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Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

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Background. We sought to identify factors associated with weight gain in randomized clinical trials of antiretroviral therapy (ART) switch.

Methods. We explored the effects of demographic factors, clinical characteristics, and ART on weight gain in a pooled analysis of 12 prospective clinical trials, wherein virologically suppressed people living with human immunodeficiency virus (PWH) were randomized to switch or remain on a stable baseline regimen (SBR).

Results. Both PWH randomized to switch ART (n = 4166) and those remaining on SBR (n = 3150) gained weight. Median weight gain was greater in those who switched (1.6 kg, interquartile range [IQR], −.05 to 4.0 vs 0.4 kg, [IQR], −1.8 to 2.4 at 48 weeks, $P < .0001$), with most weight gain occurring in the first 24 weeks after switch. Among baseline demographic and clinical characteristics, only younger age and lower baseline body mass index were associated with any or ≥10% weight gain. By week 48, 4.6% gained ≥10% weight (6.4% of switch and 2.2% of SBR), the greatest risk was with switch from efavirenz (EFV) to rilpivirine (RPV) or elvitegravir/cobicistat and switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). Switch from abacavir to TAF was associated with less weight gain than switch from TDF to TAF and was not associated with increased risk for ≥10% weight gain.

Conclusions. Moderate weight gain after ART switch was common and usually plateaued by 48 weeks. Baseline ART was a predictor of post-switch weight gain; participants who switched off of EFV and TDF had the greatest weight gain. The biological mechanisms that underlie the differential effects of switching ART agents on weight and associated clinical implications require further study.

Keywords. HIV; weight gain; obesity; antiretroviral therapy.

The last decade has seen the development of many new antiretroviral therapies (ART) with improved simplicity and tolerability, leading many people living with human immunodeficiency virus (HIV; PWH) and stable viral suppression to change to newer, guideline-supported ART regimens [1]. Numerous factors influence the decision to switch ART, including minimizing drug–drug interactions, enhancing tolerability and avoiding toxicities, and reducing pill burden [1], but risks of changing ART should also be considered. One emerging concern is the greater weight gain observed when starting treatment with newer ART agents such as the integrase strand transferase inhibitors (INSTIs), especially dolutegravir (DTG) and bictegravir (BIC) [2–4], and the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir alafenamide (TAF). A better understanding of who is at risk of weight gain after ART switch and the potential clinical implications is needed to help clinicians and PWH make informed decisions.

Several studies have demonstrated that significant weight gain occurs in some PWH after ART initiation [2, 4]. In a pooled analysis of 8 randomized, controlled trials of first-line ART, INSTI-based initial therapy was associated with greater weight gain than nonnucleoside reverse transcriptase inhibitor (NNRTI)– or protease inhibitor (PI)–based ART [5]. Weight gain is also observed in some people living with well-controlled HIV who switch ART regimens [6–9]. Several observational studies have shown significant weight gain in PWH who switched to newer ART regimens [9–11], while others have not [12–14]. These differing findings may be due to other factors that contribute to body weight, occurring amidst the trend

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of increasing obesity prevalence among people living with and without HIV [15, 16]. Prior studies have identified factors associated with weight gain that are HIV-related (viral load, CD4 count), host-related (Black race, female sex, baseline weight, genetics, comorbidities, concomitant non-ART medications), and ART-related. Disentangling the contributions of each and the degree of overlap is challenging.

Here, we sought to overcome the potential confounders that may impact observational cohort studies by exploring weight gain in the pooled Gilead Sciences clinical trial data of participants randomized to switch ART in the current era of INSTIs and TAF. Switch studies can also avoid potential confounding effects of virologic suppression and CD4 recovery on weight gain that may occur in individuals who initiate ART. Our primary goal was to compare weight gain among those randomized to switch vs remain on their stable baseline regimen (SBR). We also sought to identify those at greatest risk for weight gain or metabolic changes following switch.

METHODS

Study Design and Participants

Pooled analyses included 12 Gilead Sciences–sponsored trials that were randomized, active-controlled (double-blinded or open-label), and enrolled PWH on ART with HIV-1 viral load <50 copies/mL for a minimum of 3 months (Supplementary Table 1) [17–27]. Body weight was measured at least every 12 weeks, and follow-up duration was at least 48 weeks after ART switch. All participants provided written informed consent. Trials were undertaken in accordance with the Declaration of Helsinki and approved by center or site-specific review boards or ethics committees.

Procedures

Height was measured at baseline; body weight and vital signs, including blood pressure, were measured at each visit. CD4 cell count and HIV-1 RNA were measured at each study visit. Fasting serum glucose and lipids were measured at baseline and a minimum of every 24 weeks thereafter, except GS-US-236-0115 and GS-US-236-0121 (lipids measured at weeks 4, 8, 12, 24, 48, and 96). Laboratory evaluations were performed centrally by Covance Laboratories (Indianapolis, IN).

Adverse events (AEs) were reported by the site investigators and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Diabetes-related treatment-emergent AEs reported by the site investigators were identified by querying MedDRA terms found in the "hyperglycemia/new-onset diabetes mellitus (SMQ)" class (Supplementary Table 8).

Statistical Analyses

Body mass index (BMI) categories were defined as underweight, <18.5 kg/m^2; normal, ≥18.5 to <25 kg/m^2; overweight, ≥25 to <30 kg/m^2; and obese, ≥30 kg/m^2. Baseline participant characteristics were summarized by study and according to the presence or absence of ≥10% weight gain from baseline through 48 weeks using descriptive statistics. Weight change outliers were identified using the Tukey fences method. Comparisons of weight change between participants who switched vs remained on their SBR were performed using an analysis of variance model with group as a fixed effect. We compared participants with and without ≥10% weight gain using the Cochran-Mantel-Haenszel test for categorical data and the 2-sided Wilcoxon rank sum test for continuous data. For statistical analyses that involved ART components, we established 20 ART categories that encompassed all switch and stay-on events observed in at least 10 participants (Figure 1). Stepwise model selection was used to identify baseline risk factors associated with change in weight following switch using linear mixed effects models. A separate stepwise model identified risk factors associated with ≥10% weight gain through 48 weeks using logistic regression models. Further details are included in the Supplementary Methods.

Fasting lipid and glucose values were compared between those who gained ≥10% vs <10% weight in the first 48 weeks. To assess the impact after weight gain occurred and exclude the direct impact of ART on lipid levels, baseline for participants with ≥10% weight gain was redefined as the last available visit on or prior to the date when weight gain first reached ≥10% and assessed changes in metabolic parameters that occurred thereafter. Change from baseline in metabolic factors and systolic blood pressure were plotted over time and compared using the 2-sided Wilcoxon rank sum test. The rate ratio of diabetes AEs by ≥10% vs <10% weight gain through 48 weeks was calculated from a generalized model with a Poisson distribution and logarithmic link including ≥10% weight gain as a main effect. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Population, Demographics, and Baseline Clinical Characteristics

In the pooled dataset of 12 trials with 11 456 person-years of follow-up (Supplementary Table 1), 4166 were randomized to switch ART and 3150 to continue SBR. Duration of follow-up was 96 weeks in 7 studies and 48 weeks in 5 studies. Baseline characteristics are summarized in Tables 1 and 2. Demographics were generally similar across all 12 studies with the exception of 2 studies: GS-US-380–1961 enrolled only women and a higher proportion of Black participants and GS-US-292–1826 enrolled older participants (median age 65 years) and had <3% Black participants. Of the other 10 studies, the mean age was approximately 40–50 years, 10%–20% were women, 10%–30% were Black, 5%–25% were Hispanic/Latinx, and 15%–30% were obese by BMI.

