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Weight gain and metabolic effects in persons with HIV who switch to ART regimens containing integrase inhibitors or tenofovir alafenamide

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Abstract

Background: The timing and magnitude of antiretroviral therapy-associated weight change attributions are unclear.

Setting: HIV Outpatient Study participants.

Methods: We analyzed 2007-2018 records of virally suppressed (VS) persons without integrase inhibitor (INSTI) experience who switched to either INSTI- or another non-INSTI-based ART, and remained VS. We analyzed BMI changes using linear mixed models (LMM), INSTI-and tenofovir alafenamide (TAF) contributions to BMI change by LMM-estimated slopes, and BMI inflection points.

Results: Among 736 participants (5,316 person-years), 441 (60%) switched to INSTI-based ART; the remainder to non-INSTI-based ART. Mean follow-up was 7.15 years for INSTI recipients, 7.35 years for non-INSTI. Pre-switch, INSTI and non-INSTI groups had similar median BMI (26.3 versus 25.9 kg/m^2, p=0.41). INSTI regimens included raltegravir (178), elvitegravir (112) and dolutegravir (143). Monthly BMI increases post-switch were greater with INSTI than

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non-INSTI (0.0525 versus 0.006, p<0.001). A BMI inflection point occurred eight months after switch among INSTI users; slopes were similar regardless of TAF use immediately post-switch. Among INSTI+TAF users, during eight months post-switch, 87% of BMI slope change was associated with INSTI use, 13% with TAF use; after eight months, estimated contributions were 27% and 73%, respectively. For non-INSTI+TAF, 84% of BMI gain was TAF-associated consistently post switch. Persons switching from TDF to TAF had greater BMI increases than others (p<0.001).

Conclusion: Among VS persons who switched ART, INSTI and TAF use were independently associated with BMI increases. During eight months post-switch, BMI changes were greatest and most associated with INSTI use; afterward, gradual BMI gain was largely TAF-associated.

Keywords

integrase inhibitor; TAF; weight gain; metabolic effects; viral suppression

Introduction

The precise magnitude, timing and persistence of antiretroviral therapy (ART)-associated weight gain observed with use of integrase strand transfer inhibitors (INSTIs) and/or tenofovir alafenamide (TAF) remain unclear. Likewise unclear is whether such weight gain is associated with adverse metabolic changes and if, among virally suppressed people with HIV (PWH) switching ART, it matters whether the prior regimen included drugs that could potentially exert a suppressive effect upon weight gain[9,15,16], including efavirenz or tenofovir disoproxil fumarate (TDF).[9,15,16]

In the current report, we studied diverse virally suppressed INSTI-naïve PWH who switched to ART that did or did not include INSTIs and/or tenofovir alafenamide (TAF).

Methods

Data Source

The HIV Outpatient Study (HOPS) is an ongoing, longitudinal, observational cohort study that prospectively follows PWH receiving care at diverse HIV clinics since 1993.[17] The ten study sites that contributed data for the present analyses are located in six U.S. cities (Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL; and Washington, DC). HOPS participants may enroll at any point after a diagnosis of HIV infection regardless of treatment history, after providing informed consent, and may leave the study anytime. The HOPS is approved by institutional review boards at the Centers for Disease Control and Prevention (Atlanta, GA), Cerner Corporation (Kansas City, MO), and local sites. Trained staff abstract data from electronic medical records and enter them into a study-specific electronic database. Data abstracted includes height, weight, sociodemographic characteristics, laboratory values, diagnoses, and treatments, including ART use.

Study Design and Population

We assessed relationships between ART class switch and BMI (weight) change over time using 5,316 person-years of BMI data before and after ART switch. For this analysis,

baseline was defined as time of ART switch. We used HOPS medical records data as of June 30, 2019, and truncated observation to December 31, 2018, to allow up to six months for data verification. Eligible participants had ≥ two BMIs recorded while receiving their pre-ART switch regimen, ≥ one BMI recorded after ART switch, had pre-ART switch regimen for ≥ six months, and the post-ART switch regimen for ≥ six months. Included patients had not received an INSTI-based ART (INSTI-naïve), were virally suppressed (VL <200 copies/mL) for ≥ one year on non-INSTI-based ART, then switched to either INSTI-based or non-INSTI based ART and remained virally suppressed throughout the observation window The INSTI-based ART recipients were prescribed raltegravir (RAL), dolutegravir (DTG), or elvitegravir (EVG). The non-INSTI-based ART recipients received regimens containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). The date of FDA approval of RAL, the first available INSTI, was October 12, 2007; so, to ensure temporal comparability to participants who switched to INSTI-containing ART, for participants who switched to non-INSTI-containing ART, the time of ART switch (time=0) was defined as time of switch from prior non-INSTI ART to another non-INSTI ART regimen if it occurred after October 12, 2007. Post switch regimens were further stratified into TAF-based versus non-TAF inclusive subgroups.

