Pharmacogenetics of weight gain following switch from efavirenz- to integrase inhibitor-containing regimens

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Background **Excessive weight gain affects some persons with HIV after switching to integrase strand transfer inhibitor (INSTI)-containing antiretroviral therapy (ART). We studied associations between *CYP2B6* genotype and weight gain after ART switch among ACTG A5001 and A5322 participants.**

Methods **Eligible participants switched from efavirenz- to INSTI-containing ART, had genotype data, and had weight data at least once from 4 weeks to 2 years post-switch. Multivariable linear mixed effects models adjusted for race/ethnicity, CD4, age, BMI and INSTI type assessed relationships between *CYP2B6* genotype and estimated differences in weight change.**

Results **A total of 159 eligible participants switched ART from 2007 to 2019, of whom 138 had plasma HIV-1 RNA < 200 copies/mL (65 *CYP2B6* normal, 56 intermediate, 17 poor metabolizers). Among participants with switch HIV-1 RNA < 200 copies/mL, weight increased in all 3 *CYP2B6* groups. The rate of weight gain was greater in *CYP2B6* poor than in *CYP2B6* normal metabolizers overall, and within 9 subgroups (male, female, White, Black, Hispanic, dolutegravir, elvitegravir, raltegravir, and TDF in the pre-switch regimen); only in Hispanic and elvitegravir subgroups were these associations statistically significant ($P < 0.05$). Compared to normal metabolizers, *CYP2B6* intermediate status was not consistently associated with weight gain.**

Conclusion ***CYP2B6* poor metabolizer genotype was associated with greater weight gain after switch from efavirenz- to INSTI-containing ART, but results were inconsistent. Weight gain in this setting is likely complex and multifactorial. *Pharmacogenetics and Genomics* 34: 25–32 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Initiation of antiretroviral therapy (ART) in treatment-naive people living with HIV (PWH) is typically associated with an early period of weight gain as health improves with immunologic recovery [1,2]. Through at least the first 96 weeks of ART, PWH may have greater lean mass and total, trunk, and limb fat gain compared with HIV-negative controls [3]. In recent years, it has been repeatedly observed that some PWH with ART-suppressed HIV gain unwanted weight following a switch from non-integrase strand transfer inhibitor (INSTI)-containing regimens to INSTI-containing regimens [4–6]. The magnitude of such weight gain appears to vary by specific INSTI, being greater with dolutegravir and bictegravir, and less with elvitegravir/cobicistat. Rather than a class-specific weight-promoting effect of INSTIs, at least some observed differences in weight gain may reflect a weight-suppressive effect of the pre-switch ART. Understanding these distinctions is important, as recommended initial ART for HIV-1 includes an INSTI plus nucleos(t)ide reverse transcriptase inhibitors (NRTIs) [7–9], and as millions of individuals worldwide are switching from non-INSTI- to INSTI-containing ART.

Among individuals who switch regimens while virologically suppressed on ART, selected pre-switch antiretrovirals have been reported to predict greater post-switch weight gain. In AIDS Clinical Trials Group (ACTG) observational cohort studies A5001 and A5322, weight gain following switch to INSTI-containing ART was

most pronounced in participants who switched from efavirenz-containing regimens [5]. In a pooled analysis of data from 12 active-controlled clinical trials sponsored by Gilead Sciences, weight gain was greatest in those who switched from efavirenz to either rilpivirine or the INSTI elvitegravir/cobicistat, and also in those who switched from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) [6]. Switching from abacavir to TAF was associated with less weight gain than switching from TDF to TAF [6]. These studies support inhibitory effects of efavirenz and TDF on pre-switch weight gain, with greater weight gain post-switch after this inhibition is no longer present.

Studies of treatment-naive PWH who initiate ART have also demonstrated that the magnitude of weight gain differs with specific antiretrovirals. In a pooled analysis of data from 8 active-controlled clinical trials sponsored by Gilead Sciences, efavirenz was associated with less weight gain than rilpivirine. In addition, TDF, abacavir, and zidovudine were associated with less weight gain than TAF [1]. Similarly, in the South African ADVANCE study, a randomized trial of ART-naive PWH which compared efavirenz/TDF/3TC to dolutegravir with TAF or TDF, the efavirenz-containing arm experienced less weight gain, while in the dolutegravir-containing arms, TDF was associated with lesser weight gain than TAF, especially in females [10]. These studies further support suppressive effects of efavirenz and TDF on weight gain.