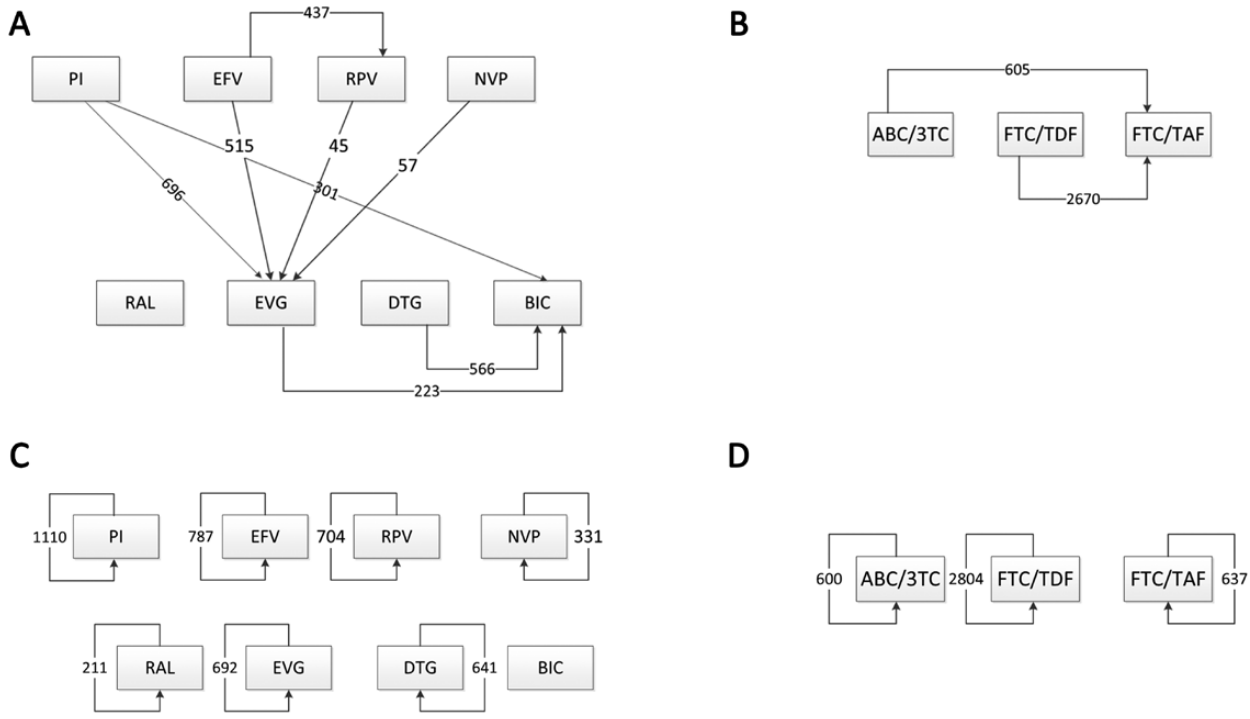

Figure 1. Schema for third-agent switch *(A)*, nucleotide reverse transcriptase inhibitor (NRTI) switch *(B)*, third-agent stable baseline regimen (SBR) *(C)*, and NRTI SBR *(D)*. Antiretroviral therapy agents are shown in boxes, with the arrows joining the pre- and post-randomization agent. Numbers indicate the number of participants within each switch or stay-on category. Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Weight Change in ART Switch Studies

As detailed in Figure 1 and Supplementary Tables 2 and 3, 1949 participants switched both NRTIs and the third agent, 1326 switched NRTIs only, and 891 switched the third agent only. Switch participants gained a median of 1.6 kg (interquartile range [IQR], −0.5 to 4.0; n = 3930) between baseline and week 48 and 2.0 kg (IQR, −0.5 to 5.2; n = 2598) between baseline and week 96 compared with 0.4 kg (IQR, −1.8 to 2.4; n = 2943) and 0.5 kg (IQR, −1.9 to 3.1; n = 1838) for SBR participants (all $P < .0001$; Figure 2A). While the distribution of weight changes fell within a narrow IQR, there were outliers with more extreme weight gain (102 [2.6%] switch and 49 [1.7%] SBR classified as outliers) (Figure 2B). The proportion of participants with an obese BMI increased from 21% to 25% over 96 weeks among switch participants (Figure 2C) but remained stable (21%) among SBR participants (Figure 2D); the proportion who were overweight increased similarly between groups. Categorical percent weight gain was greater in switch (Figure 2E) than SBR participants (Figure 2F). Furthermore, 28% of switch participants lost weight by week 96 compared with 43% of SBR participants. Longitudinal weight change by trial is shown in Supplementary Figure 1.

Factors Associated With Weight Gain

In a linear mixed effects model, only BMI category and age were associated with weight gain. Compared with participants with obesity at baseline, being underweight or having a normal BMI was associated with 0.8 kg greater weight gain, and being overweight was associated with a 0.5 kg greater weight gain (both $P < .0001$). Younger participants had 0.4 kg greater weight gain than older participants (≤ vs >35 years; $P = .0014$).

Next, we used linear mixed effects models to assess longitudinal weight change through week 48 by ART switch or SBR category. Weight gain was observed in most switch and SBR categories, reaching a plateau between weeks 24 and 36 (Figure 3).

Weight change with switch from boosted PI to elvitegravir/cobicistat (EVG/c) or BIC did not differ significantly from staying on a PI or EVG/c (Figure 3A, 3B). Switch from efavirenz (EFV) to rilpivirine (RPV) or to EVG/c was associated with 1.5 kg and 0.9 kg greater weight gain at week 48, respectively, compared with staying on EFV (both $P < .001$; Figure 3C), while switch from RPV to EVG/c was associated with 1.7 kg weight loss at week 48 ($P = .01$; Figure 3D). Switch from nevirapine (NVP) to EVG/c was associated with similar weight gain as staying on NVP (Figure 2E). Similar weight gain was seen between NNRTI SBR categories, with the exception of greater weight gain in stay-on RPV vs stay-on EVG/c ($P = .046$; Figure 3F). Among those on an INSTI at baseline, weight change with switch from DTG to BIC was not significantly

