as the interaction between DTG and melanocortin 4 receptor (MC4R). In vitro, DTG inhibits the binding of radiolabelled α-melanocyte- stimulating hormone (MSH) to MC4R [16]. This is a plausible mechanism because MC4R is involved in the regulation of energy homeostasis and caloric intake, and deficiency in MC4R is associated with obesity. It is unknown whether other INSTIs interact with MC4R, but this is also a proposed mechanism for the weight gain associated with antipsychotics and merits further study with DTG and other modern antiretrovirals.

Additionally, a retrospective study found that CYP2B6 EFV slow-metabolizers gained more weight than others after a switch from EFV to INSTI. This finding varied based on racial characteristics (associations present in white but not black participants) and specific INSTI (associations seen in EVG and RAL groups but not DTG) [17]. While these data suggest that pharmacogenetics may be playing a role (Leonard et al hypothesize that those with high EFV exposure have subclinical intolerance that resolves after the switch), the associations seen in this retrospective data do not mirror the findings noted in the study by Sax et al. In summary, large gaps in our understanding remain.

The third major finding is the absence of a clinically significant metabolic impact of the observed weight gain, as measured by fasting glucose and investigator reported adverse effects (AEs). Though there are limitations to this finding, such as limited duration of follow-up, small number of total reported AEs, and lack of more sensitive measures of glucose tolerance, these results are of particular interest for clinicians on the front lines who are concerned about the clinical implications of the observed weight gain. In other words, is this a metabolically neutral weight gain (suggesting a return to health) or is this weight gain associated with metabolic sequelae? This question is particularly relevant in light of the data from ACTG 5260s which demonstrated a significant increase in insulin resistance after 4 weeks of ART initiation that was similar between recipients of RAL, DRV and ATV [18], as well as multiple case reports of new onset hyperglycemia and diabetes following switch to INSTI-containing regimens [19, 20]. The results of this analysis offer some reassurance in terms of changes in fasting glucose, but lipid changes were more nuanced. Lipid changes were small but statistically significant. Although the clinical significance of the lipid changes are unknown, these changes raise questions about the possible synergistic role of weight gain with TAF-containing regimens versus TDF-containing regimens, given the well-described attenuated decreases in LDL and triglycerides with TAF as compared to TDF [21]. Additional analysis is warranted in both treatment initiation and switch studies before inferences regarding the metabolic consequences of weight gain following ART initiation can be made.

The last, and perhaps most novel, finding was the association between weight gain and type of ART. Importantly, associations were found at both the class (INSTIs > NNRTI > PI) and specific ART level (BIC and DTG > EVG/c; RPV > EFV; TAF> ABC > TDF > AZT). Overall, greater weight gain was observed among newer antiretroviral agents relative to the comparators.

These data answer some questions and substantiate many of the findings from cohort studies of weight gain following ART initiation, but also raise a number of additional important questions, especially as these newer regimens are expanded to populations in need. The follow-up questions clinicians are undoubtedly asking are: what do we do for patients who experience severe weight gain following initiation of ART? How long does this weight gain persist? Will a switch to an alternative regimen reverse

or attenuate some of this weight gain? If so, what regimen should they choose? Is an adjustment in both the backbone and anchor agent needed? Will adjustment in the route of administration alter the side effect profile (i.e. will long acting injectable therapy be associated with similar amounts of weight gain)?

What other mechanisms might be contributing to this observed weight gain? Sax et al hypothesize that improved gastrointestinal tolerability of the newer ART regimens may be contributing. This is a plausible mechanism and could explain the weight gain noted in both treatment naïve and switch studies as participants who feel better subsequently consume more calories. Data regarding caloric intake and energy expenditure was not collected in this analysis but could help substantiate this hypothesis if collected in future studies.

While this study is not without limitations (raltegravir and darunavir were not included in the analysis and the parent trials were not designed to compare weight changes), it is an elegant analysis that adds to the collection of evidence demonstrating that INSTIs, and, more broadly, modern ART regimens, are associated with more weight gain than older ART regimens, especially in those with more advanced disease and particularly among those of black race and female sex. The challenge for the clinician is to translate these findings into clinical practice at a time when many questions remain about the clinical implications of this weight gain. Awaiting additional data to provide clinical guidance, I concur with the advice given by Havlir, Doherty and Wood in recently published editorial commentaries [22, 23]: we must incorporate counseling and anticipatory guidance regarding potential weight changes when initiating ART and continue research to evaluate the mechanisms, consequences, management and prevention of weight gain following ART initiation and switch. Finally, I view these findings as a call to arms. As we continue to investigate the causes, consequences and management of weight gain following ART initiation (and switch), we must strive to enroll sufficient numbers of women from diverse racial and ethnic backgrounds in order to allow for sex and race-stratified analysis.

