

# Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor–Based Regimens

Jamison Norwood, MD,\* Megan Turner, MS,† Carmen Bofill, MPH,† Peter Rebeiro, PhD,† Bryan Shepherd, PhD,‡ Sally Bebwary,† Todd Hulan, MD, MPH,\*† Stephen Raffanti, MD,\*† David W. Haas, MD,\*†§ Timothy R. Sterling, MD,\*† and John R. Koethe, MD, MS\*†

**Background:** With the introduction of integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy, persons living with HIV have a potent new treatment option. Recently, providers at our large treatment clinic noted weight gain in several patients who switched from efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). In this study, we evaluated weight change in patients with sustained virologic suppression who switched from EFV/TDF/FTC to an INSTI-containing regimen.

**Methods:** We performed a retrospective observational cohort study among adults on EFV/TDF/FTC for at least 2 years who had virologic suppression. We assessed weight change over 18 months in patients who switched from EFV/TDF/FTC to an INSTI-containing regimen or a protease inhibitor (PI)-containing regimen versus those on EFV/TDF/FTC over the same period. In a subgroup analysis, we compared patients switched to DTG/ABC/3TC versus raltegravir- or elvitegravir-containing regimens.

**Results:** A total of 495 patients were included: 136 who switched from EFV/TDF/FTC to an INSTI-containing regimen and 34 switched to a PI-containing regimen. Patients switched to an INSTI-containing regimen gained an average of 2.9 kg at 18 months compared with 0.9 kg among those continued on EFV/TDF/FTC ( $P = 0.003$ ), whereas those switched to a PI regimen gained 0.7 kg ( $P = 0.81$ ). Among INSTI regimens, those switched to DTG/ABC/3TC gained the most weight at 18 months (5.3 kg,  $P = 0.001$  compared with EFV/TDF/FTC).

**Conclusion:** Adults living with HIV with viral suppression gained significantly more weight after switching from daily, fixed-dose EFV/TDF/FTC to an INSTI-based regimen compared with those remaining on EFV/TDF/FTC. This weight gain was greatest among patients switching to DTG/ABC/3TC.

**Key Words:** HIV, integrase strand transfer inhibitors, weight gain, dolutegravir, efavirenz

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## INTRODUCTION

Initiation of antiretroviral therapy (ART) is frequently associated with a short period of weight gain, particularly among patients with a lower pretreatment body mass index (BMI) or more pronounced CD4<sup>+</sup> T-cell count depletion.<sup>1–3</sup> In the early ART era, weight gain on treatment was often seen as evidence of nutritional rehabilitation and associated with improved survival and immunologic recovery.<sup>3–7</sup> However, over the past 2 decades, the BMI of HIV-infected persons on ART has steadily increased, and in 1 multisite US study over half of patients remaining on treatment at 3 years were overweight or obese.<sup>1,8</sup> Among patients on ART, a high BMI confers an increased risk of developing diabetes, neurocognitive impairment, and other comorbid conditions in HIV-infected persons, and the avoidance of weight gain may reduce these risks.<sup>9–13</sup>

Integrase strand transfer inhibitors (INSTIs; eg, raltegravir, dolutegravir, and elvitegravir) are a recent class of antiretroviral medications.<sup>14,15</sup> With the introduction of INSTI-based single-pill combination ART regimens, such as fixed-dose dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), patients have a new option to replace older nonnucleoside reverse transcriptase inhibitor–based or protease inhibitor (PI)-based regimens causing adverse central nervous system, metabolic, or other side effects. Recently, clinicians at the Vanderbilt Comprehensive Care Clinic, a large, urban HIV clinic, noted substantial weight gain in several patients with long-term viral suppression who switched from daily, fixed-dose efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to daily fixed-dose DTG/ABC/3TC.

Previous retrospective cohort studies have demonstrated that weight gain may be more pronounced in patients who were initiated on a PI-based regimen,<sup>2,3,16</sup> and a handful

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From the \*Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; †Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN; ‡Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN; and §Department of Medicine, Meharry Medical College, Nashville, TN.

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Correspondence to: John R. Koethe, MD, MS, Division of Infectious Diseases, Vanderbilt University Medical Center, A2200-MCN, 1161 21st Avenue South, Nashville, TN 37232-2582 (e-mail: john.r.koethe@vanderbilt.edu).