Table 1. Demographic Characteristics of Participants by Clinical Trial

Characteristic	236-0115 (E/C/F/TDF vs PI/r + F/TDF)	236-0121 (E/C/F/TDF vs NNRTI + F/TDF)	292-0109 (E/C/F/TAF vs F/TDF + Third Agent)	292-1826 (E/C/F/TAF vs ABC or TDF-Containing Regimen)	366-1160 (R/F/TAF vs EFV/F/TDF)	366-1216 (R/F/TAF vs R/F/TDF)	311-1089 (F/TAF + Third Agent vs F/TDF + Third Agent)	311-1717 (F/TAF + Third Agent vs ABC/3TC + Third Agent)	380-1844 (B/F/TAF vs DTG/ABC/3TC)	380-1878 (B/F/TAF vs PI/b + F/TDF or ABC/3TC)	380-1961 (B/F/TAF vs SBR)	380-4030 (B/F/TAF vs DTG + F/TAF)
Number of participants	419	431	1436	151	871	628	655	553	563	575	470	564
Year first participant screened	2011	2011	2013	2016	2015	2015	2014	2015	2015	2015	2016	2017
Age, median (range), y	40 (21–68)	42 (20–72)	41 (21–77)	65 (60–80)	49 (19–76)	45 (23–72)	48 (22–79)	52 (20–79)	46 (20–71)	48 (20–79)	39 (20–63)	51 (20–79)
Age categories, y												
≤35	128 (30.5)	133 (30.9)	467 (32.5)	0	123 (14.1)	136 (21.7)	87 (13.3)	28 (5.1)	122 (21.7)	100 (17.4)	167 (35.5)	76 (13.5)
>35	291 (69.5)	298 (69.1)	969 (67.5)	151 (100)	748 (85.9)	492 (78.3)	568 (86.7)	525 (94.9)	441 (78.3)	475 (82.6)	303 (64.5)	488 (86.5)
Sex at birth												
Male	361 (86.2)	399 (92.6)	1283 (89.3)	136 (90.1)	759 (87.1)	562 (89.5)	553 (84.4)	452 (81.7)	499 (88.6)	475 (82.6)	0	485 (86)
Female	58 (13.8)	32 (7.4)	153 (10.7)	15 (9.9)	112 (12.9)	66 (10.5)	102 (15.6)	101 (18.3)	64 (11.4)	100 (17.4)	470 (100)	79 (14)
Race												
Asian	9 (2.2)	13 (3)	94 (6.6)	0	17 (2)	24 (3.8)	6 (0.9)	10 (1.8)	18 (3.2)	15 (2.6)	102 (21.7)	6 (1.1)
Black	60 (14.5)	72 (16.7)	271 (18.9)	4 (2.8)	237 (27.5)	119 (18.9)	136 (20.8)	130 (23.5)	121 (21.6)	151 (26.3)	174 (37)	129 (23.1)
White	336 (81)	337 (78.2)	965 (67.3)	138 (96.5)	580 (67.3)	471 (75)	489 (74.9)	401 (72.5)	408 (72.9)	377 (65.6)	133 (28.3)	398 (71.2)
Pacific Islander[a]	0	1 (0.2)	0	0	0	0	3 (0.5)	0	0	0	0	0
American Indian[b]	3 (0.7)	2 (0.5)	0	0	0	0	3 (0.5)	1 (0.2)	0	0	0	0
Other	7 (1.7)	6 (1.4)	103 (7.2)	1 (0.7)	28 (3.2)	14 (2.2)	16 (2.5)	11 (2)	13 (2.3)	32 (5.6)	61 (13)	26 (4.7)
Not Reported[c]	4	0	3	8	9	0	2	0	3	0	0	5
Race categories												
Black	60 (14.5)	72 (16.7)	271 (18.9)	4 (2.8)	237 (27.5)	119 (18.9)	136 (20.8)	130 (23.5)	121 (21.6)	151 (26.3)	174 (37)	129 (23.1)
Non-Black	355 (85.5)	359 (83.3)	1162 (81.1)	139 (97.2)	625 (72.5)	509 (81.1)	517 (79.2)	423 (76.5)	439 (78.4)	424 (73.7)	296 (63)	430 (76.9)
Combination of sex and race												
Black male	41 (9.9)	53 (12.3)	216 (15.1)	2 (1.4)	174 (20.2)	78 (12.4)	79 (12.1)	72 (13)	89 (15.9)	97 (16.9)	0	90 (16.1)
Non-Black male	316 (76.1)	346 (80.3)	1065 (74.3)	128 (89.5)	576 (66.8)	484 (77.1)	472 (72.3)	380 (68.7)	407 (72.7)	378 (65.7)	0	390 (69.8)
Black female	19 (4.6)	19 (4.4)	55 (3.8)	2 (1.4)	63 (7.3)	41 (6.5)	57 (8.7)	58 (10.5)	32 (5.7)	54 (9.4)	174 (37)	39 (7)
Non-Black female	39 (9.4)	13 (3)	97 (6.8)	11 (7.7)	49 (5.7)	25 (4)	45 (6.9)	43 (7.8)	32 (5.7)	46 (8)	296 (63)	40 (7.2)
Ethnicity												
Hispanic or Latinx	56 (13.4)	46 (10.7)	330 (23.1)	21 (15)	157 (18)	93 (14.8)	124 (18.9)	35 (6.3)	98 (17.5)	107 (18.6)	74 (15.7)	110 (19.7)
Not Hispanic or Latinx	361 (86.6)	385 (89.3)	1101 (76.9)	119 (85)	713 (82)	534 (85.2)	531 (81.1)	518 (93.7)	463 (82.5)	468 (81.4)	396 (84.3)	448 (80.3)
Not Reported[c]	2	0	5	11	1	1	0	0	2	0	0	6

Data are reported as N (%) unless otherwise indicated.

Abbreviations: 3TC, lamivudine; ABC, abacavir; B, bictegravir; b; pharmacologic booster (ritonavir or cobicistat); C, cobicistat; DTG, dolutegravir; E, elvitegravir; EFV, efavirenz; F, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; R, rilpivirine; r, ritonavir; SBR, stay on baseline regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Includes Native Hawaiian.

[b]Includes Alaska Native.

[c]Participants who reported "not permitted" or "not reported" were excluded from the percentage calculation and also excluded from the combination of sex and race summary.