Statistical Analyses

We summarized demographic and clinical characteristics for INSTI and non-INSTI patient groups using median (interquartile range [IQR]) or percent [frequency], as appropriate. To assess differences in cohort characteristics at baseline, we used Kruskal-Wallis tests for continuous variables and Pearson chi-square tests for categorical variables.

We assessed BMI changes over time using linear mixed models (LMM) with random intercept terms for each subject to allow for correlation between repeated measures on subjects over time. We used splines in these models to allow for and fit BMI trajectory changes under various conditions. For each participant, estimates of longitudinal BMI change were centered at time of switch (time 0) from one ART regimen to another. We conducted residual analysis to assess distribution assumptions (QQ plots and residual histograms). The modeling approach is detailed in Appendix 2. To assess any additional effect of TAF-based ART on longitudinal BMI trends, a similar LMM was used, assuming an additive effect between INSTI- and TAF-based ART use. LMM models were presented with and without adjustment for the following covariates: age, race/ethnicity, sex at birth, BMI at time of regimen switch, and time from regimen switch. We used this LMM approach to compare the longitudinal effect upon BMI by type of INSTI.

From the LMM, linear contrasts were applied to compare and test for statistical differences in pre- and post-ART switch BMI slopes between and within study groups. For patients who switched to TAF-containing ART, the proportion of slope change attributable to TAF was calculated as one minus the percentage of slope estimates without TAF over the slope estimates with TAF for the INSTI or non-INSTI groups, respectively.

For illustration purposes, three hypothetical patient profiles were generated to predict model-based weight change at eight and 20 months after ART switch; trajectories over time were estimated using the resulting longitudinal LMM for changes over time and under

different regimen settings. Estimates over time were then compared to determine relative contributions to weight gain. Using the same model framework as with BMI, we analyzed longitudinal trends in total cholesterol, LDL, HDL, and glucose levels. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). We used these models to make general comparisons and provide model-based hypothetical scenarios to facilitate clinical interpretation of our results[19].

Results

Descriptive characteristics

Of the 7,054 HOPS patients who received ART after FDA's approval of RAL on October 12, 2007, 736 (10.4%) met inclusion criteria (Supplemental Figure 1). The average follow-up time was 7.23 years and included 40.6 BMI records. Of the 736, 543 (73.4%) were followed up to three years after switch and 202 (27.8 %) more than three years after switch and maintained viral suppression. Median age was 51.7 years, (IQR: 45.3, 58.0); 141 (19.1%) were women and 190 (25.8%) non-Hispanic/Latino Black or African American (NHB) persons. Patient characteristics by presence or absence of an INSTI in the ART regimen they switched to are depicted in Table 1. Among the 736, 441 (59.9%) who switched to INSTI-based ART were slightly older (median 51.7 years) than non-INSTI recipients (median 50.0 years, $p = 0.02$). Patients who switched to INSTI-based versus (vs) non-INSTI ART did not differ ($p > 0.05$) by sex at birth, race/ethnicity, HIV risk group, payer at baseline, CD4 cell count at ART switch, or BMI at switch.

Pre-switch ART regimens among persons who switched to INSTI versus non-INSTI-based ART did not differ ($p>0.05$) in their mean duration (5.4 vs 5.8 years, respectively) or the frequency of protease inhibitor (42.9% vs 47.1%) or an NNRTI (54.0% vs 52.2%) use. Frequency of TAF use before switch was similar among those switching to INSTI-based ART (42.6%) and to non-INSTI-based ART (43.4%) ($p=0.84$). Only 12 (2.0%) were prescribed ART with TDF prior to switch and all of them initiated INSTI-based therapy at switch. The percentage of persons receiving non-TDF, non-TAF containing ART before switch was (38.0%) and was lower among those switching to INSTI-based ART (34.0%) than switching to non-INSTI-based ART (43.0%) ($p=0.02$).

Among participants who switched to INSTI-based ART, 178 (40.4%) were prescribed RAL (112 [25.4%] EVG, and (143 [32.4%] dolutegravir). Mean duration of INSTI use was 58.7 ± 38.7 (mean ± standard deviation) months overall, 96.3 ± 30.4 months for RAL, 32.3 ± 17.9 months for EVG, and 32.9 ± 14.3 months for DTG Mean TAF use duration did not differ for recipients of INSTI-based ART (13.7 months) and non-INSTI-based ART (15.1 months, $p=0.40$). Since only 15 (3.4%) persons switched to bictegravir, their data were not analyzed for comparison of INSTI drug used (Figure 2).