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of clinical trials have assessed weight gain in treatment-naïve patients initiating INSTI-containing regimens.<sup>17–21</sup> However, there are few data on weight change in patients with effective virologic suppression who switch to an INSTI-containing regimen. Given the increased cardiometabolic disease risk associated with higher BMI in HIV-infected persons, we assessed whether a change from EFV/TDF/FTC to an INSTI-containing regimen, including DTG/ABC/3TC, among patients with virologic suppression is accompanied by an increase in body weight and hemoglobin A1c% (HbA1c).

METHODS

We conducted a retrospective observational cohort study of adults (age > 18 years) with HIV infection who were enrolled in care at the Vanderbilt Comprehensive Care Clinic (VCCC), an outpatient clinic affiliated with Vanderbilt University Medical Center in Nashville, TN. Research staff systematically extracted and validated all laboratory and clinical data, including medication start and stop dates, from the electronic medical record.

INSTI-containing regimens were defined as those with raltegravir, elvitegravir, or DTG in multi-pill or single-pill combinations. Regimens also containing EFV or PIs were excluded from this group. The analysis compared weight-over-time among patients switching from EFV/TDF/FTC to an INSTI-containing regimen or a PI-containing regimen. Among patients who were switched from EFV/TDF/FTC to a PI-containing regimen, 22 (65%) switched to a regimen which retained TDF/FTC as the nucleoside reverse transcriptase inhibitor (NRTI) component; 3 (9%) switched to a regimen-containing zidovudine (AZT)/3TC; 2 (6%) switched to a regimen-containing ABC/3TC; and 7 (21%) switched to other NRTI combinations or NRTI-sparing regimens. Among patients who were transitioned from EFV/TDF/FTC to an INSTI-containing regimen, 58 (43%) switched to DTG/ABC/3TC; 21 (15%) switched to raltegravir/TDF/FTC; and 57 (42%) switched to elvitegravir/cobicistat/TDF/FTC. In a subgroup analysis, we compared patients switched to DTG/ABC/3TC versus a raltegravir- or elvitegravir-containing regimen.

The study cohort comprised patients on fixed-dose EFV/TDF/FTC for at least 2 years. The “switch” group included patients who subsequently changed from EFV/TDF/FTC to an INSTI-containing regimen or a PI-containing regimen, and then continued on the new regimen for at least 18 months with no plasma HIV-1 RNA measurements ≥1000 copies/mL. The “sham-switch”, or control, group included patients on EFV/TDF/FTC for 2 years who then remained on EFV/TDF/FTC for an additional 18 months with no plasma HIV-1 RNA measurements ≥1000 copies/mL. Subjects contributed data to only 1 group. The first PI-group participant switched on December 10, 2005, and the first INSTI-group participant switched on June 3, 2010. All subjects, including those who remained on an EFV-based regimen, had an HIV-1 RNA <1000 copies/mL in the 6 months before the switch or sham-switch date. A HIV-1 RNA threshold of 1000 copies/mL was selected, as opposed to 400 or 50 copies/mL, to allow for occasional “blips” in detectable virus.<sup>22,23</sup> Female patients who were pregnant during the study period were excluded. Data were included through December 2015.

Median and interquartile ranges were calculated as descriptive statistics for continuous variables, and percentages for categorical variables. Linear mixed effects models with random intercepts were used to assess differences in body weight and HbA1c changes over an 18-month period between those switching from EFV/TDF/FTC to an INSTI-containing regimen or a PI-containing regimen, versus those remaining on EFV/TDF/FTC over a comparable period (ie, the “sham switch” group). The outcomes of weight and HbA1c were modeled as repeated measures, with individuals contributing as many outcome measures as were present in their clinical record after the switch date but during the study period. Models were adjusted for age, sex, race (white or nonwhite), total duration of ART, baseline CD4<sup>+</sup> T-cell count, and baseline weight. In a subgroup analysis, we also compared patients who switched to DTG/ABC/3TC versus a raltegravir- or elvitegravir-containing regimen. The effect of a regimen switch on 18-month weight change was assessed using an interaction term between regimen and time. Reported mean weight changes at 18 months were based on the predicted estimates from these adjusted models. We found less evidence of nonlinear weight changes over the 18-month period (*P* > 0.05; likelihood ratio test comparing models fit with natural splines with 3 knots).

