

Weight Gain on Contemporary Integrase Strand Transfer Inhibitors and Tenofovir Alafenamide in Persons With HIV Starting Antiretroviral Therapy in the United States and Canada

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Background. Weight gain is common following antiretroviral therapy (ART) initiation. Integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide (TAF) have been associated with greater weight gain, though prior analyses may have been confounded by the weight-suppressive effects of efavirenz (EFV) and tenofovir disoproxil fumarate (TDF).

Methods. Treatment-naïve adults in the North American AIDS Cohort Collaboration on Research and Design initiating ART between 2007 and 2021 were analyzed. Predicted weight change was modeled using linear mixed effects models adjusted for demographic and clinical factors, and nucleoside reverse transcriptase inhibitor (NRTI) backbone, with subanalyses excluding EFV and stratifying by INSTI agent, NRTI, sex, and race.

Results. A total of 32 514 persons were included. At 2 years, INSTIs (4.9 kg, 95% CI: 4.6–5.2) and protease inhibitors (PIs) (4.7 kg, 95% CI: 4.4–5.1) were associated with greater mean predicted weight gain compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (2.7 kg, 95% CI: 2.4–2.9). Differences persisted when limiting analyses to TDF-containing regimens and excluding EFV. Among INSTIs, mean predicted weight gain was numerically highest with bictegravir (6.9 kg, 95% CI: 5.8–7.9), followed by dolutegravir (5.3 kg, 95% CI: 4.8–5.9), raltegravir (4.5 kg, 95% CI: 3.8–5.3), and elvitegravir (4.0 kg, 95% CI: 3.6–4.5). Participants receiving TAF with INSTIs gained more than those on TDF. Black females on bictegravir or dolutegravir with TAF had the highest gain at 2 years (10.0 kg, 95% CI: 7.4–12.6).

Conclusions. Weight gain with non-EFV NNRTIs was lower than with PIs and INSTIs, with the greatest increases observed among Black females starting TAF with contemporary INSTIs.

Keywords. HIV; antiretroviral therapy; weight gain; integrase inhibitors; tenofovir alafenamide.

Antiretroviral therapy (ART) initiation among treatment-naïve people with human immunodeficiency virus (HIV-1) (PWH) is often accompanied by an initial period of weight gain, particularly among individuals with more advanced CD4⁺ T-cell depletion [1]. The introduction of progressively more effective and tolerable ART has extended the survival of PWH by decades [2], but this success is accompanied by an increasing burden of noncommunicable diseases, including cardiometabolic

conditions, which may be exacerbated by weight gain or a higher body mass index (BMI) [3–8]. While weight gain after ART initiation was often regarded as a “return to health” phenomenon early in the HIV epidemic, the rising prevalence of overweight and obesity among PWH across diverse geographic areas and demographics has led to a reassessment of the role of weight gain in long-term health outcomes.

Several studies have reported higher weight gain among treatment-naïve PWH starting integrase strand transfer inhibitor (INSTI)-based regimens compared to those starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, which was often more pronounced among female and Black individuals [9–11]. This finding was accompanied by reports of greater weight gain among those receiving tenofovir alafenamide (TAF) compared to other nucleoside reverse transcriptase inhibitors (NRTIs) [11, 12]. Taken together, these data suggested that INSTI and TAF-containing regimens may

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have specific weight-promoting effects as compared with older agents and combination regimens.

This initial framework for interpreting the role of ART regimens in the context of weight gain was called into question by the results of more recent treatment studies and a reassessment of pre-exposure prophylaxis (PrEP) trials. In particular, the ADVANCE trial in South Africa demonstrated that polymorphisms in the CYP2B6 enzyme responsible for efavirenz (EFV) metabolism affected weight gain trajectory, and those with higher EFV plasma levels experienced a weight-suppressing effect [11, 13]. Regarding different tenofovir prodrugs and weight gain, median weight increased by 1.5 kg at week 96 in the placebo arm of the iPrEx trial of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP, whereas those with detectable plasma tenofovir levels gained only 0.6 kg by week 72 [14], suggesting TDF may actually be weight suppressive. In contrast, stopping TAF when switching to dolutegravir/lamivudine (DTG/3TC) was not associated with weight loss in the TANGO study, as might be expected if the TAF was truly weight promoting [15]. Taken together, these findings serve as an important caveat for interpreting studies of ART and weight gain and the labeling of different agents as potentially “weight neutral” versus “weight promoting” or “weight suppressive.”

Our group previously published one of the largest retrospective cohort studies of weight gain among treatment-naïve PWH enrolled in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), utilizing data from 22 972 participants who initiated treatment between 2007 and 2016. We found that weight gain was greater with an INSTI-based regimen compared to a protease inhibitor (PI)- or NNRTI-based regimen [9]. Among INSTI drugs, weight gain was higher with DTG compared to raltegravir (RAL) and elvitegravir (EVG; coformulated with the boosting agent cobicistat). Since the study utilized data through 2016, very few participants had received TAF, and none received bictegravir (BIC). A second notable limitation of this prior study, now recognized, was the large proportion of EFV-containing regimens in the NNRTI arm and the lack of adjustment for NNRTI agents [12].