Frequent genetic polymorphisms affect plasma efavirenz exposure. Efavirenz is metabolized by cytochrome P450 (CYP) 2B6 [11]. Three *CYP2B6* polymorphisms in combination (516G→T (rs3745274), 983T→C (rs28399499), and 15582C→T (rs4803419)) explain approximately 30% of interindividual variability in plasma efavirenz exposure [12–16], and are associated with increased likelihood of suicidality on efavirenz [17], and discontinuation for central nervous system side effects [18]. Among 462 ART-naive individuals who initiated efavirenz-containing ART in ACTG clinical trials, *CYP2B6* poor metabolizers had a lesser degree of weight gain at week 48 compared to *CYP2B6* normal and intermediate metabolizers [19]. This was seen in participants receiving efavirenz with TDF, but not those receiving efavirenz with abacavir. Among 61 individuals in an observational cohort from a single clinic in the Southeast USA [4], *CYP2B6* poor metabolizers had greater weight gain after the switch, but only when the switch was to elvitegravir or raltegravir, not to dolutegravir. These observations are consistent with a concentration-dependent suppressive effect of efavirenz on weight gain, with the greater efavirenz exposure in poor metabolizers contributing to greater weight suppression.

The present analysis focused on individuals in prospective follow-up in ACTG studies to test the hypothesis that, among PWH who switched from efavirenz- to INSTI-containing ART, *CYP2B6* poor metabolizer genotypes would be associated with greater weight gain. We further sought to characterize this relationship in analyses stratified by sex, race/ethnicity, specific INSTI, and pre-switch TDF use.

Methods

Participants

Participants were from ACTG longitudinal, observational cohort studies A5001 and A5322. In 2000, A5001 (ACTG Longitudinal Linked Randomized Trials, ALLRT) [20] began enrolling participants who had previously participated in ACTG randomized interventional trials. Parent trials included both ART initiation in treatment-naive individuals and change to salvage therapy. A5001 followed participants every 4 months. In 2013, A5001 follow-up ended, and participants 40 years of age or older from treatment-naive parent trials were offered enrollment into A5322 (the HIV Infection, Aging, Immune Function Long-Term Observational Study, HAILO). HAILO involved prospective observational evaluations every 24 weeks from 2013 to 2019, and then every 48 weeks from 2020 to 2022 [21].

The present analyses include all A5001 and A5322 participants who had *CYP2B6* genotype data available from previous analyses [15], who switched from an efavirenz-containing regimen to an INSTI-containing regimen during A5001/A5322 follow-up, had at least one weight or waist circumference measurement from 4 weeks to 2 years after switch, and who had an HIV-1 RNA < 200 copies/mL at the time of switch. Participants were excluded if the post-switch INSTI-containing regimen still included efavirenz. All participants provided written informed consent including for genetic research. Race/ethnicity was by self-report. This study was approved by the Institutional Review Boards at the participating institutions. Cohort derivation is shown in Fig. 1.

Outcomes

Outcomes that we evaluated included change in weight (in kilograms) from the time of INSTI switch to 2 years after switch, and change in waist circumference (in centimeters) from the time of INSTI switch to 2 years, both collected using a standardized protocol.