Table 2. Clinical Characteristics of Participants by Clinical Trial

Characteristic	236-0115 (E/C/F/TDF vs PI/r + F/TDF)	236-0121 (E/C/F/TDF vs NNRTI + F/TDF)	292-0109 (E/C/F/TAF vs F/TDF + Third Agent)	292-1826 (E/C/F/TAF vs ABC or TDF-Containing Regimen)	366-1160 (R/F/TAF vs EFV/F/TDF)	366-1216 (R/F/TAF vs R/F/TDF)	311-1089 (F/TAF + Third Agent vs F/TDF + Third Agent)	311-1717 (F/TAF + Third Agent vs ABC/3TC + Third Agent)	380-1844 (B/F/TAF vs DTG/ABC/3TC)	380-1878 (B/F/TAF vs PI/b + F/TDF or ABC/3TC)	380-1961 (B/F/TAF vs SBR)	380-4030 (B/F/TAF vs DTG + F/TAF)
Number of participants	419	431	1436	151	871	628	655	553	563	575	470	564
CD4 count, median (IQR), cells/μL	573 (429–757)	561 (440–728)	669 (522–831)	623 (468–803)	667 (506–852)	670 (521–858)	646 (490–836)	671 (510–873)	695 (510–910)	624 (452–820)	686 (541–867)	646 (474–830)
CD4 count categories, cells/μL												
<200	14 (3.3)	5 (1.2)	9 (0.6)	2 (1.3)	7 (0.8)	6 (1)	9 (1.4)	1 (0.2)	10 (1.8)	12 (2.1)	2 (0.4)	13 (2.3)
≥200	405 (96.7)	426 (98.8)	1427 (99.4)	149 (98.7)	864 (99.2)	622 (99)	646 (98.6)	552 (99.8)	553 (98.2)	563 (97.9)	468 (99.6)	551 (97.7)
HIV disease status												
Asymptomatic	313 (74.7)	337 (78.2)	962 (83.8)	125 (82.8)	732 (84)	553 (88.1)	539 (82.4)	400 (72.6)	488 (86.7)	473 (82.3)	425 (90.4)	466 (82.6)
Symptomatic HIV Infection	51 (12.2)	50 (11.6)	103 (9)	12 (7.9)	56 (6.4)	35 (5.6)	50 (7.6)	54 (9.8)	18 (3.2)	36 (6.3)	33 (7)	35 (6.2)
AIDS	55 (13.1)	44 (10.2)	83 (7.2)	14 (9.3)	83 (9.5)	40 (6.4)	65 (9.9)	97 (17.6)	57 (10.1)	66 (11.5)	12 (2.6)	63 (11.2)
Unknown	0	0	288	0	0	0	1	2	0	0	0	0
Years since first ART, median (IQR)	3 (2–4)	4 (2–4)	3 (3–3)	10 (6–16)	8 (5–14)	6 (3–10)	8 (4–16)	13 (8–18)	5 (3–10)	8 (4–14)	3 (2–3)	9.5 (4–18.5)
Years since first ART categories												
<3	193 (46.1%)	133 (30.9%)	175 (12.2%)	8 (5.3%)	48 (5.5%)	106 (16.9%)	77 (11.9)	26 (4.8)	136 (24.2)	63 (11.0)	127 (27.0)	85 (15.1)
≥3	226 (53.9%)	298 (69.1%)	1261 (87.8%)	143 (94.7%)	823 (94.5%)	522 (83.1%)	569 (88.1)	521 (95.2)	427 (75.8)	511 (89.0)	343 (73.0)	479 (84.9)
Missing	0	0	0	0	0	0	9	6	0	1	0	0
Baseline weight, median (IQR), kg	78.9 (69.5–88.7)	80 (70.7–90.0)	80 (70.8–90.7)	76 (70.0–85.8)	80.8 (71.9–91.0)	79.2 (70.9–90.2)	80.7 (72.3–92.5)	78.7 (71.0–89.3)	80.2 (71.9–91.6)	79.5 (70.4–90.5)	67.1 (57.9–78.9)	81.4 (72.0–94.2)
Baseline BMI, median (IQR), kg/m^2	25.5 (23.1–28.1)	25.3 (23.1–28.4)	25.9 (23.1–29.2)	25.2 (23.6–28.4)	26 (23.6–29.0)	25.5 (23.1–28.3)	26.3 (23.7–29.7)	26 (23.7–29.4)	26.1 (23.7–29.3)	26.1 (23.5–29.2)	25.6 (22.1–30.5)	26.5 (24.0–30.7)
Baseline BMI categories												
Underweight, <18.5	3 (0.7%)	3 (0.7)	18 (1.3)	3 (2.0)	15 (1.7)	11 (1.8)	3 (0.5)	4 (0.7)	7 (1.2)	6 (1.0)	13 (2.8)	8 (1.4)
Normal, ≥18.5 to <25	192 (45.8%)	199 (46.4)	585 (40.8)	68 (45.0)	318 (36.5)	266 (42.4)	249 (38.0)	220 (39.9)	212 (37.7)	237 (41.2)	208 (44.3)	191 (33.9)
Overweight, ≥25 to <30	152 (36.3%)	157 (36.6)	537 (7.5)	56 (37.1)	366 (42.0)	234 (37.3)	249 (38.0)	213 (38.6)	226 (40.1)	210 (36.5)	125 (26.6)	204 (36.2)
Obese, ≥30	72 (17.2%)	70 (16.3)	293 (20.4)	24 (15.9)	172 (19.7)	117 (18.6)	154 (23.5)	115 (20.8)	118 (21.0)	122 (21.2)	124 (26.4)	161 (28.5)

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; B, bictegravir; b; pharmacologic booster (ritonavir or cobicistat); BMI, body mass index; C, cobicistat; DTG, dolutegravir; E, elvitegravir; EFV, efavirenz; F, emtricitabine; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; R, rilpivirine; r, ritonavir; SBR, stay on baseline regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