The current analysis is a reappraisal of weight gain on ART among NA-ACCORD cohorts of PWH in the United States and Canada. To assess whether previously reported weight differences between INSTIs and NNRTIs may have been driven by the weight-suppressive effects of EFV and/or TDF, we modeled weight among those starting regimens containing an INSTI, PI, or NNRTI with TDF/FTC only and excluding EFV. A second objective was to estimate weight changes over the initial 2 years of ART among treatment-naïve PWH initiating individual INSTI drugs (RAL, EVG, DTG, and BIC). To assess whether previously reported differences in predicted weight gain by INSTI drugs may be attributable to differences in the NRTI

backbone, we separated those starting TDF with RAL, EVG, or DTG and those starting TAF with EVG, DTG, or BIC. Finally, we examined differences in weight gain by sex and race among participants starting newer INSTIs (BIC and DTG) with TAF/FTC.

METHODS

NA-ACCORD is a multisite collaboration comprising 27 interval and clinical cohorts representing over 200 clinical and research facilities across the United States and Canada. NA-ACCORD is one of the regional cohort study groups supported by the International epidemiologic Databases to Evaluate AIDS (IeDEA) consortium of the National Institutes of Health and collects standardized, individual-level data on demographics, clinical characteristics, ART use, laboratory measurements, medical diagnoses, and vital status. These data undergo rigorous quality control and harmonization procedures to ensure accuracy and completeness. The human subjects' activities of the NA-ACCORD are overseen by the local cohorts' institutional review boards (IRB) and the Johns Hopkins Bloomberg School of Public Health IRB.

Study Participants

We incorporated data from 13 clinical cohorts with available weight, height, and other covariates from 1 January 2007 (the year of the first INSTI regulatory approval in the United States) to 31 December 2021. We included treatment-naïve adults starting ART in this period who remained on the same regimen for at least 12 months. Antiretroviral therapy regimens were categorized as NNRTI, PI, or INSTI. The NRTI backbone was classified as TDF/FTC, TAF/FTC, abacavir (ABC)/3TC, or other. Participants were considered treatment naïve if they had no reported prior ART exposure and a viral load (VL) of >400 copies/mL at the time of ART initiation. Participants with no follow-up weights, those with a baseline viral load of <400 copies/mL, and participants starting a combination of NNRTI, PI, and/or INSTI were excluded.

Statistical Analysis

Demographic and clinical characteristics were summarized across the ART/drug categorization using medians (interquartile range [IQR]) or percentages, as appropriate. Baseline (treatment initiation) weight, CD4⁺ T-cell count, and BMI were defined using values closest to the start of the index regimen within a window of −180 to +30 days, while baseline viral load was captured within −180 to +7 days. Baseline height measured closest to ART initiation within the same time window was used to calculate BMI (in kg/m²).

We modeled weight over time using a multivariable linear mixed effects model, treating participants as a random effect. Participants were censored if they experienced virological failure,

defined as having one HIV-1 RNA VL measurement > 1000 copies/mL or 2 consecutive measurements > 400 copies/mL after achieving viral suppression. Participants were also censored at the time of ART switch, discontinuation of ART (lapse of more than 365 days), loss to follow-up, or the end of the study period. Loss to follow-up was defined as having no clinic visit, laboratory result, or other documented healthcare encounter for more than 12 months since the prior recorded visit.

Models were adjusted for birth sex, race/ethnicity, study cohort, ART initiation year, NRTI backbone (TDF/FTC, TAF/FTC, ABC/3TC, or other), and baseline measurements of age, weight, viral load (log10 transformed), and CD4⁺ T-cell count (square root transformed). To relax linearity assumptions, baseline age, weight, viral load, CD4 count, ART initiation year, and years between the weight measurement and ART initiation date were modeled using restricted cubic splines with 4 knots. Missing baseline data were multiply imputed using 10 imputation replicates, and the resulting pooled estimates were derived following Rubin's rules. Predicted weight changes over time, along with the corresponding 95% CIs, were calculated using the Delta method for each analysis and reported at multiple predefined time periods. Model assumptions and goodness of fit were evaluated through residual diagnostics, including assessments of normality, homoscedasticity, and linearity. In all analyses, statistical significance was set at $P < .05$. Individuals initiating dual-agent ART regimens (eg, dolutegravir/lamivudine, dolutegravir/rilpivirine, and cabotegravir/rilpivirine) were excluded from the analysis because the number of such regimens was very small during the study period. In total, 47 participants initiating dual therapy were excluded.