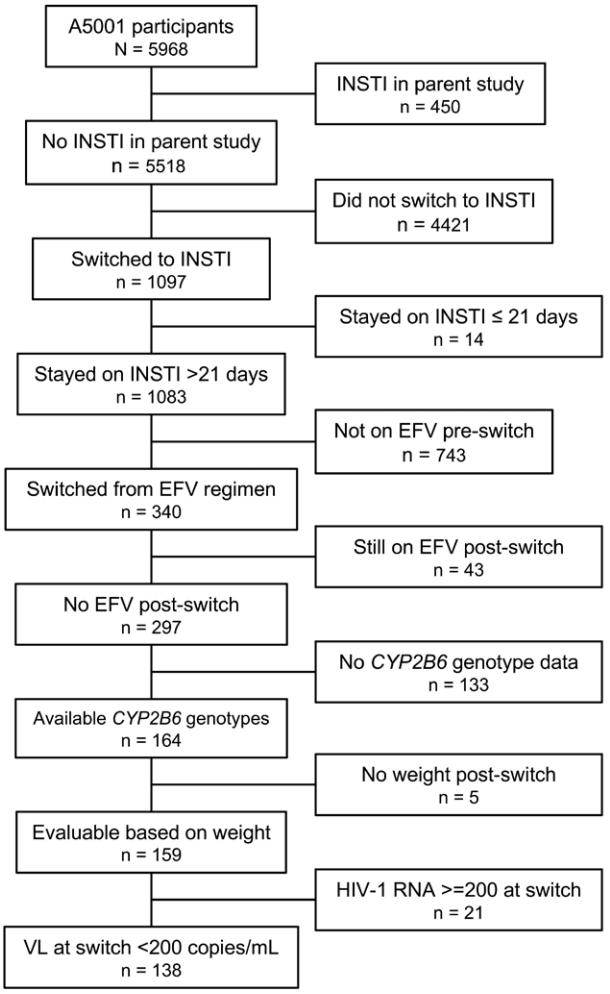
Genotyping

Genotypes for *CYP2B6* were generated for previous analyses as described elsewhere [15,19,22]. Three *CYP2B6* polymorphisms that define 10 ordinal composite genotype levels and predict progressively greater efavirenz exposure were collapsed into 3 metabolizer levels (normal, intermediate, and poor) [18].

Statistical analyses

Basic summary statistics for demographics and baseline covariates at time of entry into the parent ACTG

Fig. 1



Derivation of the study cohort. ACTG, AIDS Clinical Trials Group; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; VL, viral load (HIV-1 RNA).

protocol, and at time of INSTI switch, were calculated by *CYP2B6* metabolizer genotype. Linear mixed-effects models were fit to assess the relationship between *CYP2B6* metabolizer genotype, weight change, and waist circumference change after the first switch to INSTI. First, unadjusted linear mixed-effects models were fit for weight (or waist circumference) and *CYP2B6* metabolizer group on all participants who had at least one weight measurement (or waist circumference) within 2 years after switch. Models were also fit for the subset of participants who had weight (or waist circumference) measured both at time of INSTI switch and also within 2 years after this switch. The above models were also fit by subgroups: self-ascertained sex (separate models for male and female); race/ethnicity (non-Hispanic Black, non-Hispanic White, Hispanic); and specific INSTI (raltegravir, elvitegravir, and dolutegravir). Bictegravir was excluded from this analysis due to small sample size. Separate models were also fit only among participants who switched from regimens that included TDF.

For all of the above, multivariable models were fit adjusting for potential confounding variables, including age at switch, sex, race/ethnicity, parent study, BMI at switch, specific INSTI, nadir and current CD4 + T-cell count, history of smoking, history of diabetes, years of stavudine (D4T)/didanosine (DDI)/zidovudine (ZDV) prescribing before switch, percent follow-up time with HIV-1 RNA < 200 copies/mL, and use of psychiatric medications at switch. These covariates were evaluated individually by adding them to the unadjusted model. Factors that changed unadjusted effect estimates by at least 10% were retained in multivariable models.

Results

Participant characteristics

A total of 159 individuals switched from efavirenz- to INSTI-containing regimens (between 2007 and 2019), had *CYP2B6* genotype data, and had weight data within 2 years after switch. Of these individuals, 138 had plasma HIV-1 RNA < 200 copies/mL at time of switch and were included in these analyses. Participant characteristics are shown in Table 1. Of the switches, 76 (55%) occurred in the years 2015 through 2017. The INSTI prescribed at switch was dolutegravir in 67 (49%), elvitegravir in 38 (28%), raltegravir in 26 (19%), and bictegravir in 7 (5%). Concomitant NRTIs in the first INSTI regimen included abacavir in 49 (36%), TAF in 40 (29%), and TDF in 39 (28%). Of the participants who had weight data after switch, 81 had weight data at the time of switch (defined as from 12 weeks prior to switch to up to 4 weeks after switch).

Weight gain after switch to INSTI-containing regimens

In unadjusted models of estimates of weight change, there was post-switch weight gain among all participants combined, and among *CYP2B6* normal, intermediate, and poor metabolizers analyzed separately. The post-switch weight gain was greatest among *CYP2B6* poor metabolizers (estimate 3.5 kg/year; 95% C.I., 2.1, 5.0 kg/year) and normal metabolizers (2.2 kg/year; 95% C.I., 1.5, 3.0 kg/year), and least among intermediate metabolizers (1.0 kg/year; 95% C.I., 0.2, 1.8 kg/year) (Table 2, columns to left).