Average total BMI follow-up time used in the model for persons who switched to INSTI-based ART was 7.15 years (mean 41.0 BMI measurements), in comparison with 7.35 years (mean 40.1 BMI measurements) for persons switching to non-INSTI-based ART. For INSTI-based ART recipients, average BMI follow-up time before switch was 4.61 years (mean of 26.7 BMI measurements) and post-switch it was 2.29 years (mean of 14.3 BMI

measurements). For the non-INSTI group, average pre-switch BMI follow-up time was 4.70 years (mean of 25.8 BMI measurements) whereas post-switch it was 2.39 years (mean of 14.4 BMI measurements).

Additionally, participants whose ART contained TAF had an average 5.07 years of follow-up (a mean of 27.5 BMI measurements) pre-ART switch and 2.24 years (a mean of 13.3 BMI measurements) after ART switch.

Modeled changes in BMI

We evaluated BMI slope changes among those switching to ART that did or did not contain an INSTI and TAF, as shown in Figure 1. The spline model fit indicated an inflection point at eight months; hence, “early phase” refers to the first 8 months after ART switch and “late phase” refers to the ninth month and later. Residual analyses (assessments QQ plots and residual histograms) indicated no concerning violations from the assumed LMM. Key findings from this unadjusted model relevant to interpretation of BMI changes (Supplemental Table 1), included: 1) Switchers to INSTI-based ART gained weight more rapidly (as evidenced by the steeper BMI slope) during the first eight months after switching than switchers to non-INSTI ART regimens, regardless of whether the new regimen contained TAF [solid green lines versus blue/red line during the first eight months ($p<0.001$)]; 2) Switchers to TAF gained weight slightly more rapidly after switching than persons who did not switch to TAF-containing ART [upper versus lower solid green lines for INSTI and solid blue line versus solid red line for non-INSTI any time after switch ($p=0.08$)]; 3) After the first eight months’ INSTI-based treatment, BMI changes were similar for persons on INSTI-based ART without/with TAF and on non-INSTI-based ART without/with TAF [upper solid green versus solid blue lines ($p=0.61$) and lower solid green line versus solid red lines ($p=0.15$)]; 4) After the first eight months post-ART switch, BMI changes among TAF recipients remained slightly greater than those for non-TAF recipients [upper versus lower solid green for INSTI and solid red lines versus solid blue for non-INSTI ($p=0.08$)];5) Among INSTI+TAF users, during the first eight months 87% of weight gain (BMI slope increase) was associated with INSTI and 13% with TAF (upper solid green versus lower solid green); after eight months, estimated contributions were 27% and 73%, respectively; 6) Among switchers to non-INSTI-based ART including TAF, the proportion of TAF-attributable weight gain (BMI slope change) observed after switch that was attributable to TAF (solid blue versus red line) was consistently 84%, indicating no evidence of a non-linear trend in weight gain for these persons.

Based on longitudinal analyses among persons who switched to TAF containing ART (n=316), those who switched from ART with TDF gained BMI by 0.32 (95% CI: 0.18, 0.46)) post switch, while those who switched from ART without TDF gained BMI by 0.21 (95% CI: 0.00, 0.44) post switch.

Mean weight changes before ART switch were similar for switchers to INSTI-containing regimens (2.0 kg) and switchers to non-INSTI-containing regimen (2.2 kg) (Table 1). Pre-ART switch BMI slope trajectories were similar for persons who subsequently switched to INSTI-based ART with or without TAF (dashed green line in figure 1). While longitudinal model-estimated pre-switch BMI trajectories visually appear different between INSTI and

non-INSTI groups, shown in figure 1, this apparent difference was driven by the unbalanced nature of available pre-switch BMI measures between these two groups; measures were fewer at earlier years before regimen switch, when greater proportions of patients with higher baseline BMI (BMI>30) were represented.