To estimate whether differences in weight gain by ART class may be influenced by the NRTI backbone or the weight-suppressive effects of EFV, we conducted a second analysis adjusting for the same covariates (except NRTI backbone) and restricted to individuals receiving TDF/FTC-containing regimens and excluding those with EFV.

We further modeled the predicted weight change over 2 years among participants receiving INSTI-based regimens, stratified by core INSTI agent (RAL, EVG, DTG, and BIC). Additional subgroup analyses were conducted for individuals on TDF/FTC- and TAF/FTC-based regimens. Lastly, we limited the analysis to participants receiving a second-generation INSTI (DTG or BIC) plus TAF and evaluated predicted weight changes stratified by sex and race (Black female, Black male, non-Black female, and non-Black male).

RESULTS

Baseline Demographics

Clinical and demographic characteristics are summarized in [Table 1](#). The analysis included 32 514 treatment-naïve participants who initiated ART between 2007 and 2021 and met

inclusion criteria. The study population was predominantly male (84%), with 45% identifying as Black and 41% as men who have sex with men (MSM). At baseline, the median age at ART initiation was 41 years, the median BMI was 25.4 kg/m², and the median CD4⁺ T-cell count was 329 cells/μL. Notably, 54% of participants were overweight (BMI 25.0–29.9 kg/m²) or obese (BMI ≥ 30.0 kg/m²) at the time of ART initiation, while 3% were underweight (BMI ≤ 18.5 kg/m²). Baseline BMI differed modestly by demographic subgroup ([Supplementary Table 1](#)). Black females had the highest median BMI at ART initiation (27.7 kg/m²; IQR, 22.7–33.2), followed by non-Black females (26.6 kg/m²; IQR, 22.9–31.6). Median BMI was similar among Black and non-Black males (25.2 kg/m² and 25.1 kg/m², respectively). Obesity prevalence was highest among Black females (40%).

A total of 13 344 participants (41%) started NNRTI-based, 8876 (27%) PI-based, and 10 294 (32%) INSTI-based regimens. Most participants (72%) started regimens containing TDF/FTC, while 12% initiated TAF/FTC and 12% ABC/3TC. Among participants starting TAF-containing regimens, the majority also received an INSTI. Participants initiating INSTI-based regimens started treatment at a later year, with a median ART start year of 2016 compared to 2011 for NNRTI-based regimens and 2010 for PI-based regimens. Among NNRTI recipients, 11 041 (82%) were on EFV-based regimens, while 1792 (13%) received rilpivirine-based regimens.

Among participants initiating INSTI-based regimens, 1581 (15%) started BIC, 3150 (31%) started DTG, 3560 (35%) started EVG, and 2003 (20%) started RAL. Those initiating RAL-based regimens were older (median age 44 years), more likely to be female, and had an earlier ART initiation year (median 2011) compared to participants on other INSTI regimens. Bictegravir and DTG were more commonly used in recent years, with median ART initiation years of 2018 and 2016, respectively. This trend reflects evolving prescribing practices following the later approval of these drugs.

Changes in Weight Over Time by Class

The predicted weight changes over time across ART regimen classes, adjusted for NRTI backbone and other covariates, is shown in [Figure 1](#). At year 2, participants on INSTI-based and PI-based regimens experienced comparable weight gains of approximately 4.9 kg (95% CI: 4.6–5.2) and 4.7 kg (95% CI: 4.4–5.1), respectively, both significantly higher than the 2.7 kg (95% CI: 2.4–2.9) gain observed among those on NNRTI-based regimens. By year 5, weight gain was highest in the INSTI group with 5.7 kg gained (95% CI: 5.1–6.2), slightly exceeding that of the PI group with 5.3 kg weight gain (95% CI: 4.8–5.8), while the NNRTI group continued to have significantly lower weight gain of 3.0 kg (95% CI: 2.6–3.3). Notably,

Table 1. Clinical and Demographic Characteristics of Participants Included in Analysis.