Analyses were performed using Statistical Analysis System (SAS) version 9.4 and R version 3.3.2. The study protocol was approved by the institutional review board of Vanderbilt University Medical Center.

RESULTS

The cohort consisted of 495 patients: 136 who switched from EFV/TDF/FTC to an INSTI-containing regimen (58 to

TABLE 1. Baseline Characteristics Among Patients Switching ART Regimen Versus Remaining on EFV/TDF/FTC

	Switch to an Integrase Inhibitor Regimen,† n = 136	Switch to PI Regimen, n = 34	Continuation of EFV/TDF/FTC, n = 325
Age, median, y (IQR)	39.7 (29.7–47.6)	38.6 (30.8–47.6)	38.5 (32.1–44.5)
Female, %	14	29	14
Nonwhite, %	38	41	46
CD4 <sup>+</sup> count, median, cells/μL	662 (488–850)*	516 (407–678)	576 (410–775)
BMI, median, kg/m <sup>2</sup>	26.0 (23.0–29.4)	25.8 (22.4–29.8)	25.6 (22.5–29.5)
Weight, median, kg	82.5 (72.7–93.0)	75.2 (67.0–91.8)	80.3 (69.6–92.8)
Weight change after 18 months among patients switching ART regimen versus remaining on EFV/TDF/FTC			
Mean weight change, kg	+2.9**	+0.7	+0.9

\**P* < 0.05 and \*\**P* < 0.01 for comparison of patients switching to new regimen versus remaining on EFV/TDF/FTC.  
†Among integrase inhibitor regimens, those switched to DTG/ABC/3TC gained the most weight at 18 months (5.3 kg, *P* = 0.001 compared with EFV/TDF/FTC).  
IQR, interquartile range.

DTG/ABC/3TC and 78 to a raltegravir or elvitegravir regimen), 34 patients who switched from EFV/TDF/FTC to a PI-containing regimen, and 325 patients who remained on EFV/TDF/FTC (comparison group; Table 1). Median age and weight at the time of regimen switch were not significantly different in the INSTI and PI arms as compared to the EFV/TDF/FTC continuation arm, but median CD4<sup>+</sup> T-cell count was higher among patients switched to an INSTI compared with those continued on EFV/TDF/FTC (662 versus 576 cells/ $\mu$ L,  $P = 0.03$ ). All subjects had a HIV-1 RNA <1000 copies/mL in the 6 months before the switch or sham-switch date, and 98% had <400 copies/mL.