In models adjusting for race/ethnicity, CD4 + T-cell count at switch, age, BMI at switch, and specific INSTI, similar to unadjusted models, there was similar post-switch weight gain among all participants analyzed together, and among *CYP2B6* normal, intermediate, and poor metabolizers analyzed separately. The weight gain was again greatest among *CYP2B6* poor metabolizers (3.7 kg/year; 95% C.I., 2.2, 5.1 kg/year) and normal metabolizers (2.3 kg/year; 95% C.I., 1.5, 3.1 kg/year), and least among

Table 1 Participant characteristics at first INSTI switch by *CYP2B6* metabolizer genotype among participants with viral suppression at time of switch

Characteristic		*CYP2B6* metabolizer group			
		Total (N = 138)	Normal (N = 65)	Intermediate (N = 56)	Poor (N = 17)
Sex[a]	M	115 (83%)	58 (89%)	45 (80%)	12 (71%)
	F	23 (17%)	7 (11%)	11 (20%)	5 (29%)
Race/ethnicity	White non-Hispanic	74 (54%)	36 (55%)	31 (55%)	7 (41%)
	Black non-Hispanic	37 (27%)	15 (23%)	15 (27%)	7 (41%)
	Hispanic	25 (18%)	12 (18%)	10 (18%)	3 (18%)
	Other	2 (1%)	2 (3%)	0 (0%)	0 (0%)
First post-switch INSTI	RAL	26 (19%)	13 (20%)	10 (18%)	3 (18%)
	EVG	38 (28%)	20 (31%)	13 (23%)	5 (29%)
	DTG	67 (49%)	30 (46%)	29 (52%)	8 (47%)
	BIC	7 (5%)	2 (3%)	4 (7%)	1 (6%)
Age at first INSTI switch	Median (Q1, Q3)	55 (48, 61)	53 (47, 60)	57 (49, 64)	54 (52, 60)
TDF in regimen before switch	No	49 (36%)	24 (37%)	20 (36%)	5 (29%)
	Yes	89 (64%)	41 (63%)	36 (64%)	12 (71%)
Selected NRTIs in first post-switch regimen	ABC	49 (36%)	25 (38%)	19 (34%)	5 (29%)
	TDF	39 (28%)	19 (29%)	15 (27%)	5 (29%)
	TAF	40 (29%)	16 (25%)	19 (34%)	5 (29%)
	OTHER	10 (7%)	5 (8%)	3 (5%)	2 (12%)
Years prior D4T exposure	Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Years prior DDI exposure	Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Years prior ZDV exposure	Median (Q1, Q3)	2.0 (0.0, 6.6)	2.7 (0.0, 6.0)	1.2 (0.0, 6.8)	0.0 (0.0, 6.8)
Years prior D4T/DDI/ZDV exposure	Median (Q1, Q3)	3.3 (0.0, 7.2)	3.3 (0.0, 6.6)	3.4 (0.0, 9.1)	0.0 (0.0, 8.3)
Most recent CD4 count before switch	Median (Q1, Q3)	709 (512, 916)	717 (553, 933)	640 (487, 818)	878 (622, 1042)
Nadir CD4 before switch	Median (Q1, Q3)	164 (39, 275)	200 (55, 297)	157 (38, 271)	43 (20, 149)
Most recent BMI on or before switch	Median (Q1, Q3)	26.9 (24.0, 30.0)	27.1 (23.7, 29.3)	26.5 (24.3, 29.8)	28.1 (25.2, 31.4)
Weight at INSTI switch in kg	N	81	36	33	12
	Median (Q1, Q3)	82.2 (72.2, 94.0)	81.8 (74.0, 93.6)	79.0 (70.2, 91.8)	88.8 (74.7, 104.5)
History of diabetes at switch		20 (14%)	6 (9%)	11 (20%)	3 (18%)
History of smoking at switch		76 (55%)	34 (52%)	34 (61%)	8 (47%)
Week of first INSTI regimen from baseline	Median (Q1, Q3)	687 (501, 837)	651 (450, 817)	716 (535, 858)	687 (582, 807)
Duration of first INSTI regimen (weeks)	Median (Q1, Q3)	143 (78, 203)	152 (78, 209)	134 (76, 194)	141 (94, 163)
Study	A5001	22 (16%)	13 (20%)	6 (11%)	3 (18%)
	A5001+A5322	116 (84%)	52 (80%)	50 (89%)	14 (82%)
Psychiatric medication at switch	No	135 (98%)	64 (98%)	55 (98%)	16 (94%)
	Yes	3 (2%)	1 (2%)	1 (2%)	1 (6%)

D4T, stavudine; DDI, didanosine; INSTI, integrase strand transfer inhibitor; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.
[a]Information regarding gender identity is not available from study participants.

intermediate metabolizers (1.0 kg/year; 95% C.I., 0.1, 1.8 kg/year) (Table 2, columns to right).