		ART Regimen Type					INSTI Subtypes				
		Total	NNRTI ^c	PI ^d	INSTI	<i>P</i> Value ^a	BIC	DTG	EVG	RAL	<i>P</i> Value ^b
Characteristic		Total	NNRTI ^c	PI ^d	INSTI	<i>P</i> Value ^a	BIC	DTG	EVG	RAL	<i>P</i> Value ^b
<i>N</i> (%)		32 514	13 344 (41%)	8876 (27%)	10 294 (32%)	N/A	1581 (15%)	3150 (31%)	3560 (35%)	2003 (20%)	N/A
Baseline age (years)		41 (31, 51)	42 (31, 51)	42 (32, 50)	39 (29, 50)	<.001	37 (29, 50)	39 (29, 52)	36 (28, 48)	44 (33, 52)	<.001
Birth sex, <i>N</i> (%)	Female	5271 (16%)	1791 (13%)	1957 (22%)	1523 (15%)	<.001	219 (14%)	455 (14%)	434 (12%)	415 (21%)	<.001
	Male	27 243 (84%)	11 553 (87%)	6919 (78%)	8771 (85%)		1362 (86%)	2695 (86%)	3126 (88%)	1588 (79%)	
Race category, <i>N</i> (%)	Black	14 497 (45%)	5985 (45%)	3999 (45%)	4513 (44%)	<.001	796 (50%)	1350 (43%)	1619 (45%)	748 (37%)	<.001
	Non-Black	18 017 (55%)	7359 (55%)	4877 (55%)	5781 (56%)		785 (50%)	1800 (57%)	1941 (55%)	1255 (63%)	
HIV risk category, <i>N</i> (%)	MSM	13 213 (41%)	5609 (42%)	3102 (35%)	4502 (44%)	<.001	731 (46%)	1326 (42%)	1744 (49%)	701 (35%)	<.001
	Other HIV risk	19 301 (59%)	7735 (58%)	5774 (65%)	5792 (56%)		850 (54%)	1824 (58%)	1816 (51%)	1302 (65%)	
ART initiation year		2014 (2009, 2014)	2011 (2009, 2012)	2010 (2009, 2012)	2016 (2014, 2018)	<.001	2018 (2018, 2019)	2016 (2015, 2017)	2015 (2014, 2017)	2011 (2010, 2012)	<.001
Baseline BMI (kg/m ²)		25.4 (22.5, 29.1)	25.4 (22.5, 28.8)	25.1 (22.2, 28.7)	25.6 (22.6, 29.6)	<.001	25.7 (22.7, 29.8)	25.8 (22.8, 29.7)	25.4 (22.4, 29.3)	25.7 (22.6, 29.6)	<.007
Baseline BMI category, <i>N</i> (%)	Underweight	819 (3%)	324 (3%)	237 (2%)	258 (3%)	<.001	42 (3%)	80 (3%)	86 (3%)	50 (3%)	.21
	Normal	11 103 (43%)	4500 (44%)	3070 (45%)	3533 (41%)		523 (40%)	1022 (40%)	1309 (44%)	679 (40%)	
	Obese	5260 (21%)	1981 (19%)	1309 (19%)	1970 (23%)		321 (24%)	610 (24%)	649 (22%)	390 (23%)	
	Overweight	8411 (33%)	3440 (34%)	2192 (32%)	2779 (33%)		428 (33%)	833 (33%)	954 (32%)	564 (34%)	
Baseline CD4 cell count (cells/ μ L)		329 (182, 495)	329 (202, 480)	273 (118, 422)	382 (219, 569)	<.001	371 (214, 581)	385 (217, 585)	405 (241, 592)	345 (181, 505)	<.001
Baseline log HIV-1 RNA (copies/mL)		4.6 (3.8, 5.1)	4.5 (3.8, 5.0)	4.6 (3.9, 5.2)	4.6 (3.8, 5.1)	<.001	4.6 (3.8, 5.1)	4.5 (3.8, 5.0)	4.6 (3.9, 5.2)	4.6 (3.9, 5.2)	<.007
NRTI backbone, <i>N</i> (%)	ABC/3TC	3782 (12%)	447 (3%)	1073 (12%)	2262 (22%)	.001	0 (0%)	2098 (67%)	0 (0%)	164 (8%)	<.001
	TAF/FTC	3721 (11%)	265 (2%)	102 (1%)	3354 (33%)		1577 (100%)	431 (14%)	1327 (37%)	19 (1%)	
	TDF/FTC	23 287 (72%)	12 107 (91%)	6723 (76%)	4457 (43%)		0 (0%)	482 (15%)	2223 (62%)	1752 (87%)	
	Other backbone	1724 (5%)	525 (4%)	978 (11%)	221 (2%)		4 (0%)	139 (4%)	10 (0%)	68 (3%)	

Continuous variables are reported as median (interquartile range, IQR). BMI is calculated as weight (in kilograms) divided by height (in meters squared). BMI categories are defined as follows: underweight, BMI < 18.5 kg/m²; normal, BMI 18.5–24.9 kg/m²; overweight, BMI 25.0–29.9 kg/m²; obese, BMI $\geq$ 30.0 kg/m².

Abbreviations: ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; BIC, bictegravir; BMI, body mass index; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

^aP value compares characteristics across ART regimen types (NNRTI, PI, and INSTI).

^bP value compares characteristics across INSTI subtypes (BIC, DTG, EVG, and RAL).

^cNNRTI core drug distribution: efavirenz 11 157 (83%), rilpivirine 1823 (14%), nevirapine 425 (3%), and other NNRTIs 95 (<1%).

^dPI core drug distribution: atazanavir 4268 (47%), darunavir 3244 (36%), and other PIs 1544 (17%).

the weight gain associated with INSTI- and PI-based regimens did not differ significantly at either year 2 or year 5.