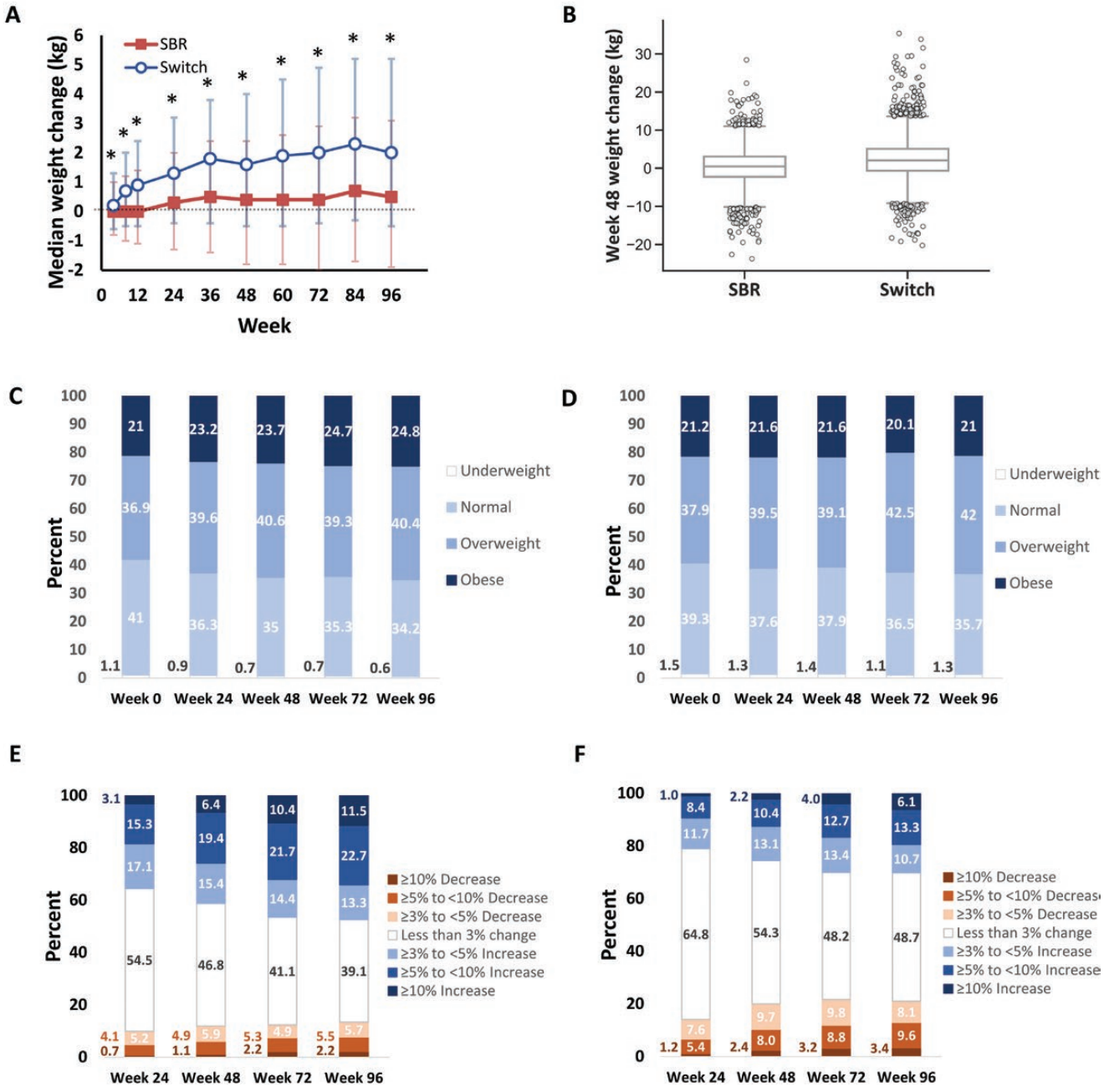

Figure 2. Weight change in the pooled dataset. *A,* Weight change by visit in the full pooled cohort stratified by participants who were randomized to switch or stay-on SBR. *B,* Distribution of week 48 weight change in participants who were randomized to switch or stay on SBR. *C* and *D,* Body mass index distribution of switch *(C)* or SBR *(D)* participants by visit. *E* and *F,* Categorical distribution of percent weight change in switch *(E)* and SBR *(F)* participants by visit. Line plot data are median (interquartile range [IQR]), with asterisks denoting $P < .05$ by analysis of variance. Box plot boxes depict median and IQR, and whiskers depict Q1–1.5 × IQR and Q3 + 1.5 × IQR; outliers are shown as open markers and are defined as values outside the whisker range. Abbreviation: SBR, stable baseline regimen.

different from remaining on DTG; switch from EVG/c to BIC was associated with a 0.7 kg greater weight gain at week 48 compared with no switch ($P = .034$; Figure 3G, 3H). Staying on DTG was associated with a 0.6 kg greater weight gain than staying on EVG/c at week 48 ($P = .02$; Figure 3I). Among NRTI switches, weight gain was seen when switching from tenofovir disoproxil fumarate (TDF; 1.6 kg or abacavir (ABC) to TAF (both $P < .001$; Figure 3J, 3K). Participants who stayed on TDF or ABC had weight changes similar to those who remained on TAF (Figure 3L).

Factors Associated With ≥10% Weight Gain

At week 48, 4.6% of participants had ≥10% weight gain (6.4% of switch and 2.2% of SBR). Participants with ≥10% weight gain were younger and had lower baseline weight and BMI; other characteristics were similar between groups (Table 3). Baseline

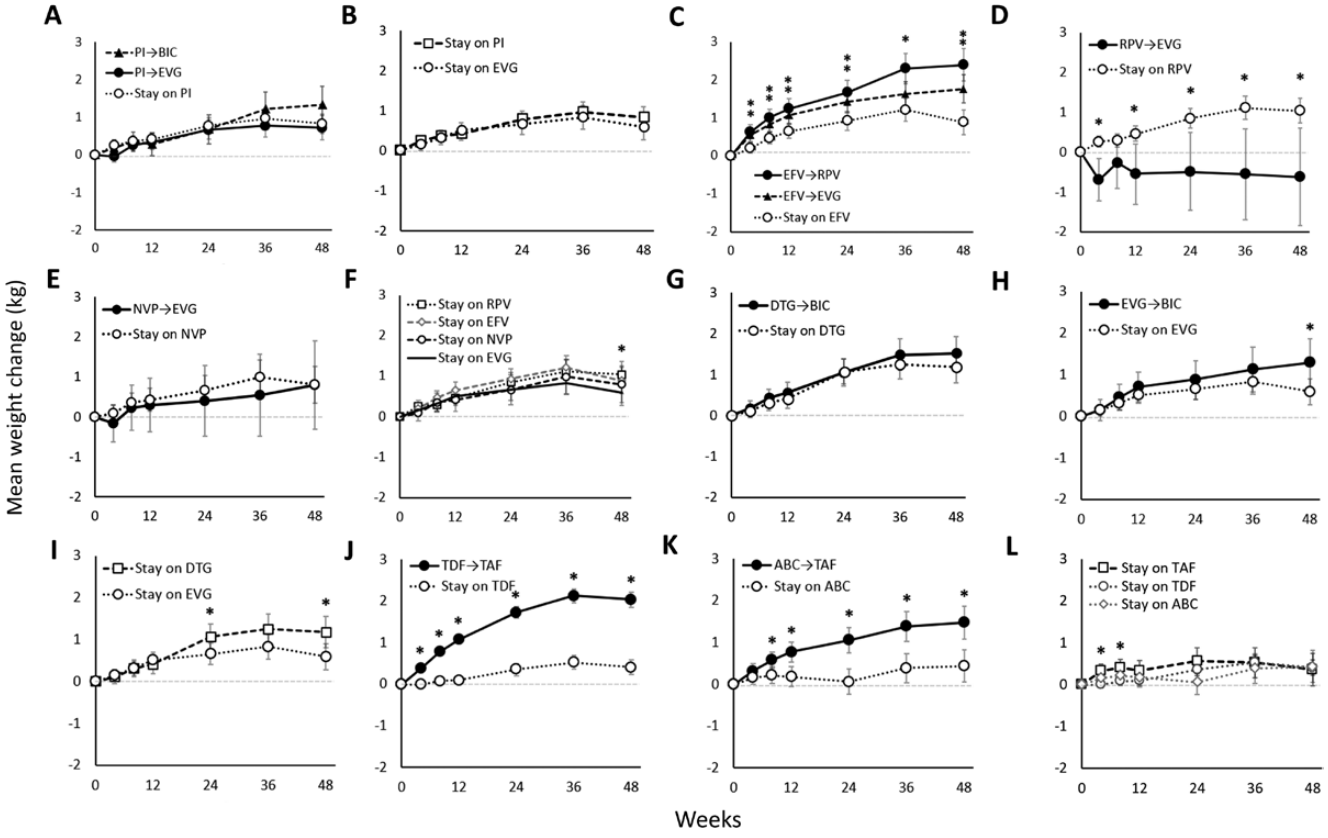

Figure 3. Longitudinal weight change by antiretroviral therapy (ART) switch category. Data depict least squares mean weight change (95% confidence interval) for the indicated ART switch or stay-on categories derived from mixed effects models including visit as a repeated measurement and interaction terms between visit and body mass index, age, third-agent switch, and nucleotide reverse transcriptase inhibitor switch as fixed effects. Single asterisks indicate $P < .05$ compared with the stable baseline regimen (SBR) weight change, and double asterisks indicate $P < .05$ for each of 2 switch categories compared with SBR weight change. Abbreviations: ABC, abacavir; BIC, bictegravir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; NVP, nevirapine; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

characteristics were generally well balanced between switch and SBR participants within the ≥10% gain and <10% gain groups (Supplementary Tables 4 and 5). In logistic regression models that included demographic and clinical variables as above, only baseline underweight/normal BMI category and age ≤35 years were associated with ≥10% weight gain. In a subsequent logistic regression model also including ART switch categories, there was increased risk for ≥10% weight gain with switch from EFV to RPV or to EVG/c but not with other third agent switches. Among NRTI switch categories, switch from TDF to TAF was associated with ≥10% weight gain, while switch from ABC to TAF was not (Table 4, Supplementary Table 6).