Stratified analyses of weight gain after switch to INSTI-containing regimens

We repeated the above analyses stratified by sex (115 males, 23 females), by race/ethnicity (74 White, 37 Black, and 25 Hispanic participants), by INSTI type (26 raltegravir, 38 elvitegravir, 67 dolutegravir), and restricted to those with TDF in pre-switch regimen (n = 89). These stratifications provided nine subgroups for analysis. In unadjusted models, post-switch weight gain was greater in *CYP2B6* poor metabolizers than in normal metabolizers in 8 of 9 subgroups (only among dolutegravir recipients was this not so). Only among Hispanic participants, and those receiving elvitegravir, was the difference in weight gain among *CYP2B6* poor metabolizers compared to normal metabolizers statistically significant. In adjusted models, post-switch weight gain was greater in *CYP2B6* poor metabolizers than in normal metabolizers in all 9 subgroups, including among dolutegravir recipients. Again, only among Hispanic participants, and those receiving elvitegravir, was the difference in weight gain among *CYP2B6* poor metabolizers compared to normal metabolizers statistically significant.

With regard to *CYP2B6* intermediate metabolizers, in most subgroup analyses both unadjusted and adjusted, the change in weight post-switch was less in intermediate metabolizers than in *CYP2B6* normal metabolizers. The exceptions were among females, and among dolutegravir recipients, in whom change in weight post-switch was greater in *CYP2B6* intermediate metabolizers.

The above analyses were limited to 138 participants with plasma HIV-1 RNA < 200 copies/ml at time of switch. In analyses that included all 159 evaluable individuals regardless of plasma HIV-1 RNA at time of switch, results were generally consistent, including the finding that only among Hispanic participants, and those receiving elvitegravir, was the difference in weight gain among *CYP2B6* poor metabolizers compared to normal metabolizers statistically significant (data not shown).

Table 2 Estimates of weight change by *CYP2B6* metabolizer group, and difference in weight change between groups, among participants with viral suppression at time of switch, time points within 2 years after INSTI switch