To assess whether the observed differences in weight gain between ART classes were attributable to the NRTI backbone or the weight-suppressive effects of EFV, we performed subgroup

analyses restricted to individuals on TDF/FTC-containing regimens and stratified by NNRTI type. Efavirenz was analyzed as a separate NNRTI stratum in [Figure 2A](#), while [Figure 2B](#) was restricted to non-EFV NNRTI regimens. In both analyses, differences in predicted weight gain by regimen class persisted.

In the analysis examining EFV as a distinct NNRTI stratum (Figure 2A), participants receiving EFV with TDF/FTC ($n = 10\,315$) experienced lower predicted weight gain over time compared with those receiving INSTI- or PI-based regimens. At year 2, the predicted weight gain was 2.9 kg (95% CI: 2.6–3.1) for EFV, compared with 4.1 kg (95% CI: 3.6–4.6) for INSTIs and 4.8 kg (95% CI: 4.4–5.2) for PIs; this separation persisted through year 5.

In the parallel analysis restricted to non-EFV NNRTI regimens with TDF/FTC (Figure 2B), differences in predicted

weight gain by regimen class persisted. Participants receiving non-EFV NNRTI-based regimens ($n = 1792$) with TDF/FTC experienced significantly less weight gain compared to those on INSTI-based ($n = 4457$) or PI-based regimens ($n = 6723$). At year 2, the predicted weight gain was 2.0 kg (95% CI: 1.5–2.6) for non-EFV NNRTIs, compared to 4.2 kg (95% CI: 3.7–4.6) for INSTIs and 4.9 kg (95% CI: 4.5–5.3) for PIs. By year 5, weight gain increased to 3.3 kg (95% CI: 2.2–4.3) for non-EFV NNRTIs, while remaining significantly higher with INSTIs 5.3 kg (95% CI: 4.5–6.0) and PIs 5.7 kg (95% CI: 5.1–6.2).

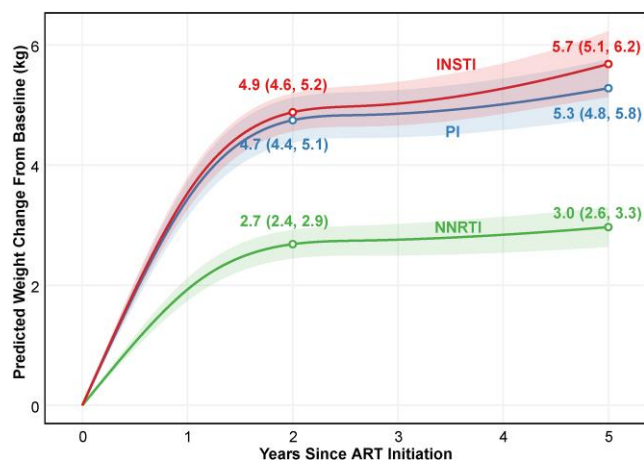


Figure 1. Change in predicted weight over 5 years by ART regimen among all participants. (NNRTI: $n = 13\,344$ vs PI: $n = 8876$ vs INSTI: $n = 10\,294$). Lines represent model-predicted mean weight change from baseline by ART class over time. Shaded regions indicate 95% CIs around the predicted estimates derived from the regression model. Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Changes in Weight Over Time by INSTI Drug

Given the shorter available follow-up time for many participants receiving more recent INSTI-based regimens, weight was modeled over the 2 years after ART initiation among all INSTI recipients (adjusted for NRTI backbone and other covariates), as well as separately for those starting RAL, EVG, or DTG with TDF/FTC, and EVG, DTG, or BIC with TAF/FTC. The predicted weight gain by INSTI core agent among all participants initiating INSTI-based regimens (BIC, $n = 1581$; DTG, $n = 3150$; EVG, $n = 3560$; RAL, $n = 2003$) is shown in Figure 3A. At 2 years, the predicted weight gain differed numerically across INSTI agents, with overlapping CIs between BIC and DTG and between DTG and RAL. The estimated weight gain was 6.9 kg (95% CI: 5.8–7.9) with BIC, 5.3 kg (95% CI: 4.8–5.9) with DTG, 4.5 kg (95% CI: 3.8–5.3) with RAL, and 4.0 kg (95% CI: 3.6–4.5) with EVG. Weight gain with EVG was significantly lower than that observed with BIC and DTG.