Longitudinal Weight Change by Sex and Race

As the lack of associations between race, sex, and 10% weight gain was unexpected, we performed additional analyses, focusing on sex and race. Females had a 0.3 kg greater weight gain compared with males at week 48 ($P = .0046$; Figure 4A); Black and non-Black participants did not significantly differ (Figure 4B). In models that assessed sex and race interactions, Black males had 0.3 kg greater weight gain than non-Black males ($P = .041$); non-Black females had 0.5 kg greater weight gain than non-Black males at week 48 ($P = .013$; Figure 4C). In contrast, females had similar weight gain regardless of race, and Blacks had a similar weight gain regardless of sex. We further explored the race and sex differences in study 380–1961, a trial that enrolled only women, of whom 37% were Black. Non-Black females (15.7% of whom were Hispanic or Latinx) experienced numerically greater weight gain after switching from TDF to TAF compared with Black females (3.2 vs 1.9 kg, $P = .07$). A sensitivity analysis that excluded study 380–1961 revealed similar results as for the full cohort (week 48 difference between Black and non-Black females, 0.23 kg, $P = .42$).

Metabolic Impact of Weight Gain in Switch Study Participants

Next, we sought to assess the metabolic consequences of substantial weight gain in switch and SBR participants by assessing metabolic parameters at 48 weeks, following the occurrence of 10% weight gain. Absolute values and changes in cholesterol components and systolic blood pressure were similar between switch and SBR participants who experienced ≥10% weight gain (Figure 5A, 5B). Participants with ≥10% weight gain had

Table 3. Demographic and Clinical Characteristics of Participants With and Without 10% Weight Gain

Characteristic	Weight Increase ≥ 10% Up to Week 48	Weight Increase < 10% Up to Week 48	Total	*P* Value
Number of participants	466	6850	7316	
Age, median (range), y	43 (20–71)	46 (19–80)	46 (19–80)	<.0001
Age categories, y				
≤35	139 (29.8)	1428 (20.8)	1567 (21.4)	<.0001
>35	327 (70.2)	5422 (79.2)	5749 (78.6)	
Sex at birth				
Male	368 (79.0)	5596 (81.7)	5964 (81.5)	.1428
Female	98 (21.0)	1254 (18.3)	1352 (18.5)	
Race				
Asian	15 (3.2)	299 (4.4)	314 (4.3)	.2992
Black	113 (24.3)	1491 (21.9)	1604 (22.0)	
White	313 (67.3)	4720 (69.2)	5033 (69.1)	
Pacific Islander[a]	1 (0.2)	3 (<0.1)	4 (<0.1)	
American Indian[b]	0	9 (0.1)	9 (0.1)	
Other	23 (4.9)	295 (4.3)	318 (4.4)	
Not Permitted/Not Reported[c]	1	0	34	
Race categories				
Black	113 (24.3)	1491 (21.9)	1604 (22.0)	.2214
Non-Black	352 (75.7)	5326 (78.1)	5678 (78.0)	
Combination of sex and race				
Black male	70 (15.1)	921 (13.5)	991 (13.6)	.2850
Non-Black male	297 (63.9)	4645 (68.1)	4942 (67.9)	
Black female	43 (9.2)	570 (8.4)	613 (8.4)	
Non-Black female	55 (11.8)	681 (10.0)	736 (10.1)	
Ethnicity				
Hispanic or Latinx	83 (17.9)	1168 (17.1)	1251 (17.2)	.6696
Not Hispanic or Latinx	381 (82.1)	5656 (82.9)	6037 (82.8)	
Not Permitted/Not Reported	2	26	28	
Baseline weight, kg	75 (33.7–131.5)	79.5 (36.2–218.6)	79.3 (33.7–218.6)	<.0001
Baseline height, cm	175.3 (145.0–198.1)	175.3 (134.6–204.0)	175.3 (134.6–204.0)	.8563
Baseline BMI, kg/m^2	24.3 (13.4–46.0)	26 (15.6–72.9)	25.9 (13.4–72.9)	<.0001
Baseline BMI categories, kg/ m^2				
Underweight, < 18.5	15 (3.2)	79 (1.2)	94 (1.3)	<.0001
Normal, ≥18.5 to <25	249 (53.4)	2696 (39.4)	2945 (40.3)	
Overweight, ≥25 to <30	144 (30.9)	2585 (37.8)	2729 (37.3)	
Obese, ≥30	58 (12.4)	1484 (21.7)	1542 (21.1)	

Data are reported as N (%) unless otherwise indicated. *P* values are from the Cochran-Mantel-Haenszel (CMH) test for categorical data and from the 2-sided Wilcoxon rank sum test for continuous data.

Abbreviation: BMI, body mass index.

[a]Includes Native Hawaiian.

[b]Includes Alaska Native.

[c]Participants who reported "not permitted" or "not reported" were excluded from the percentage calculation and also excluded from the combination of sex and race summary.

small reductions in high-density lipoprotein cholesterol; other metabolic parameters were largely stable (Supplementary Table 7). Treatment-emergent AEs related to diabetes or hyperglycemia were not significantly greater among those with ≥10% compared with <10% weight gain (rate ratio, 1.52; 95% confidence interval, .70 to 3.27; $P = .29$; Table 5).

DISCUSSION

In this pooled analysis of 12 randomized studies of ART switch, we found that weight gain occurred in both switch and SBR participants, with the magnitude of weight gain generally greater with switches to newer regimens, consistent with observations from other ART-naive and switch studies [2, 4–11]. Additionally, baseline ART regimen was a significant predictor of weight gain after switch. For example, in participants who switched to EVG/c, switch from EFV was associated with weight gain, switch from a PI or NVP to EVG/c was weight-neutral, and switch from RPV to EVG/c was associated with weight loss. Among the NRTIs, switch from TDF to TAF was associated with greater weight gain than switch from ABC to TAF. Younger age and lower baseline BMI were associated with weight gain, while race, ethnicity, sex, and CD4 count were not.