	Unadjusted models		Adjusted models[a]	
Variable	Estimate [95% CI]	*P*-value	Estimate [95% CI]	*P*-value
All (n = 138)				
Weight change in normal metabolizers (kg/yr)	2.23 [1.45 to 3.02][b]	< 0.001	2.29 [1.51 to 3.07]	< 0.001
Weight change in intermediate metabolizers (kg/yr)	0.99 [0.15 to 1.83]	0.02	0.93 [0.09 to 1.77]	0.03
Weight change in poor metabolizers (kg/yr)	3.53 [2.06 to 5.01]	< 0.001	3.67 [2.21 to 5.14]	< 0.001
Difference in weight change (Inter. vs. Normal)	−1.25 [−2.40 to −0.10]	0.03	−1.36 [−2.50 to −0.22]	0.02
Difference in weight change (Poor vs. Normal)	1.30 [−0.37 to 2.97]	0.1	1.39 [−0.27 to 3.04]	0.1
Male (n = 115)				
Weight change in normal metabolizers (kg/yr)	2.55 [1.67 to 3.42]	< 0.001	2.64 [1.77 to 3.51]	< 0.001
Weight change in intermediate metabolizers (kg/yr)	0.57 [−0.40 to 1.54]	0.3	0.53 [−0.43 to 1.49]	0.3
Weight change in poor metabolizers (kg/yr)	3.73 [2.03 to 5.42]	< 0.001	3.66 [1.98 to 5.34]	< 0.001
Difference in weight change (Inter. vs. Normal)	−1.98 [−3.29 to −0.68]	0.003	−2.10 [−3.40 to −0.81]	0.002
Difference in weight change (Poor vs. Normal)	1.18 [−0.73 to 3.09]	0.2	1.03 [−0.87 to 2.92]	0.3
Female (n = 23)				
Weight change in normal metabolizers (kg/yr)	0.80 [−0.91 to 2.50]	0.4	0.80 [−0.90 to 2.51]	0.4
Weight change in intermediate metabolizers (kg/yr)	2.50 [0.89 to 4.10]	0.003	2.32 [0.63 to 4.01]	0.008
Weight change in poor metabolizers (kg/yr)	2.46 [−0.40 to 5.32]	0.09	2.62 [−0.24 to 5.48]	0.07
Difference in weight change (Inter. vs. Normal)	1.70 [−0.64 to 4.04]	0.2	1.52 [−0.88 to 3.91]	0.2
Difference in weight change (Poor vs. Normal)	1.66 [−1.66 to 4.99]	0.3	1.82 [−1.51 to 5.15]	0.3
White (n = 74)				
Weight change in normal metabolizers (kg/yr)	2.71 [1.60 to 3.82]	< 0.001	2.64 [1.53 to 3.75]	< 0.001
Weight change in intermediate metabolizers (kg/yr)	0.90 [−0.35 to 2.16]	0.2	0.86 [−0.38 to 2.10]	0.2
Weight change in poor metabolizers (kg/yr)	3.10 [0.46 to 5.74]	0.02	3.42 [0.82 to 6.02]	0.01
Difference in weight change (Inter. vs. Normal)	−1.81 [−3.49 to −0.13]	0.03	−1.78 [−3.44 to −0.11]	0.04
Difference in weight change (Poor vs. Normal)	0.38 [−2.48 to 3.25]	0.8	0.78 [−2.05 to 3.61]	0.6
Black (n = 37)				
Weight change in normal metabolizers (kg/yr)	1.21 [−0.50 to 2.92]	0.2	1.30 [−0.42 to 3.02]	0.1
Weight change in intermediate metabolizers (kg/yr)	0.61 [−1.12 to 2.34]	0.5	0.85 [−0.95 to 2.64]	0.4
Weight change in poor metabolizers (kg/yr)	2.81 [0.27 to 5.34]	0.03	2.81 [0.26 to 5.36]	0.03
Difference in weight change (Inter. vs. Normal)	−0.59 [−3.03 to 1.84]	0.6	−0.46 [−2.96 to 2.05]	0.7
Difference in weight change (Poor vs. Normal)	1.60 [−1.46 to 4.65]	0.3	1.51 [−1.57 to 4.58]	0.3
Hispanic (n = 25)				
Weight change in normal metabolizers (kg/yr)	2.16 [0.71 to 3.61]	0.004	2.26 [0.76 to 3.76]	0.004
Weight change in intermediate metabolizers (kg/yr)	1.74 [0.47 to 3.01]	0.008	1.75 [0.47 to 3.03]	0.008
Weight change in poor metabolizers (kg/yr)	5.61 [3.55 to 7.67]	< 0.001	5.63 [3.49 to 7.76]	< 0.001
Difference in weight change (Inter. vs. Normal)	−0.42 [−2.35 to 1.51]	0.7	−0.51 [−2.47 to 1.45]	0.6
Difference in weight change (Poor vs. Normal)	3.45 [0.93 to 5.97]	0.008	3.37 [0.82 to 5.91]	0.01
Raltegravir (n = 26)				
Weight change in normal metabolizers (kg/yr)	2.32 [0.67 to 3.97]	0.006	2.52 [0.88 to 4.16]	0.003
Weight change in intermediate metabolizers (kg/yr)	−2.18 [−3.82 to −0.53]	0.01	−2.21 [−3.84 to −0.57]	0.009
Weight change in poor metabolizers (kg/yr)	3.50 [0.04 to 6.97]	0.05	3.53 [0.09 to 6.97]	0.04
Difference in weight change (Inter. vs. Normal)	−4.50 [−6.83 to −2.17]	< 0.001	−4.73 [−7.04 to −2.41]	< 0.001
Difference in weight change (Poor vs. Normal)	1.18 [−2.66 to 5.02]	0.5	1.01 [−2.80 to 4.82]	0.6
Elvitegravir (n = 38)				
Weight change in normal metabolizers (kg/yr)	2.74 [1.86 to 3.63]	< 0.001	2.73 [1.83 to 3.63]	< 0.001
Weight change in intermediate metabolizers (kg/yr)	1.41 [0.35 to 2.46]	0.009	1.40 [0.33 to 2.46]	0.01
Weight change in poor metabolizers (kg/yr)	5.73 [4.20 to 7.25]	< 0.001	5.75 [4.19 to 7.31]	< 0.001
Difference in weight change (Inter. vs. Normal)	−1.33 [−2.71 to 0.04]	0.06	−1.33 [−2.72 to 0.05]	0.06
Difference in weight change (Poor vs. Normal)	2.98 [1.22 to 4.74]	0.001	3.02 [1.24 to 4.80]	0.001
Dolutegravir (n = 67)				
Weight change in normal metabolizers (kg/yr)	1.91 [0.70 to 3.12]	0.002	1.93 [0.72 to 3.14]	0.002
Weight change in intermediate metabolizers (kg/yr)	2.43 [1.14 to 3.73]	< 0.001	2.34 [1.05 to 3.63]	< 0.001
Weight change in poor metabolizers (kg/yr)	1.87 [−0.47 to 4.20]	0.1	2.06 [−0.27 to 4.38]	0.08
Difference in weight change (Inter. vs. Normal)	0.52 [−1.25 to 2.29]	0.6	0.41 [−1.35 to 2.17]	0.6
Difference in weight change (Poor vs. Normal)	−0.05 [−2.67 to 2.58]	0.9	0.12 [−2.50 to 2.75]	0.9
Pre-switch regimen included TDF (n = 89)				
Weight change in normal metabolizers (kg/yr)	2.70 [1.52 to 3.88]	< 0.001	2.69 [1.50 to 3.87]	< 0.001
Weight change in intermediate metabolizers (kg/yr)	1.33 [0.04 to 2.61]	0.04	1.37 [0.07 to 2.67]	0.04
Weight change in poor metabolizers (kg/yr)	3.61 [1.58 to 5.64]	< 0.001	3.86 [1.84 to 5.89]	< 0.001
Difference in weight change (Inter. vs. Normal)	−1.37 [−3.11 to 0.38]	0.1	−1.31 [−3.07 to 0.44]	0.1
Difference in weight change (Poor vs. Normal)	0.92 [−1.43 to 3.26]	0.4	1.18 [−1.17 to 3.52]	0.3