Acknowledgements:

Thanks to our patients and all of the participants in these studies for allowing us to learn with and from them as we strive to improve care and outcomes for all. And a special thanks to my mentors and sponsors (many of whom are authors on this manuscript), especially Susan Swindells and Kimberly Scarsi.

Conflicts of Interest

Dr. Bares reports grants to her institution from Gilead Sciences, outside the submitted work.

References:

1. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. Clin Infect Dis **2015**; 60(12): 1852-9.
2. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV Med **2016**; 17(4): 255-68.
3. Herrin M, Tate JP, Akgun KM, et al. Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals. J Acquir Immune Defic Syndr **2016**; 73(2): 228-36.
4. Kumar S, Samaras K. The Impact of Weight Gain During HIV Treatment on Risk of Pre-diabetes, Diabetes Mellitus, Cardiovascular Disease, and Mortality. Front Endocrinol (Lausanne) **2018**; 9: 705.
5. Sax PE, Erlandson K. M., Lake J.E., McComsey G.M., Orkin C, Esser S., Brown T., Rockstroh J.K., Wei L, Carter C, Zhong L, Brainard D.M., Melbourne K, Das M, Stellbrink H, Post F.A., Waters L, Koethe J.R. . Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Clinical Trials. Clinical Infectious Diseases
6. Koethe JR, Jenkins CA, Lau B, et al. Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res Hum Retroviruses **2016**; 32(1): 50-8.
7. McDermott AY, Terrin N, Wanke C, Skinner S, Tchetgen E, Shevitz AH. CD4+ cell count, viral load, and highly active antiretroviral therapy use are independent predictors of body composition alterations in HIV-infected adults: a longitudinal study. Clin Infect Dis **2005**; 41(11): 1662-70.
8. Waters L, Assoumou L, Rusconi S et al. Switch to dolutegravir from a boosted protease inhibitor associated with a significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial HIV Glasgow. October 2018. Glasgow, UK: Abstract P102.
9. Lake JE, Wu K, Erlandson KM, et al. Risk factors for weight gain following switch to integrase inhibitor-based ART. In: Conference on Retroviruses and Opportunistic Infections; Seattle; March 2019. Abstract 669.
10. Kerchberger AM, Sheth AN, Angert CD, et al. Weight Gain Associated with Integrase Stand Transfer Inhibitor Use in Women. Clin Infect Dis **2019**.
11. Group NAS, Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1. N Engl J Med **2019**; 381(9): 816-26.
12. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med **2019**; 381(9): 803-15.
13. CDC. Diagnoses of HIV infection in the United States and dependent areas, 2017. HIV Surveillance Report 2018;29.
14. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS data brief, no 288. Hyattsville, MD: National Center for Health Statistics. 2017.
15. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. Mol Cell Endocrinol **2014**; 382(1): 740-57.
16. European Medicines Agency Assessment report. Dolutegravir (Tivicay) Available at: www.ema.europa.eu/documents/assessment-report/tivicay-epar-public-assessment-report_en.pdf (accessed September 2019).
17. Leonard M, Bourgi K, Koeth J, et al. Pharmacogenetics of weight gain after switch from efavirenz to integrase inhibitors. In: Conference on Retroviruses and Opportunistic Infections; Seattle; March 2019. Abstract 472.

18. Dirajlal-Fargo S, Moser C, Brown TT, et al. Changes in Insulin Resistance After Initiation of Raltegravir or Protease Inhibitors With Tenofovir-Emtricitabine: AIDS Clinical Trials Group A5260s. Open Forum Infect Dis **2016**; 3(3): ofw174.
19. Fong PS, Flynn DM, Evans CD, Korthuis PT. Integrase strand transfer inhibitor-associated diabetes mellitus: A case report. Int J STD AIDS **2017**; 28(6): 626-8.
20. McLaughlin M, Walsh S, Galvin S. Dolutegravir-induced hyperglycaemia in a patient living with HIV. J Antimicrob Chemother **2018**; 73(1): 258-60.
21. Cid-Silva P, Fernandez-Bargiela N, Margusino-Framinan L, et al. Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine. Basic Clin Pharmacol Toxicol **2019**; 124(4): 479-90.
22. Havlir DV, Doherty MC. Global HIV Treatment - Turning Headwinds to Tailwinds. N Engl J Med **2019**; 381(9): 873-4.
23. Wood BR. Do Integrase Inhibitors Cause Weight Gain? Clin Infect Dis **2019**.