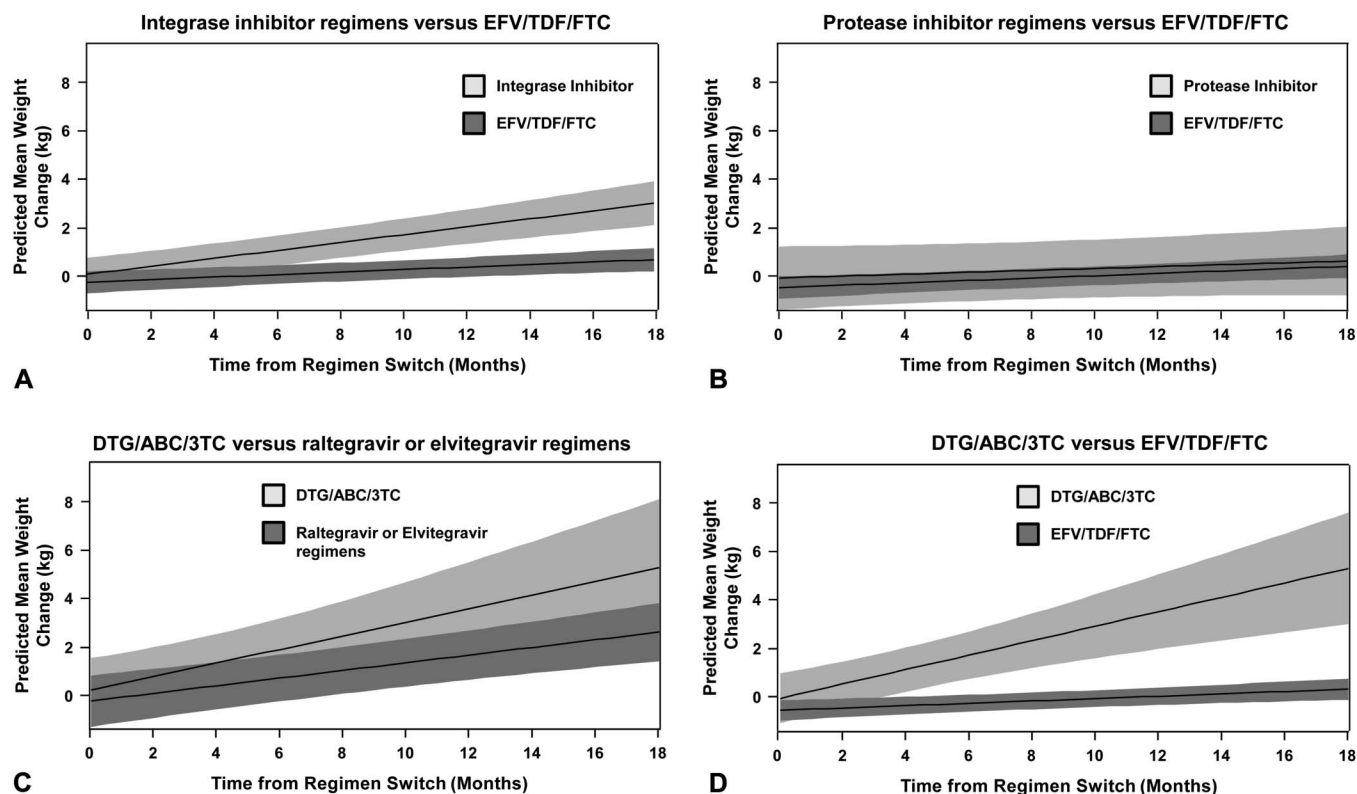
Patients who remained on EFV/TDF/FTC gained significantly less weight at 18 months (mean +0.9 kg) compared with those switched to an INSTI-containing regimen (+2.9 kg,  $P = 0.003$ ; Fig. 1A and Table 1), but weight change was similar at 18 months among those changed to a PI-containing regimen (+0.7 kg,  $P = 0.81$ ; Fig. 1B) after adjusting for age, sex, race, duration of ART, and baseline CD4<sup>+</sup> T-cell count and weight. In the subgroup analysis, patients switched to DTG/ABC/3TC gained 5.3 kg at 18 months, which was greater than the 2.8-kg weight gain at 18 months among patients switched to a raltegravir- or elvitegravir-containing regimen, although this difference was not statistically significant ( $P = 0.19$ , Fig. 1C). However, weight gain on DTG/ABC/3TC was significantly greater compared with the EFV/TDF/FTC

continuation arm ( $P = 0.001$ , Fig. 1D). Results were similar in 2 sensitivity analyses that separately adjusted for hepatitis C status and a history of intravenous drug use.

Last, we assessed the change in HbA1c among patients switched to an INSTI regimen ( $n = 26$  with values available before 18 months) with the caveat that the analysis models were overfit. Mean HbA1c in the EFV/TDF/FTC group fell from 6.4% to 6.0% over 18 months, but increased from 6.4% to 6.9% among those switched to INSTIs, although changes were not statistically significant ( $P = 0.30$ ). There were too few HbA1c observations to assess change in the PI ( $n = 3$ ) or DTG/ABC/3TC ( $n = 11$ ) groups.

## DISCUSSION

In this analysis, we found that patients with viral suppression gained significantly more weight after switching from fixed-dose EFV/TDF/FTC to an INSTI-containing regimen as compared to those remaining on EFV/TDF/FTC, and weight gain was particularly high among those switching to fixed-dose DTG/ABC/3TC. In addition, there was a non-significant increase in HbA1c in those switching to an INSTI-containing regimen, which should be investigated further in larger studies. Although PIs are classically associated with an accumulation of central adiposity, we found that 18-month weight was relatively stable in patients who switched from



**FIGURE 1.** Weight change at 18 months among patients switching to an integrase inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel A), switching to a protease inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel B), switching to DTG/ABC/3TC versus a raltegravir or elvitegravir-based regimen (panel C), or switching to DTG/ABC/3TC versus remaining on EFV/TDF/FTC (panel D). Models adjusted for age, sex, race, total duration of ART, and baseline CD4<sup>+</sup> T-cell count and weight.