[a]Models were adjusted for race/ethnicity, CD4, age, BMI and INSTI type when they were not stratification factors.
[b]Positive values for estimates indicate that participants gained weight post-switch. Positive values for estimates of difference on weight gain indicate that weight gain post-switch was greater than weight gain in *CYP2B6* normal metabolizers.

Analyses of waist circumference after switch to INSTI-containing regimens

The above analyses were repeated with change in waist circumference as the outcome of interest. Briefly, results of both unadjusted and adjusted models of estimates of slope of waist circumference among 126 evaluable participants were somewhat consistent with results based on change in weight. In adjusted mixed-effects models of estimates of slope of waist circumference among participants with plasma HIV-1 RNA < 200 copies/ml at

time of switch, there was greater post-switch waist circumference gain with all *CYP2B6* groups combined, and among *CYP2B6* normal, intermediate, and poor metabolizers analyzed separately, with the greatest gain in waist circumference among *CYP2B6* poor metabolizers. The increase in waist circumference among intermediate metabolizers was less than among either *CYP2B6* normal or poor metabolizers (data not shown).

Additional stratified analyses found post-switch increases in waist circumference were greatest in *CYP2B6* poor metabolizers among the 104 males, the 21 Hispanic participants, the 24 raltegravir recipients, the 36 elvitegravir recipients, and the 81 participants whose pre-switch regimen included TDF. In comparing *CYP2B6* poor vs. normal metabolizers, none of these differences were statistically significant. Post-switch increase in waist circumference was greatest in groups other than *CYP2B6* poor metabolizers among the 22 females, 68 White participants, 36 Black participants, and 63 dolutegravir recipients.

Discussion

Among virologically suppressed PWH on ART, unwanted weight gain has been reported following a switch to INSTI-containing regimens [4]. The objective of the present study was to determine whether, following a switch from efavirenz-containing regimens to INSTI-containing regimens, post-switch weight gain was explained by *CYP2B6* metabolizer status. We show that, among 138 individuals who switched from efavirenz-containing regimens to INSTI-containing regimens, and with plasma HIV-1 RNA < 200 copies/ml at time of switch, post-switch weight gain was greatest among *CYP2B6* poor metabolizers. In subgroup analyses, there was also evidence of greater weight gain post-switch among *CYP2B6* poor metabolizers in nearly all of our stratified analyses. The differences were only statistically significant in selected subgroup analyses.

This finding is generally consistent with a previous observational study of 61 individuals who switched from efavirenz- to INSTI-containing regimens at a clinic in the Southeastern USA [19]. In that study, *CYP2B6* poor metabolizers had overall greater weight gain after switch. It was hypothesized that the association between *CYP2B6* genotype and weight gain might reflect withdrawal of an effect of higher efavirenz concentrations (i.e. poor metabolizers) on weight gain. This hypothesis is supported by ART-naive studies showing that, following initiation of efavirenz-containing regimens, weight gain may be less among *CYP2B6* poor metabolizers than among *CYP2B6* intermediate and normal metabolizers. Among 168 participants randomly assigned to initiate efavirenz/TDF/3TC in the South African ADVANCE study, weight gain from baseline to week 48 was the least among *CYP2B6* poor metabolizers, especially among women [23]. Similarly, among 462 individuals who initiated efavirenz-containing ART in ACTG clinical trials, *CYP2B6* poor metabolizers had the least weight gain at week 48 [19].