Supplemental Table 1 illustrates findings from our mixed model that included BMI slope estimates by ART regimen type from both models with and without covariate-adjustment for age, sex at birth, race/ethnicity, and BMI at time of ART switch. Including these covariates, we found that older age ($p=0.02$), higher BMI at time of ART switch ($p<0.001$), and non-Hispanic/Latino Black ($p<0.001$) or Hispanic/Latino ($p<0.01$), but not sex at birth ($p=0.52$), were associated with higher longitudinal BMI measures in this analyses. However, covariate adjustment did not substantially change post-switch BMI trajectories compared with modeling without age, sex at birth, race/ethnicity, and [baseline or at switch] BMI adjustments. Table 2 depicts estimated rates of monthly change in BMI and 95% confidence intervals by ART (INSTI versus non-INSTI) and TAF at time of switch with all covariates. Figure 2 depicts BMI changes for switchers whose regimens contained individual INSTI (RAL, DTG, or EVG) or non-INSTI. BMI slopes increased more rapidly among INSTI switchers than non-INSTI switcher ($p<0.001$); however, BMI slopes did not differ by INSTI type ($p>0.49$ for all pairwise comparisons).

Longitudinal trends in serum total cholesterol, glucose, LDL, and HDL concentrations are shown in Supplemental Figure 3. Testing for post-switch slope differences by INSTI use revealed a trend toward association ($p=0.06$) of increases in LDL trajectories associated with INSTI compared with non-INSTI use. To contextualize, this difference implied that eight months after ART switch, persons switched to INSTI-based ART experienced a 2.2 mg/dl greater increase in LDL than persons who switched to non-INSTI based regimens. We observed no significant differences in total cholesterol, glucose, and HDL trajectories post-ART switch by INSTI use.

Using our fitted LMM estimates to predict weight change at eight and 20 months (Table 3, Supplemental Figure 2), three hypothetical patient profiles, differing by BMI, race/ethnicity, age, and sex at birth, are depicted. Black race was associated with greater BMI, but not sex at birth. Regarding the hypothetical patients discussed in Table 3, our model suggests the magnitude of weight change in such patients at 20 months post ART switch would range from about 1.4 to 3.4 kg increase for persons receiving INSTI with TAF, 0.9 to 2.9 kg increase for those receiving INSTI without TAF, 0.2 to 2.0 kg for non-INSTI with TAF, and −0.2 to +1.5 kg for non-INSTI without TAF.

Discussion

In this large, diverse, cohort of virally suppressed adult PWH without history of INSTI use, switches to ART regimens that included an INSTI and/or TAF were independently and additively associated with BMI (weight) gain. During the first eight months post-switch, the rate of weight gain was greatest and mostly accounted for by INSTI use; after that, more gradual continued weight gain was largely associated with TAF use. Older age and greater BMI at time of ART switch were associated with steeper BMI slopes (more rapid weight

gain). We noted no significant associations with BMI slope by race/ethnicity, sex at birth, specific INSTI used, pre-switch BMI, though persons whose pre-switch ART included TDF who switched to TAF-containing ART gained more weight than otherwise similar persons switching from non-TDF regimens. As noted earlier, differences in longitudinal BMI among race/ethnicity groups existed, but only minimally by sex at birth. However, adjustment for such effects along with age and pre-switch BMI did not significantly change BMI slopes by specific INSTI used; this was true despite that persons whose pre-switch ART included TDF and subsequently switched to TAF-containing ART gained more weight than otherwise similar persons switching from non-TDF regimens.

These findings are unique in describing the proportional attribution of weight gain (BMI slope trajectories) associated with use of INSTIs and of TAF in a large virally suppressed group of PWH followed over an extended period of time that included within-person measurements preceding and after ART switch. This approach allowed for characterization of distinct “phases” of weight change occurring after INSTI and/or TAF introduction and avoided capturing weight changes potentially associated with a “return to health” had we studied treatment-naïve PWH who initiated ART. Our finding of an initial rapid period of weight gain followed by weight trajectories that were similar for patients switching to INSTI-based and non-INSTI-based ART is novel. The finding supports a hypothesis that INSTI-associated weight gain becomes apparent shortly after INSTI introduction and is fairly short-lived. Other reports[2,4,6,7,8,10] of INSTI-associated weight gain have demonstrated variability in the duration of periods of time over which weight gain was observed, usually limited by the duration of patient observation.

In contrast, the rate of TAF-associated weight gain, which was of a lesser magnitude per unit of time than INSTI-associated weight gain, remained constant over the time of TAF use, regardless of time since ART switch and whether an INSTI was co-prescribed. The effects of INSTI and TAF use upon weight gain were additive, as evidenced by the BMI trajectories illustrated in Figure 1.