Weight gain after switch from TDF to TAF was observed in this study and others [11, 28], but it remains unknown whether these observations result from removal of a weight-suppressive

Table 4. Factors Associated with ≥10% Weight Gain Up to Week 48

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Third-agent switch		
EFV→RPV vs stay on EFV	4.2 (2.36–7.47)	<.0001
EFV→EVG vs stay on EFV	3.01 (1.72–5.27)	.0001
NVP→EVG vs stay on NVP	1.65 (0.44–6.19)	.4548
DTG→BIC vs stay on DTG	1.38 (0.78–2.42)	.2641
PI→BIC vs stay on PI	1.26 (0.75–2.10)	.3871
EVG→BIC vs stay on EVG	0.95 (0.48–1.90)	.8879
PI→EVG vs stay on PI	0.93 (0.60–1.45)	.7563
Stay on DTG vs stay on EFV	1.77 (0.92–3.38)	.0853
Stay on PI vs stay on EFV	1.55 (0.90–2.68)	.1144
Stay on RAL vs stay on EFV	1.5 (0.67–3.36)	.32
Stay on EVG vs stay on EFV	1.35 (0.74–2.45)	.3284
Stay on RPV vs stay on EFV	1.32 (0.73–2.39)	.3533
Stay on NVP vs stay on EFV	1.16 (0.54–2.49)	.696
NRTI switch		
TDF→TAF vs stay on F/TDF	2.58 (1.94–3.43)	<.0001
ABC→TAF vs stay on ABC/3TC	1.12 (0.59–2.12)	.7383
Stay on ABC/3TC vs stay on F/TAF	1.23 (0.64–2.34)	.5382
Stay on FTC/TDF vs stay on F/TAF	1.08 (0.62–1.89)	.7797
Baseline characteristics		
BMI category (underweight/normal vs obese)	2.42 (1.80–3.26)	<.0001
BMI category (underweight/normal vs overweight)	1.67 (1.34–2.08)	<.0001
Age category (≤35 vs >35 y)	1.5 (1.20–1.87)	.0003

P values are derived from a logistic regression model that included baseline BMI and age as risk factors and third agent switch and NRTI switch as fixed effects.

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; F, emtricitabine; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, Raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

effect of TDF, TAF-associated weight increase, or a combination of both [11, 28]. Preexposure prophylaxis (PrEP) trials suggest an initial weight-suppressive effect of TDF in a setting where confounding effects of HIV and other agents are absent. In iPrEX, participants who took emtricitabine (F)/TDF had initial weight loss followed by a weight gain trajectory similar to the placebo arm. A similar pattern was observed in DISCOVER and HPTN 083, where the F/TDF arm exhibited initial weight loss, followed by a weight gain trajectory similar to the F/TAF and cabotegravir (CAB) arms, resulting in 1–1.5 kg greater weight gain in the F/TAF and CAB arms [29–31]. HPTN 077 found similar weight gain between CAB and placebo, suggesting that initial TDF weight suppression may have contributed to the weight differences in HPTN 083 [32]. The potential for TDF to suppress weight gain is also supported by the GEMINI 1 and 2 studies, where treatment-naive PWH randomized to DTG + lamivudine (3TC) gained more weight than those taking DTG + F/TDF (3.7 vs 2.4 kg at week 144) [33]. Additionally, switch from TAF-containing regimens to DTG/3TC led to similar weight gain as staying on TAF-containing ART in the TANGO study [34], although these findings are confounded by a high proportion of study participants also switching from non-DTG–containing regimens. The TDF weight-suppressive effect does not exclude TAF-associated weight gain and does not entirely explain the weight gain differences among NRTIs we observed in our study; switch from ABC to TAF was also associated with smaller but statistically significant weight gain. ABC/3TC/DTG was associated with more frequent gastrointestinal AEs than BIC/F/TAF in study GS-US-380–1844 (included in our analysis), but the contribution of this observation to weight differences is unknown [24]. Further research including mechanistic studies, healthy volunteer studies, and single-variable ART switch studies may help disentangle these complex observations.

Among the NNRTIs, we observed significant weight gain associated with switch from EFV to RPV; switch off EFV was the only third-agent switch associated with ≥10% weight gain. As with TDF, this observation may be explained, at least in part, by

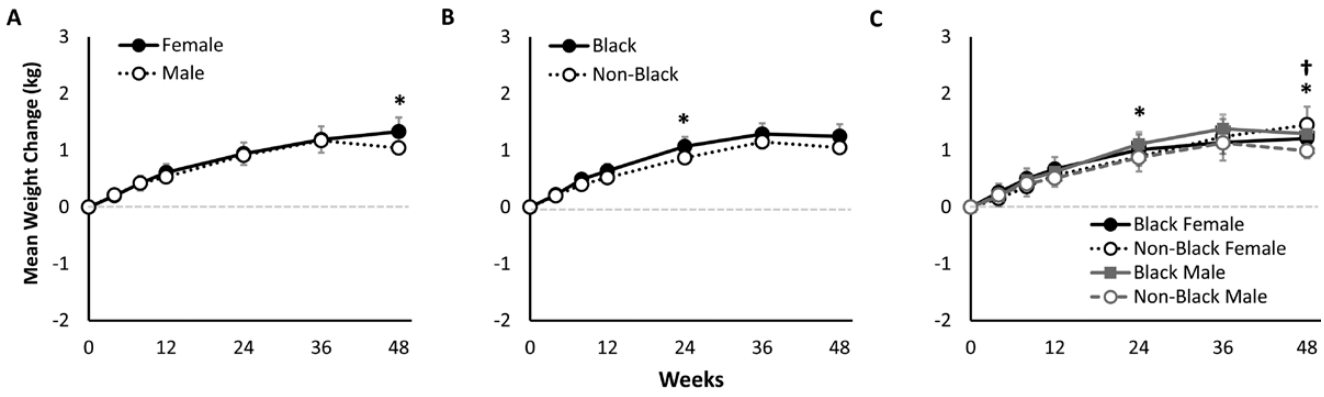

Figure 4. Longitudinal weight change by sex and race. Data depict least squares mean weight change (95% confidence interval) for the indicated demographic categories derived from mixed effects models including visit as a repeated measurement and interaction terms between visit and body mass index, age, third-agent switch, nucleotide reverse transcriptase inhibitor switch as fixed effects. In addition, an interaction term between visit and race is included for panel *(A)*, an interaction term between visit and sex is included for panel *(B)*, and a 3-way interaction term among visit, race, and sex is included for panel *(C)*. Single asterisks indicate $P < .05$ in panels *(A)* and *(B)* and $P < .05$ for Black male vs non-Black male in panel *(C)*. Dagger indicates $P < .05$ for non-Black male vs non-Black female.