The analysis was next restricted to participants initiating TDF/FTC-containing INSTI-based regimens (DTG, $n = 482$; EVG, $n = 2223$; RAL, $n = 1752$) in Figure 3B. In this group, at year 2, the predicted weight gain was highest with DTG + TDF/

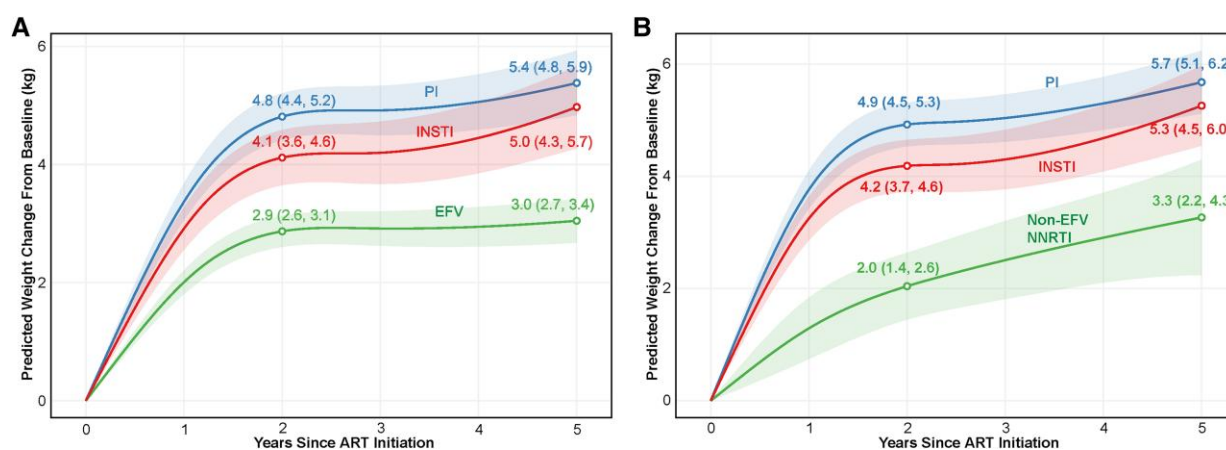


Figure 2. A, Change in predicted weight over 5 years by ART regimen among participants starting TDF/FTC-containing regimens (EFV: $n = 10\,315$ vs PI: $n = 6723$ vs INSTI: $n = 4457$). B, Change in predicted weight over 5 years by ART regimen among participants starting TDF/FTC-containing regimens, excluding EFV (non-EFV NNRTI: $n = 1792$ vs PI: $n = 6723$ vs INSTI: $n = 4457$). Lines represent model-predicted mean weight change from baseline by ART class over time. Shaded regions indicate 95% CIs around the predicted estimates derived from the regression model. Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