The clinical relevance of the observed weight gain is difficult to gauge, particularly because its magnitude was variable across patient types (as indicated in the hypothetical patients presented in Table 3 and supplemental figure 2), and because we did not document cardiometabolic consequences of weight gain. However, weight gain of ≥5% over a fairly short period of time after ART initiation or switch may be of clinical concern[18], a threshold that was generally not reached by participants at 20 months in analyses. Building upon our earlier findings[11] we did not observe significant differences in BMI/weight gain trajectories by specific INSTI agent used. Furthermore, pre-ART switch BMI trajectories did not differ significantly by type of pre-switch ART, except when pre-switch ART included TDF, again in distinction from some other reports[9]. Importantly, all included participants maintained HIV viral suppression before, during and after ART switch, thereby avoiding any impact upon weight that intermittent viral non-suppression may have had. To date, in some reports describing changes in weight among ART-naïve persons who initiated ART and among virally suppressed persons (“stable switchers”) for whom the first exposure to an INSTI occurred in the context of the switch regimen, within-INSTI drug class differences in the magnitude of weight gain have been observed; however, fewer reports of bictegravir

-associated weight gain use exist[4], particularly among stable switchers.[2,6,11] While our data identified the steepest post-switch BMI slope trajectory (most rapid weight gain) in association with DTG use, differences between INSTIs were not statistically significant in fully adjusted models.

Differences in rate and duration of weight gain associated with INSTI and TAF use may stem from distinct mechanisms by which these drugs influence weight change. DTG-related weight gain has been linked *in vitro* to inhibition of melanocortin-4 receptor (MC4R) activity, the latter involved in energy homeostasis and obesity[20]. A mechanism by which inhibition of melanocortin-4 receptor (MC4R) activity may influence weight change involves leptin- induced stimulation of production of pro-opiomelanocortin peptides; these reduce food intake and body weight through agonistic effects on MC4R[21,22]. As for TAF use, potential weight-influencing mechanisms are unclear at this time but may include, among persons switching from TDF-based ART, the absence of weight gain suppression exerted by TDF use, involving much higher plasma levels of tenofovir.[12-14]

Long-term metabolic and overall health implications of INSTI and/or TAF-associated weight are unclear. Our data indicate modest but positive associations between weight gain and plasma concentrations of LDL but not other serum lipids nor glycemic control, findings of questionable clinical significance depending upon specific patient characteristics. Preliminary research from two other cohorts suggested INSTI-associated dysglycemia[23] and metabolic syndrome with the use of ART including DTG with TAF and emtricitabine[24] and another an increase in LDL concentration.[25] Whether these alterations can be linked to adverse clinical endpoints associated with similar metabolic changes in the general population, like coronary artery disease or diabetes mellitus, is not yet apparent.

Our analysis had limitations, including that, since these are observational data from routine HIV care settings, clinical measurements were undertaken with varying frequency across participants and did not include standardized weight measurement instruments. All participants contributed data around the time of ART switch but fewer measurements further away from time of ART switch. Likewise, given the calendar period of observation covered in this report, insufficient data were available regarding the now commonly used INSTI bictegravir. There could have been some confounding by indication; reasons for undertaking ART switches were not available for analysis. Likewise, there were probably unmeasured factors influencing the timing and nature of ART switches that we could not take into account, including use of non-ART medications. Nevertheless, significant strengths of our report include that HOPS participants are demographically diverse, including many persons with chronic comorbidities. Also, the modeling used in this analysis was well-suited to identify and estimate longitudinal trajectories and allowed trajectories to change.

The complexity of determining whether or not observed weight changes are clinically significant also involves the consideration of other factors, not all of which were evaluable in the context of this analysis. These include baseline or treatment-emergent comorbidities and competing risks for weight gain like family history, tobacco smoking, and other substance use. Our participants were diverse in these and potentially other characteristics for which we did not have complete data, including anthropomorphic measures (particularly

waist circumference), sleep abnormalities, neurologic abnormalities, and some psychiatric diagnoses. Parsing out the nuances of observed weight changes in the context of these factors, while potentially important clinically, is beyond the scope of this paper. We encourage medical care providers to interpret the significance of our findings in the context of these other factors.