Multiple studies have associated *CYP2B6* poor metabolizer genotypes with efavirenz adverse events including central nervous system symptoms, suicidality, hepatic injury, and QTc prolongation [16,18,24,25]. Our study lends evidence to the hypothesis that an additional effect of *CYP2B6* poor metabolizer genotypes may be unwanted weight gain following switch from efavirenz- to INSTI-containing regimens.

Cellular mechanisms of efavirenz adverse effects may include altered energy metabolism, mitochondrial function, or other processes involved in stress responses such as inflammation [26]. In ACTG study A5170, which involved asymptomatic participants with chronic ART exposure, neurocognition improved after treatment interruption, particularly with efavirenz-containing regimens [27]. Improvements in everyday life following switch from efavirenz-containing regimens have also been reported in asymptomatic persons [28]. Subjective improvement after discontinuing efavirenz may include increased appetite, especially among individuals with higher efavirenz concentrations.

There is evidence that TDF has a weight-suppressive effect. Weight gain has been reported in ART-experienced individuals following switch from TDF- to TAF-containing ART [29]. Among ADVANCE study participants who had been randomized to receive dolutegravir plus either TAF/FTC or TDF/FTC, weight gain was less with TDF than with TAF, especially in females [10]. In a placebo-controlled trial of preexposure prophylaxis for HIV-negative individuals, TDF/emtricitabine was associated with a lesser increase in weight through 72 weeks than with placebo [30]. Among 462 individuals randomly assigned to initiate efavirenz-containing ART in ACTG trials, the association of *CYP2B6* poor metabolizer status with lesser weight gain was seen among those receiving TDF but not those receiving abacavir [19], suggesting that TDF exposure in the presence of higher efavirenz concentrations may particularly interfere with expected weight gain [19].

The present study did not find a strong association between *CYP2B6* poor metabolizer status and weight change after switch to dolutegravir, which is surprising considering that dolutegravir is often associated with greater weight gain than raltegravir or elvitegravir. Greater weight gain has also been reported in ART-naive participants initiating a dolutegravir-containing regimen [2]. This finding is generally consistent with the previous report based on an observational cohort of 61 participants [19], in which the association of *CYP2B6* poor metabolizer status with greater weight gain was only apparent following switch to elvitegravir or raltegravir, but not dolutegravir. In the South African ADVANCE study, dolutegravir-containing arms experienced greater weight

gain than the control efavirenz/TDF/3TC arm, especially with TAF [10]. We cannot explain why we did not see a strong association with dolutegravir in our observational cohort.

Our study had limitations. The sample size for participants who met criteria for evaluation was relatively small, particularly for participants with *CYP2B6* poor metabolizer genotypes. Because the cohort was not specifically designed to study weight gain at time of switch, not all participants had weight data at the time of switch. Findings should be replicated in larger cohorts. Such future cohort analyses should ideally be used for meta-analyses, together with results from the present study and from the prior study [19].

In summary, among participants who switched from efavirenz- to INSTI-containing therapy during observational follow-up in A5001 and A5322, participants with *CYP2B6* poor metabolizer genotypes had greater increase in weight following switch when considering all 138 participants, and in 8 of 9 stratified analysis, although the difference in change in weight between *CYP2B6* poor metabolizers and *CYP2B6* normal metabolizers was statistically significant only among Hispanic participants and among elvitegravir recipients. Weight gain in this setting is likely complex and multifactorial. This is particularly relevant given the global transition to INSTI-containing ART regimens for HIV-1 infection [31].

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Conflicts of interest

JK has served as a consultant to Gilead, Merck, ViiV Healthcare, Theratechnologies and Janssen, and has received research support from Gilead Sciences and Merck. KE has received grant funding from Gilead and provided consultation for Gilead, ViiV, and Merck. SHB reports research grants to her institution from ViiV Health Care and Janssen, and scientific advisory to Gilead Sciences. TB has served as consultant to Gilead Sciences, Merck, ViiV Healthcare, and Janssen. JL has received research grants from Gilead and has consulted to Theratechnologies.

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