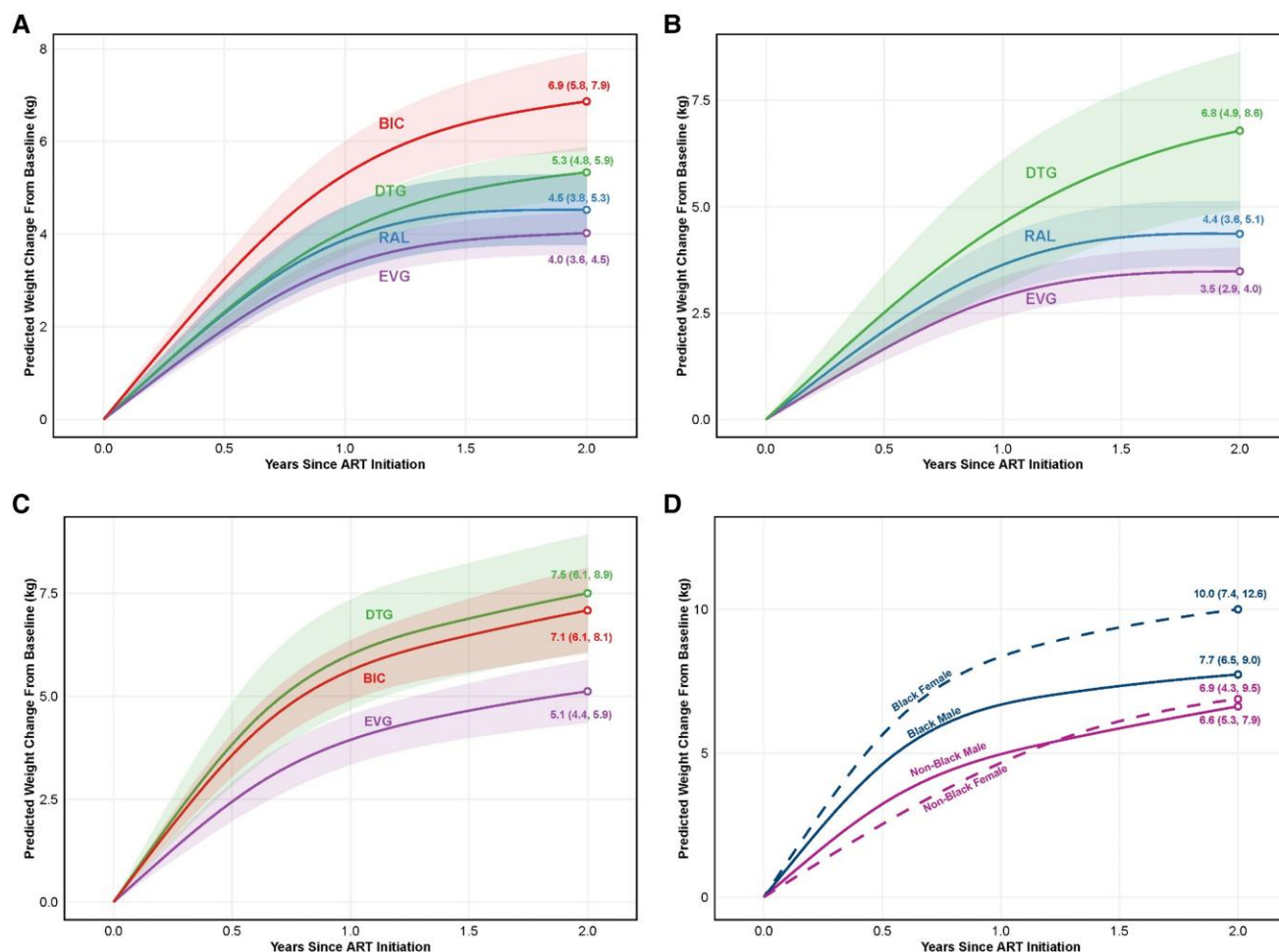


Figure 3. A, Change in weight by INSTI drug in participants starting INSTI-based regimens (BIC, $n = 1581$; DTG, $n = 3150$; RAL, $n = 2003$; EVG, $n = 3560$). B, Change in weight by INSTI drug in TDF/FTC-containing INSTI-based regimens (DTG, $n = 482$; RAL, $n = 1752$; EVG, $n = 2223$). C, Change in weight by INSTI drug in TAF/FTC-containing INSTI-based regimens (BIC, $n = 1577$; DTG, $n = 431$; EVG, $n = 1327$). D, Change in weight stratified by sex and race for participants on (DTG or BIC) + TAF/FTC (Black female, $n = 182$; Black male, $n = 794$; non-Black female, $n = 90$; non-Black male, $n = 942$). Participants with unknown race were categorized as “non-Black.” Lines represent model-predicted mean weight change from baseline by ART class over time. Shaded regions indicate 95% CIs around the predicted estimates derived from the regression model. Abbreviations: BIC, bicitegravir; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; RAL, raltegravir; TAF/FTC, tenofovir alafenamide/emtricitabine.; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

FTC (6.8 kg, 95% CI: 4.9–8.6), followed by RAL + TDF/FTC (4.4 kg, 95% CI: 3.6–5.1) and EVG + TDF/FTC (3.5 kg, 95% CI: 2.9–4.0). Weight gain with DTG was significantly greater than that observed with EVG, but not significantly different from RAL.

The analysis was next restricted to participants receiving TAF/FTC-containing INSTI-based regimens (BIC, $n = 1577$; DTG, $n = 431$; EVG, $n = 1327$) in Figure 3C. Weight gain in this cohort was more pronounced with DTG + TAF/FTC (7.5 kg, 95% CI: 6.1–8.9), followed by BIC + TAF/FTC (7.1 kg, 95% CI: 6.1–8.1) and EVG + TAF/FTC (5.1 kg, 95% CI: 4.4–5.9). Weight gain with BIC and DTG was similar, and both were significantly greater than that seen with EVG.

Lastly, to evaluate whether the weight gain associated with INSTIs combined with TAF differed by sex or race, Figure 3D

presents predicted weight gain among individuals receiving BIC or DTG plus TAF/FTC (Black female, $n = 182$; Black male, $n = 794$; non-Black female, $n = 90$; non-Black male, $n = 942$). At year 2, Black females had the highest predicted weight gain (10.0 kg, 95% CI: 7.4–12.6), followed by Black males (7.7 kg, 95% CI: 6.5–9.0), non-Black females (6.9 kg, 95% CI: 4.3–9.5), and non-Black males (6.6 kg, 95% CI: 5.3–7.9), highlighting important demographic differences in ART-associated weight trajectories within this treatment subgroup.

DISCUSSION

Many prior studies from varied settings observed greater weight gain among PWH starting ART regimens containing an INSTI and/or TAF as compared with regimens containing TDF and/

or NNRTI agents as a class [16]. Early reports of this weight differential were interpreted mainly as evidence of a weight-promoting effect of the newer agents when set against the assumed weight-neutral trajectories of the older drugs. As evidence accumulated that EFV, among the NNRTIs, and TDF, among the NRTIs, may have particular weight-suppressive properties in some individuals, the potential confounding effects of these two drugs in prior analyses, including our 2020 NA-ACCORD study, have come to light [9]. Here, we reassessed weight gain after ART initiation in NA-ACCORD and found that weight gain on non-EFV NNRTI-class medications still appears to be lower than for PI- or INSTI-based regimens, even after limiting NRTI exposure to TDF/FTC alone. Furthermore, our data confirm that Black females are prone to the greatest increase in weight when initiated on TAF/FTC with current first-line INSTIs (DTG and BIC). Black females in our cohort had the highest baseline BMI and obesity prevalence at ART initiation, mirroring national patterns in the United States and Canada. These background differences suggest that the greater weight increases observed among Black women on contemporary ART may reflect an interaction between ART-related effects and broader structural and environmental factors that influence weight in the general population.