In summary, among virally suppressed persons who switched ART, both INSTI and TAF use were independently and additively associated with weight gain. During the initial months after ART switch, rate of weight gain was greatest and mostly accounted for by INSTI use; after that, more gradual continued weight gain was largely associated with TAF use. Older age and higher pre-switch BMI were associated with more rapid weight gain, but no associations of other demographic factors or specific INSTI use were detected. Long-term cardiometabolic and overall health consequences of such weight gain remain unclear. Future work should include assessment of pathophysiologic mechanisms by which ART exerts observed effects. Although the data presented help define the contribution, magnitude, and duration of effect upon weight change, , the implications of our findings for ART management and risk: benefit assessment among PWH with various co-morbidity profiles are unclear, warranting further study in clinical trials and large observational cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Conceptualization: F.P, J.L., M.D., D.W., J.F., E.T., R.N., K.B.; data curation: Q.H., J.M.; formal analysis: Q.H., J.M.; investigation: F.P., Q.H., J.L., J.M., K.C., K.B.; methodology: F.P., Q.H., J.L., J.M., K.B.; project administration: F.P., J.L., K.C., M.D., K.B. software: Q.H.; validation: F.P., Q.H., J.L., J.M., K.B.; visualization: Q.H., J.M.; writing – original draft: F.P., Q.H., J.L., J.M., K.C., K.B.; writing – review & editing: F.P., Q.H., J.L., J.M., K.C., M.D., D.W., J.F., E.T., R.N., K.B; F.P., Q.H. and K.C. have verified the underlying data. All authors read and approved the manuscript.

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Appendix 1: HIV Outpatient Study Investigators

The HIV Outpatient Study (HOPS) Investigators include the following persons and sites:

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Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, Princess Davenport, Lewis Katz School of Medicine at Temple University, Philadelphia, PA; Richard M. Novak, Andrea Wendrow, Stockton Mayer, University of Illinois at Chicago, Chicago, IL; Cynthia Mayer, Karen Maroney, Mark Waggoner, Kimberly Braden, Anicette Richardson, St. Joseph's Hospital Comprehensive Research Institute, Tampa, FL.

Appendix 2: Modeling approach

Initial trend investigations of longitudinal trajectories were conducted to visualize and suggest patterns for modelling; based on these analyses we produced spline models to fit to trajectories. To identify the spline function and knots we performed a grid search, allowing for cubic and linear splines fits across various knots. The knot locations considered ranged from four to 36 months post ART switch. This grid search range was based on *a priori* hypothesized weight change trajectories, and then was empirically determined through this process. For each participant, all available BMI measures were used to estimate pre-switch and post-switch trajectories on each side of these empirically-placed spline knots. We identified the best fitting model comparing Akaike's information criterion (AIC) and Bayesian information criterion (BIC) statistics from our grid search. The resulting spline model was coded into LMM explanatory factors using various time and interactions with time to estimate our model, which included the linear spline effects when indicated. We used this LMM approach to compare the longitudinal effect upon BMI by type of INSTI. For this subgroup analysis, all trajectories were assumed linear with a knot at time of regimen switch identified from the model with the INSTI effect combined. We analyzed data using linear trajectories (as opposed to higher-ordered spline functions) for these time periods for two reasons: 1) Local regression trend analysis did not provide evidence of nonlinearity; 2) model fit statistics revealed better fit in LMM than the cubic spline model.

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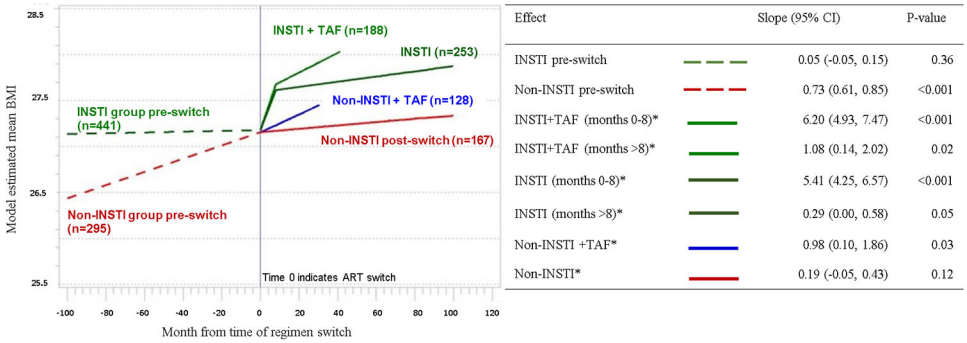
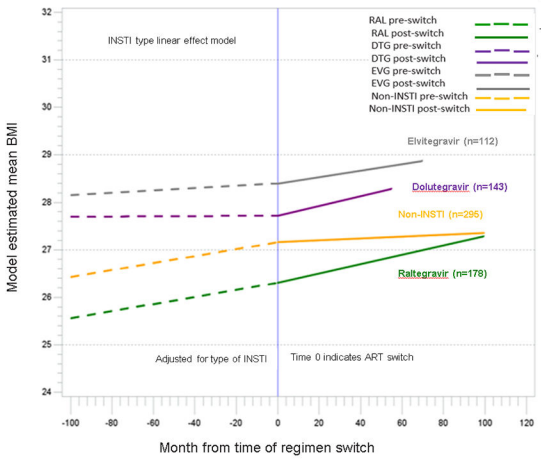


Figure 1. Predicted BMI trajectories (slope $\times 10^2$) with linear splines for persons who switched ART, by INSTI and TAF use, the HIV Outpatient Study, 2007-2018, N = 736.