EFV/TDF/FTC to these regimens, which may be due to the fact that patients were switching therapy as opposed to starting when treatment naive. Whether the observed weight gain with INSTI-containing regimens is only present in patients transitioning off EFV/TDF/FTC, or unique to specific INSTI and NRTI combinations (ABC and 3TC in the case of DTG), is an area for further study in larger cohorts.

Given the relatively recent introduction of the integrase inhibitors, the effect of this drug class on body composition and metabolism is an area of ongoing research. In AIDS Clinical Trials Group (ACTG) study 5257, larger gains in waist circumference were observed among treatment-naïve patients randomized to raltegravir versus darunavir at 48 and 96 weeks, but no difference was observed in comparison with atazanavir.<sup>19</sup> The PROGRESS study randomized treatment-naïve patients to a regimen of lopinavir/ritonavir in combination with either raltegravir or TDF/FTC and found a significantly greater increase in leg fat in the raltegravir arm (29% increase from baseline versus 15%, respectively) and arm fat (22% versus 7%, respectively), but no difference in trunk fat change.<sup>18</sup> By contrast, the STARTMRK trial randomized treatment-naïve adults to raltegravir versus EFV, each in combination with TDF/FTC, and found mean gain in combined trunk and limb fat was actually lower in the raltegravir versus EFV arms (19% versus 31%).<sup>17</sup>

Two recent studies of DTG in treatment-naïve patients did not report weight change. The SPRING-2 study compared DTG versus raltegravir, whereas the FLAMINGO trial compared DTG versus darunavir (both studies also included NRTIs).<sup>20,21</sup> The SAILING study randomized patients with detectable plasma viremia and resistance to 2 or more ART classes to receive DTG versus raltegravir with an investigator-selected background regimen, but weight change was not reported.<sup>24</sup> Last, the SINGLE trial compared DTG with ABC/3TC versus fixed-dose EFV/TDF/FTC, essentially the same regimens as our study except the DTG regimen was not coformulated, in treatment-naïve patients.<sup>25</sup> At 48 weeks, the incidence of weight increase recorded as an adverse event was 6 of 414 subjects on DTG/ABC/3TC versus 3 of 419 subjects on EFV/TDF/FTC.

Weight gain observed in many patients shortly after ART initiation is believed to be due in part to a reduction in basal metabolic rate after suppression of plasma viremia, improved appetite because of lower inflammatory cytokine effects on the hypothalamus, and a reduction in the rate of protein turnover.<sup>26–33</sup> By contrast, the etiology of weight gain in patients with undetectable plasma HIV RNA who change to another regimen and remain suppressed is unclear. A recent case report of acute onset diabetes mellitus after a switch to an INSTI-containing regimen (raltegravir/ABC/3TC) postulated that medication effects on bioavailable magnesium could alter muscle insulin signaling characteristics.<sup>34</sup> An abrupt reduction in insulin sensitivity could promote storage of excess circulating glucose and lipids in adipose tissue, but this is speculative and requires further clinical study.

Our study was limited by a small sample size. Our cohort was too small to adequately model HbA1c and serum lipid profiles to determine whether the observed weight gain among patients switched to an INSTI-containing regimen was

accompanied by increased cardiometabolic risk markers. Our use of an 18-month follow-up period was based on the interval from coformulated DTG/ABC/3TC approval to the data set end date, and could not capture weight change over a longer period. Given that our study is retrospective, we were unable to assess the reasons for patients switching from EFV/TDF/FTC to another regimen. It is possible that the reasons for their regimen switch impacted their weight and metabolic health; however, we were unable to control for this in our current study. Furthermore, our cohort was predominantly male and located at the single center in the Southeastern United States, and the findings may not fully generalize to other populations.

In summary, HIV patients with long-term viral suppression gained significantly more weight after switching from daily, fixed-dose EFV/TDF/FTC to an INSTI-containing regimen compared with those remaining on EFV/TDF/FTC. The weight gain was particularly pronounced among those switching to DTG/ABC/3TC. Future studies are needed to confirm these findings in larger, multicenter cohorts and investigate the effects on cardiometabolic disease risk factors.

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