While there is considerable evidence for a weight-suppressive effect of EFV, the finding that exposure to non-EFV NNRTIs was still associated with lower weight gain was unexpected. We observed an estimated 3.3 kg weight gain over 5 years in the non-EFV NNRTI group when limited to those receiving TDF/FTC. This was 2.0–2.4 kg lower than the estimated gain for the INSTI and PI arms (both with TDF/FTC).

Our analysis supports prior evidence for the weight-suppressive effects of TDF. In a large pooled analysis of weight in 8 randomized clinical trials, weight gain was significantly lower with TDF compared to TAF [12]. Furthermore, TAF exposure was associated with a significantly increased risk of >10% weight gain, whereas TDF was not. In the GEMINI 1 and 2 trials of treatment-naïve adults randomized to DTG/3TC or DTG/TDF/FTC, participants receiving DTG/TDF/FTC experienced less weight gain, supporting a potential weight-suppressive effect of TDF [17]. Similarly, in the TANGO study, participants were randomized to either switch from TAF-based regimens to DTG/3TC or continue their current treatment [15]. No significant differences in weight change over time were observed between the two groups, suggesting that discontinuing TAF does not lead to weight loss. This observation was further supported by the SALSA study, in which participants either continued their baseline ART or switched to DTG/3TC. Those switching from TDF-based regimens to DTG/3TC gained significantly more weight than those who remained on TDF, whereas participants switching from TAF-based regimens had similar weight changes to those

who continued TAF [18]. In CHARACTERISE, a follow-up analysis of the ADVANCE trial, women initially randomized to DTG/TAF/FTC and switched to DTG/3TC/TDF (TLD) had a statistically significant 1.6 kg reduction in weight [19], highlighting the weight suppressive effect of TDF.

Additional evidence comes from the DISCOVER trial for HIV PrEP, where participants receiving TAF/FTC experienced significantly greater weight gain compared to those on TDF/FTC [20]. Furthermore, in a recent cross-study comparison, the weight trajectory for participants on TAF/FTC in DISCOVER was statistically similar to that of participants receiving placebo in the iPrEx trial, supporting the idea of a weight-neutral profile for TAF [14, 20, 21].

The similar magnitude of weight gain observed with PI- and INSTI-based regimens is consistent with data from the DEFINE study, which demonstrated no meaningful differences in weight change when virologically suppressed individuals continued INSTI-based therapy versus switched to boosted darunavir while maintaining a tenofovir alafenamide backbone [22]. Together, these data suggest that contemporary PI- and INSTI-based regimens may have more similar weight profiles than previously assumed.

Limitations

This study has several limitations. First, although we adjusted for multiple baseline covariates and included a large, diverse cohort, residual confounding remains possible, particularly due to changes in ART prescribing practices over time and unmeasured factors, such as diet, physical activity, and socioeconomic status. Second, censoring due to ART regimen changes or loss to follow-up, potentially triggered by rapid weight gain or metabolic complications, may have influenced the results. Weight was captured during routine clinical care rather than at standardized intervals, which could introduce variability; however, our models accounted for the timing of weight measurements. We also did not adjust for use of non-HIV medications associated with weight change (eg, hormonal or psychotropic agents and glucagon-like peptide-1 receptor agonists), nor did we account for pregnancy, as these data were not consistently available. Finally, the shorter follow-up period for more recently approved agents, such as BIC, may limit the ability to assess their long-term effects.

Conclusions

This reappraisal of ART-associated weight changes in a large North American cohort highlights significant differences in weight gain between PWH starting NNRTI-based regimens versus INSTI- or PI-based regimens. Notably, even after excluding EFV and restricting the analysis to TDF-containing backbones, NNRTI-based regimens remained associated with significantly lower weight gain. This observation raises important questions about the potential role of other NNRTIs in

modulating weight. While evidence for a weight-suppressive effect of RPV remains limited, the lower weight gain observed in the non-EFV NNRTI group in our study merits further exploration. Prospective studies and pharmacologic analyses are needed to clarify whether NNRTIs other than EFV may attenuate weight gain and to elucidate the biological mechanisms underlying ART-associated weight changes.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Data availability. “Data are available upon reasonable request and circulation and approval of a scientific concept sheet through the standard NA-ACCORD process, outlined here: <https://naaccord.org/concept-sheet>.”

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