Abbreviations: BMI, body mass index; ART, antiretroviral therapy INSTI, integrase strand transfer inhibitors; TAF, tenofovir alafenamide.

n's listed in the graph indicate the number of patients contributing data to the estimation.

*Regimens post-switch; all persons naïve to INSTI pre-switch



Effect	Slope (95%CI)	P-value
RAL pre-switch	0.75 (0.53, 0.96)	<0.001
DTG pre-switch	0.02 (-0.13, 0.17)	0.77
EVG pre-switch	0.24 (0.05, 0.44)	0.02
Non-INSTI pre-switch	0.73 (0.61, 0.86)	<0.001
RAL post-switch	0.99 (0.74, 1.24)	<0.001
DTG post-switch	1.05 (0.45, 1.64)	<0.001
EVG post-switch	0.69 (-0.12, 1.5)	0.09
Post non-INSTI	0.20 (-0.05, 0.44)	0.11
Contrasts of slopes*		
RAL vs DTG post-switch	-0.06 (-0.70, 0.58)	0.86
RAL vs EVG post-switch	0.30 (-0.55, 1.14)	0.49
DTG vs EVG post-switch	0.35 (-0.65, 1.35)	0.49
INSTI vs non-INSTI post-switch	0.71 (0.29, 1.13)	<0.001

Figure 2. BMI trajectories from linear model for persons who switched ART, by INSTI drug used, the HIV Outpatient Study, 2007-2018, N = 728.

Abbreviations: BMI, body mass index; ART, antiretroviral therapy; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitors; RAL, raltegravir; TAF, tenofovir alafenamide.

Table 1.

Cohort characteristics, by type of ART regimen received, the HIV Outpatient Study, 2007-2018, N = 736.

Characteristics	Switching to INSTI-based or another non-INSTI-based ART regimen		P-value
	INSTI-based ART regimen N(%)	Non-INSTI-based ART regimen N(%)	
Total	441 (59·9)	295 (40·1)	
Age (years) at baseline			0·05
<50	189 (42·9)	148 (50·2)	
≥50	252 (57·1)	147 (49·8)	
Median IQR	51·7 (45·3,58·0)	50·0 (43·0,56·5)	0·02
Sex at birth			0·64
Female	82 (18·6)	59 (20·0)	
Male	359 (81·4)	236 (80·0)	
Race/ethnicity			0·41
Non-Hispanic/Latino white	259 (58·7)	156 (52·9)	
Non-Hispanic/Latino black	110 (24·9)	80 (27·1)	
Hispanic/Latino	54 (12·2)	46 (15·6)	
Other/unknown	18 (4·1)	13 (4·4)	
HIV risk group			0·19
MSM	292 (66·2)	176 (59·7)	
Heterosexual	90 (20·4)	66 (22·4)	
PWID	32 (7·3)	33 (11·2)	
Other/unknown HIV risk	27 (6·1)	20 (6·8)	
Payer at baseline			0·38
Private	295 (66·9)	185 (62·7)	
Public	130 (29·5)	101 (34·2)	
No/other/unknown	16 (3·6)	9 (3·1)	
CD4 count (cells/μL) at initiation of ART switch			0·37
<200	19 (4·3)	6 (2.0)	
200-349	31 (7·0)	27 (9·2)	
350-499	81 (18·4)	60 (20·3)	
≥500	284 (64·4)	183 (62)	
Missing	26 (5·9)	19 (6·4)	
BMI at switch			0·93
<25	175 (39·7)	113 (38·3)	
25-29·9	165 (37·4)	112 (38·0)	
30+	101 (22·9)	70 (23·7)	
Median (IQR)	26.3 (23·5, 29·5)	25.9 (23·3, 29·7)	0·41
Pre-switch ART regimen			
Mean duration in months (95% CI)	64.8 (61.2,69.6)	69.6 (64.8,75.6)	0·13