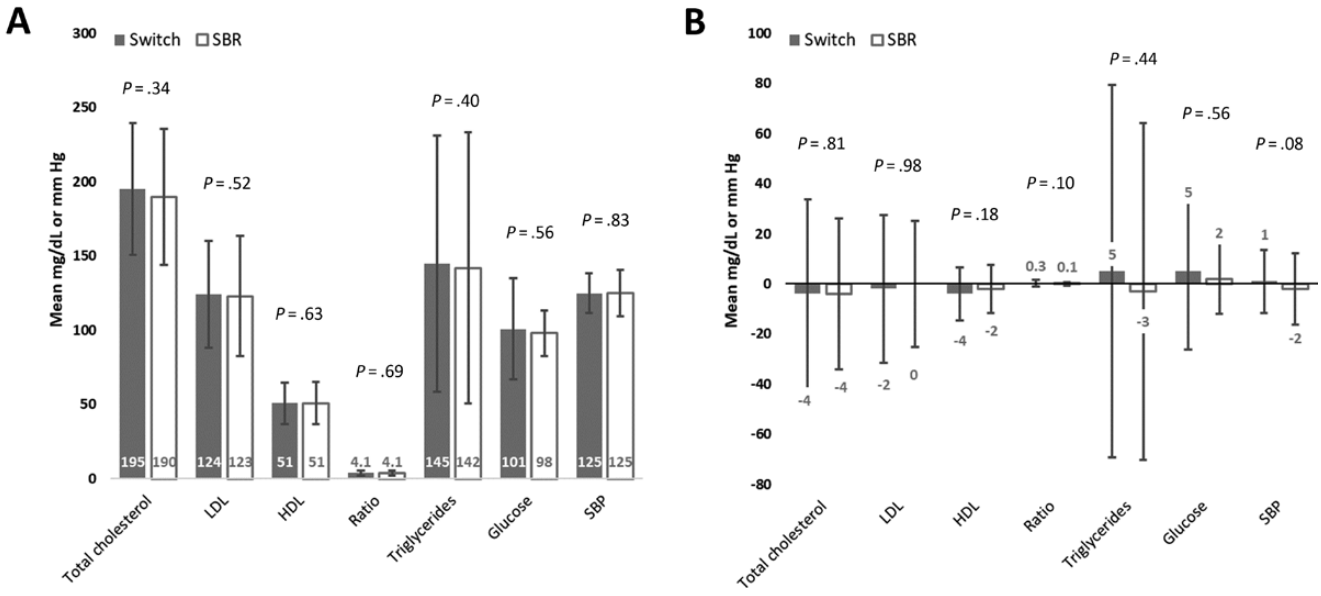

Figure 5. Metabolic outcomes. Metabolic parameters at 48 weeks following a ≥10% weight increase stratified by switch (gray bars) and SBR (open bars). Absolute values are shown in panel *(A)*, and changes are shown in panel *(B)*. Values are mean with 1 standard deviation error bars. *P* values are from the Wilcoxon rank sum test. Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ratio, total cholesterol to HDL ratio; SBP, systolic blood pressure; SBR, stable baseline regimen.

a weight-suppressive effect of EFV. In an observational cohort study, slow metabolizers gained a median 2.0 kg after switch to INSTI, while those with normal EFV metabolizer genotypes gained 0.1 kg after switch [35]. Similar findings were reported from the ADVANCE study, which compared randomized EFV + F/TDF to DTG + F/TDF or F/TAF in ART-naive PWH in southern Africa. While greater weight gain was observed in the DTG-containing arms, a pharmacogenomic substudy found that participants with a slow EFV metabolizer genotype lost weight, while those with an extensive EFV metabolizer genotype gained a similar amount of weight as those in the DTG + F/TDF arm [36]. Further studies focusing on pharmacogenomics of ART metabolism and individual genetic factors associated with weight gain may provide additional insights into the mechanisms of ART-associated weight gain.

Increasing attention has recently been paid to the association between INSTIs and weight gain, an issue of growing relevance as the second-generation INSTIs (DTG and BIC) are first-line recommended therapy [34]. Our findings in the pooled switch data are consistent with the existing literature [8, 34]: weight gain with switch to DTG and BIC is greater than that observed with switch to EVG/c. Potential mechanisms to explain the weight gain observed with newer INSTIs are a topic of intensive study (reviewed in [34]).

An important question is whether the weight changes following ART switch stabilize or continue to increase over time. Across our pooled data, we observed a period of accelerated weight gain that lasted approximately 24 weeks followed by a gradual plateau, although data past 48 weeks were limited. The proportion of those who gained ≥10% continued to increase to week 96 (Figure 2). We and others have observed a similar plateau of weight gain in treatment-naïve participants [4, 5, 37] or following TAF switch [28]. In contrast, other studies showed continued weight gain 2 or more years post-switch [7, 38].

In contrast to our prior pooled analysis in ART-naive persons [5], we did not observe an association between weight gain and Black race or female sex; the reasons for this are unclear. Our pooled dataset included approximately 1600 Black participants (600 women), suggesting the analysis was not underpowered. Sociogeographic characteristics of Black participants could

Table 5. Incidence of Diabetes-Associated Adverse Events in Participants With ≥10% Weight Gain Up to Week 48

Parameter	≥10% Increase	<10% Increase	Rate Ratio (95% CI)	*P* Value
Person-years of follow-up	504.4	10 487	1.52 (.704–3.266)	.29
N with at least 1 TEAE	7	96		
TEAE rate per 100 person-years (95% CI)	1.388 (0.558–2.859)	0.915 (0.741–1.118)		

Data and *P* values are from a generalized model with a Poisson distribution and logarithmic link and including significant weight gain status as the main effect.

Abbreviations: CI, confidence interval; TEAE, treatment emergent adverse event related to diabetes or hyperglycemia as defined in the Methods section.

have contributed as well as regional differences in the obesity epidemic. For instance, Black females in the ADVANCE study resided in southern Africa, which has the highest prevalence of female obesity in the world, while Black females in GS-US-380–1961 (who constitute nearly one-third of Black females in our pooled dataset) resided primarily in East Africa, where obesity rates are markedly lower [39]. Similarly, a study of ART switch in Nigeria did not find greater weight gain among women [37].

Similarly, we did not observe an association between baseline CD4 count and weight gain. This is most likely because substantial immune recovery had already occurred for most participants during the pre-ART switch period. However, we cannot exclude the possibility of lingering metabolic impacts of HIV infection that could be reversed with longer ART duration or be differentially impacted by certain ART regimens.

We found no clinically significant changes in metabolic parameters following ≥10% weight increase, albeit with short follow-up. The intrinsic effects of some ART drugs on lipid levels, which we avoided by resetting the lipid baseline to the time of 10% weight gain, makes the impact of weight change on lipids challenging to assess. Long-term follow-up studies are needed to assess metabolic changes associated with ART-associated weight gain.

Our pooled analyses are strengthened by randomized, controlled data from more than 7300 persons enrolled in switch studies, with diversity in geographic location, sex, age, race, and ethnicity. However, several important host factors that may have impacted weight gain were not assessed in these clinical trials, including diet, exercise, alcohol use and smoking, comorbidities including mood disorders, and comedications. Additionally, randomized, clinical trials preclude the assessment of preswitch weight trajectories, lack general population controls, and tend to enroll participants who are younger and healthier than observational cohorts and thus may not be reflective of weight changes in clinical practice. The regimen changes were limited to those studied in these clinical trials and thus did not include other switch regimens of interest (ie, RAL to DTG) and fewer switches to ABC than TAF. Weight and metabolic outcomes were not prespecified in any trial, and imaging was not available to explore distribution of weight gain.

In summary, our results demonstrate that modest weight gain is common after ART switch and is correlated more strongly with baseline regimen, especially switch off of TDF or EFV, than with sex-, race-, or HIV-related factors. It remains uncertain whether this is due to the loss of a weight suppressive effect of prior regimens or a weight gain effect of the newer regimen. A better understanding of the underlying biological mechanisms and the clinical implications is needed to fully understand these observations. Close monitoring of weight and counseling to maintain a healthy diet and remain physically active, as well as optimize other lifestyle factors, is imperative for all patients on ART [40].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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