Characteristics	Switching to INSTI-based or another non-INSTI-based ART regimen		P-value
	INSTI-based ART regimen N(%)	Non-INSTI-based ART regimen N(%)	
ART regimen contains protease inhibitor			0·25
Yes	189 (42·9)	139 (47·1)	
No	252 (57·1)	156 (52·9)	
ART regimen contains NNRTI			0·64
Yes	238 (54·0)	154 (52·2)	
No	203 (46·0)	141 (47·8)	
ART regimen contains NRTI			0·31
Yes	429 (97·3)	283 (95·9)	
No	12 (2·7)	12 (4·1)	
ART regimen contains TAF			
Yes	188 (42·6)	128 (43·4)	0·84
No	253 (57·3)	167 (56·6)	
ART regimen contains TDF			
Yes	277 (62·8)	169 (57·3)	0·13
No	164 (37·2)	126 (42·7)	
Change in weight (kg) during pre-ART regimen (mean 95% CI)	2·0 (1·1,2·8)	2·2 (1·3,3·1)	0·73
Post-switch ART regimen			
Mean duration in months (95% CI)	30.0 (28.8, 32.4)	31.2 (28.8,34.8)	0·41
INSTI type			
Dolutegravir	143 (32·4)	N/A	
Elvitegravir	112 (25·4)	N/A	
Raltegravir	178 (40·4)	N/A	
ART regimen contains protease inhibitor			<0·01
Yes	48 (10·9)	108 (36·6)	
No	393 (89·1)	187 (63·4)	
ART regimen contains NNRTI			<0·001
Yes	43 (9·8)	173 (58·6)	
No	398 (90·2)	122 (41·4)	
ART regimen contains NRTI			0·18
Yes	420 (95·2)	274 (92·9)	
No	21 (4·8)	21 (7·1)	

Note: baseline is defined as time of ART switch

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; ART, antiretroviral therapy; CI confidence interval; INSTI, integrase strand transfer inhibitors; IQR, interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase

Table 2.

Rate of monthly change in BMI (kg/m^2) and associated 95% confidence intervals, according to treatment group, HIV Outpatient Study, 2007-2018, N=736.

Group/stratum after switch*	Trajectory 0-8 months after switch	Trajectory 8+ months after switch	Trajectory before switch	Difference (before switch vs early phase (0-8 months) after switch)	Difference (before switch vs late phase (8+ months) after switch)
INSTI with TAF (n =188)	0.06 (0.05, 0.08)	0.01 (0.001, 0.02)	0.00 (0.00, 0.00)	0.06 (0.05, 0.07)	0.01 (0.00, 0.020)
INSTI without TAF (n = 253)	0.05 (0.04, 0.07)	0.00 (0.00, 0.01)	0.00 (0.00, 0.00)	0.05 (0.04, 0.07)	0.00 (−0.00, 0.01)
Non-INSTI with TAF (n = 128)	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01) **
Non-INSTI without TAF (n = 167)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.01 (0.01, 0.01)	−0.01 (−0.01, 0.00)	−0.01 (−0.01,0.00)

*Model adjusted for age, sex, race/ethnicity, and BMI measured at time of treatment switch. Ns show number of unique persons contributing data to each of the estimates

**Fully based on model estimated trajectory since no patients in the study cohort had been on non-INSTI and TAF for more than 8 months.

Abbreviations: BMI, body mass index; INSTI, integrase strand transfer inhibitors; TAF, tenofovir alafenamide.

Table 3.

Model-predicted weight change for twelve scenarios, each of three hypothetical patients undergoing four different ART switch regimens, the HIV Outpatient Study.

		White male, 52 years old, 175 cm, 72 kg, BMI 23.5		Black male, 23 years old, 183 cm, 68 kg, BMI 20.3		Hispanic/Latina Female, 37 years old, 163 cm, 78 kg, BMI 29.4	
Regimen after switch	**Month[1]**	**Predicted weight (kg)**	**Gain (kg)**	**Predicted weight (kg)**	**Gain (kg)**	**Predicted weight (kg)**	**Gain (kg)**
INSTI with TAF	8	73.67	1.67	70.99	2.99	79.01	1.01
INSTI with TAF	20	74.07	2.07	71.43	3.43	79.35	1.35
INSTI without TAF	8	73.47	1.47	70.78	2.78	78.84	0.84
INSTI without TAF	20	73.58	1.58	70.9	2.90	78.94	0.94
Non-INSTI with TAF	8	72.37	0.37	69.58	1.58	77.9	−0.10
Non-INSTI with TAF	20	72.73	0.73	69.97	1.97	78.21	0.21
Non-INSTI without TAF	8	72.18	0.18	69.37	1.37	77.73	−0.27
Non-INSTI without TAF	20	72.25	0.25	69.45	1.45	77.79	−0.21

[1]Month refers to time in months since ART switch. Weight gain compared with weight measured at the time of ART switch, listed in the header for each hypothetical patient.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cm, centimeters; INSTI, integrase strand transfer inhibitors; kg, kilograms; TAF, tenofovir alafenamide